Annex to:

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Annex A – Additional information for the risk assessment for human and animal health related to the presence of dioxins and DL-PCBs in food and feed

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ANNEX A.1. STRATEGY FOR THE RISK ASSESSMENT FOR HUMAN AND ANIMAL HEALTH RELATED TO THE PRESENCE OF PCDD/Fs AND DL-PCBs IN FOOD AND FEED

In the context of the on-going EFSA Prometheus project (PROMoting METHods for Evidence Use in Science) aimed at further enhancing the methodological rigour, transparency and openness of EFSA scientific assessments, this risk assessment was chosen as a case-study to test the importance of performing the assessment in two steps, i.e. planning phase and implementing phase. For the planning phase of the risk assessment, the current strategy is being developed with the aim of performing a priori the whole process of problem formulation and defining as much as possible beforehand the strategy for gathering the data, the criteria for selecting and appraising the evidence, and for the synthesis of the results.

The experience gained with this specific risk assessment will provide guidance for further refinement of the Methodological Framework developed in the Prometheus project.

A.1.1. Problem formulation

A.1.1.1. Objectives of the risk assessment

This present risk assessment aims at assessing (i) the risk for adverse effects in humans associated with the dietary exposure to polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and dioxin-like polychlorinated biphenyls (DL-PCBs) in food, and (ii) the risk for adverse effects in farm and companion animals associated to the dietary exposure to PCDD/Fs and DL-PCBs in feed.

The scientific evidence needed to directly address these two main objectives will be dealt with by applying a narrative or a structured approach according to the specific sub-questions identified for each risk assessment pillar and by target population (humans/farm and companion animals).

In order not to exclude any related papers the bibliography of the key full text papers will be checked for further potential relevant studies. This technique is known as snowballing. The expertise of the working group will be used in deciding whether to pursue these further to complement the evidence collection.

Relevant information about previous risk assessments by international bodies, chemistry, analytical methods, current EU legislation, previously reported occurrence data in food and feed and exposure assessments (including time trends), as reported in the literature, will be gathered and summarised in a narrative way based on expert knowledge/judgement.

A.1.1.2. Target populations

The target population of the human risk assessment is the EU population, including specific vulnerable groups (foetus and breast-fed infants) and groups with high exposure due to dietary preferences, e.g. people eating fish from contaminated areas.

The target populations of the animals risk assessment are farm and companion animals including cattle, sheep, goats, pigs, poultry, rabbits, farmed fish, fur producing animals, horses, dogs and cats.

A.1.1.3. PCDD/Fs and DL-PCBs of concern and route of exposure

The risk assessment is limited to the dietary exposure to the 17 PCDD/Fs substituted in the 2,3,7,8-positions, and the 12 DL-PCBs (Table 1). Other persistent dioxin-like compounds (e.g. brominated dioxins) are not part of the Terms of Reference for the scientific opinion, their potential influence on the outcome of epidemiological studies will be addressed in the uncertainty analysis.

In order to assess and compare the toxicity of a mixture of congeners analysed in complex samples, the CONTAM Panel applied the concept of toxic equivalents (TEQs) based on different toxicity equivalency factors (TEFs) for the toxic congeners. It should be noted that the TEFs are an order of magnitude estimates of the toxicity of TCDD, which adds uncertainty to the risk assessment and will be addressed in the uncertainty analysis.

In the European legislation, all regulatory levels for PCDD/Fs and DL-PCBs in food and feed are presently expressed as TEQs using the WHO_{2005}-TEFs proposed by the World Health Organization (WHO) in 2005 (van den Berg et al., 2006). Therefore, current occurrence data are generally expressed as WHO_{2005}-TEQs. If relevant for this opinion, older data which are expressed as WHO_{1998}-TEQs are recalculated with the WHO_{2005}-TEFs.

The effect of potential deviations of the WHO_{2005}-TEF values, based on the outcome of studies published since its last revision, will be addressed in the uncertainty analysis.

In addition, consideration will be given to potential non-dietary sources of exposure (such as soil and air) to indicate the relative importance of the diet to the overall PCDD/Fs and DL-PCBs exposure.

Table 1. Compounds of concern for the risk assessment

Congener	Structure	WHO-TEF_{2005} value[(a)]
PCDDs		
2,3,7,8-TCDD	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin	1
1,2,3,7,8-PeCDD	1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin	1
1,2,3,4,7,8-HxCDD	1,2,3,4,7,8-Hexachlorodibenzo-*p*-dioxin	0.1
1,2,3,6,7,8-HxCDD	1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin	0.1
1,2,3,7,8,9-HxCDD	1,2,3,7,8,9-Hexachlorodibenzo-*p*-dioxin	0.1
1,2,3,4,6,7,8-HpCDD	1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin	0.01
1,2,3,4,6,7,8,9-OCDD	1,2,3,4,6,7,8,9-Octachlorodibenzo-*p*-dioxin	0.0003
PCDFs		
2,3,7,8-TCDF	2,3,7,8-Tetrachlorodibenzofuran	0.1
1,2,3,7,8-PeCDF	1,2,3,7,8-Pentachlorodibenzofuran	0.03
2,3,4,7,8-PeCDF	2,3,4,7,8-Pentachlorodibenzofuran	0.3
1,2,3,4,7,8-HxCDF	1,2,3,4,7,8-Hexachlorodibenzofuran	0.1
1,2,3,6,7,8-HxCDF	1,2,3,6,7,8-Hexachlorodibenzofuran	0.1
2,3,4,6,7,8-HxCDF	2,3,4,6,7,8-Hexachlorodibenzofuran	0.1
1,2,3,7,8,9-HxCDF	1,2,3,7,8,9-Hexachlorodibenzofuran	0.1
1,2,3,4,6,7,8-HpCDF	1,2,3,4,6,7,8-Heptachlorodibenzofuran	0.01
1,2,3,4,7,8,9-HpCDF	1,2,3,4,7,8,9-Heptachlorodibenzofuran	0.01
1,2,3,4,6,7,8,9-OCDF	1,2,3,4,6,7,8,9-Octachlorodibenzofuran	0.0003
DL-PCBs (non-*ortho* PCBs)		
PCB-77	3,3',4,4'-Tetrachlorobiphenyl	0.0001
PCB-81	3,4,4',5-Tetrachlorobiphenyl	0.0003
PCB-126	3,3',4,4',5-Pentachlorobiphenyl	0.1
PCB-169	3,3',4,4',5,5'-Hexachlorobiphenyl	0.03
DL-PCBs (mono-*ortho* PCBs)		
PCB-105	2,3,3',4,4'-Pentachlorobiphenyl	0.00003
PCB-114	2,3,4,4',5-Pentachlorobiphenyl	0.00003
PCB-118	2,3',4,4',5-Pentachlorobiphenyl	0.00003
PCB-123	2,3',4,4',5'-Pentachlorobiphenyl	0.00003
PCB-156	2,3,3',4,4',5-Hexachlorobiphenyl	0.00003
PCB-157	2,3,3',4,4',5'-Hexachlorobiphenyl	0.00003
PCB-167	2,3',4,4',5,5'-Hexachlorobiphenyl	0.00003
PCB-189	2,3,3',4,4',5,5'-Heptachlorobiphenyl	0.00003
Toxic equivalents		
WHO_{2005}-TEQs	Toxic equivalents (based on WHO_{2005}-TEFs)	

DL-PCBs: dioxin-like polychlorinated biphenyls; PCDDs: polychlorinated dibenzo-*p*-dioxins; PCDFs: polychlorinated dibenzofurans; TEQ: toxic equivalent; WHO: World Health Organization.
(a): According to Van den Berg et al. (2006).

A.1.1.4. Adverse effects and endpoints

The human and animal risk assessments will address the adverse effects associated with the exposure to PCDD/Fs and DL-PCBs as identified in the hazard identification step.

Adverse effects of PCDD/Fs and DL-PCBs are well known based on animal and human data, and are addressed in previous risk assessments. These have identified skin lesions, i.e. chloracne, hepatic

alterations and cancer after exposure to high levels of PCDD/Fs and other dioxin-like compounds (WHO/FAO, 2002). Exposure to lower levels has been documented to cause developmental and reproductive toxicity, immunotoxicity and neurodevelopmental effects, among others. However, they are not considered to be genotoxic.

A.1.1.5. Identification of the risk assessment sub-questions

The general principles of the risk assessment process for chemicals in food as described by WHO/IPCS (2009) will be applied, which include hazard identification and characterisation, exposure assessment and risk characterisation. In addition, the following EFSA guidances pertaining to risk assessment will be followed for the development of the risk assessment:

- Guidance of the Scientific Committee on a request from EFSA related to uncertainties in Dietary Exposure Assessment (EFSA Scientific Committee, 2006);
- Guidance of the Scientific Committee on use of the benchmark dose approach in risk assessment (EFSA Scientific Committee, 2009a);
- Guidance of the Scientific Committee on transparency in the scientific aspects of risk assessments carried out by EFSA. Part 2: General principles (EFSA Scientific Committee, 2009b);
- Management of left-censored data in dietary exposure assessment of chemical substances (EFSA, 2010a);
- Use of BMDS and PROAST software packages by EFSA Scientific Panels and Units for applying the Benchmark Dose (BMD) approach risk assessment (EFSA, 2011a);
- Guidance of EFSA on the use of the EFSA Comprehensive European Food Consumption Database in exposure assessment (EFSA, 2011b);
- Overview of the procedures currently used at EFSA for the assessment of dietary exposure to different chemical substances (EFSA, 2011c);
- Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data (EFSA Scientific Committee, 2012a);
- Scientific Opinion on Risk Assessment terminology (EFSA Scientific Committee, 2012b).

This section illustrates the objectives of each risk assessment pillar (i.e. hazard identification, hazard characterisation and exposure assessment) and identifies the risk assessment sub-questions that will be answered and combined for performing the assessment for humans (Table 2), and for farm and companion animals (Table 3).

As indicated in the EFSA Prometheus deliverable, 'EFSA assessments are rarely represented by narrow, focussed questions; in most cases they are broad and require more than one sub-question to be answered. A sub-question is a scientific question that does not need to be further broken down to be answered and is formulated in a way that is directly answerable in an experimental or observational study (or as a single question in an expert elicitation study) (EFSA, 2015). Most common sub-questions fall into three main types (EFSA, 2010b): (1) sub-questions on the association between an exposure or intervention and outcome(s); (2) sub-questions on occurrence (or prevalence or incidence) of a given condition (i.e. descriptive statistics); and (3) sub-questions on test accuracy. The degree to which the question is broken down into sub-questions depends in part on several factors including: i) the complexity of the problem, ii) the different expertise needed for each part, iii) the time available. This must be discussed explicitly by the assessors'.

For the human risk assessment, studies on both humans and experimental animals will be used for the hazard identification and characterisation. In experimental animals, PCDD/Fs and DL-PCBs cause adverse effects, and these have been extensively described in previous risk assessment by international bodies such as SCF (2000, 2001), WHO/FAO (2002) and US-EPA (2012). The dose levels used in these studies vary considerably. The Working Group concluded that studies in which the

target compounds have been administered at doses that result in higher body burdens[1] in the animal than those that formed the basis of the point of departure in these previous assessments are not informative for the hazard characterisation. SCF (2000, 2001) evaluated studies with lowest-observed-adverse-effects levels (LOAELs) corresponding to estimated maternal body burdens of 40–100 ng/kg bw or a no-observed-adverse-effect level (NOAEL) corresponding to 20 ng/kg bw for deriving the estimated human daily intake leading to these body burdens and subsequently the tolerable weekly intake (TWI) of 14 pg TEQ/kg bw. Therefore, only experimental animal studies in which the administration of the target compounds included measured/estimated body burdens lower than 100 ng WHO-TEQ_{2005}/kg bw will be considered to answer the sub-question. The present assessment will therefore include all studies after the WHO (1998) and the SCF assessments (2000, 2001), with focus in the adverse effects observed at low levels of exposure as indicated above.

For the farm and companion animal risk assessment, studies in the target species will be used for the hazard identification and characterisation. No previous risk assessments have addressed the adverse effects of the target compounds in the target species. The European Commission's former Scientific Committee on Animal Nutrition (SCAN, 2000) evaluated the contribution of PCDD/Fs and PCBs (including DL-PCBs) in feedingstuffs to the contamination of food of animal origin, but did not include a risk assessment of PCDD/Fs and/or DL-PCBs in feed for the farm/companion target species. Therefore, the farm and companion animal risk assessment will include studies published in the open literature since 1950.

The potential association between the target compound(s) and the endpoints of interest for the human and farm/companion animal risk assessment will be evaluated. It will include an assessment of the dose-response relationship and an evaluation of possible uncertainties, for example those derived from consideration of the toxicokinetic and toxicodynamic properties of the target compounds and from considerations of inter-species variability in case animal data are being used for deriving a health based guidance value (HBGV).

As a next step, the human and the farm and companion animal dietary exposure to the target compounds will be estimated.

The final step will be the comparison of the exposure estimates to the HBGVs established (e.g. tolerable intake), or estimation of the margin of exposure.

Table 2. Human risk assessment sub-questions to be answered

Risk assessment step	N.	Risk assessment sub-questions	Approach
Hazard identification	1	What adverse outcomes are associated with exposure to PCDD/Fs and DL-PCBs in humans?	Structured approach A
Hazard identification	2	What adverse outcomes are caused by exposure to PCDD/Fs and DL-PCBs in experimental animals?	Narrative approach
Hazard identification	3	Which adverse outcomes occur following exposure to PCDD/Fs and DL-PCBs in experimental animals at body burdens measured/estimated to be lower than 100 ng WHO_{2005}-TEQ/kg bw?	Structured approach B
Hazard identification	4	Are PCDD/Fs and DL-PCBs genotoxic?	Narrative approach
Hazard characterisation	5	What is the absorption, distribution, metabolism and excretion (ADME) of the target compounds in humans?	Structured approach C
Hazard characterisation	6	What is the ADME of the target compounds in experimental animal species/strains?	Structured approach D
Hazard characterisation	7	What is the difference in ADME of the target compounds between humans and experimental animals?	Informed by sub-questions 5 and 6
Hazard characterisation	8	What is the dose-response relationship between PCDD/Fs and DL-PCBs and relevant endpoints in humans?	Structured approach A

[1] The total amount of a chemical in the body.

Risk assessment step	N.	Risk assessment sub-questions	Approach
Hazard characterisation	9	What is the dose-response relationship between PCDD/Fs and DL-PCBs and relevant endpoints in experimental animals at body burdens measured/estimated to be lower than 100 ng WHO_{2005}-TEQ/kg bw?	Structured approach B
Hazard characterisation	10	What molecular mechanisms can explain the observed adverse effects?	Narrative approach
Exposure assessment	11	What are the levels of PCDD/Fs and DL-PCBs in food in Europe?	Structured approach E
Exposure assessment	12	What is the effect of processing on the levels of PCDD/Fs and DL-PCBs in food?	Narrative approach
Exposure assessment	13	What are the consumption levels of foods among the target European population?	Structured approach F
Exposure assessment	14	What is the estimate of exposure to PCDD/Fs and DL-PCBs from the diet in the target European population?	Informed by Sub-question 11 and 13
Exposure assessment	15	What are the concentrations of PCDD/Fs and DL-PCBs in, e.g. blood, breast milk, adipose tissue, placenta in the target European population?	Narrative approach

bw: body weight; DL-PBCs: dioxin-like polychlorinated biphenyls; PCDD/Fs: polychlorinated dibenzo-*p*-dioxins/dibenzofurans; TEQ: toxic equivalents; WHO: World Health Organization.

Table 3. Farm and companion animals risk assessment sub-questions to be answered

Risk assessment step	N.	Risk assessment sub-questions	Approach
Hazard identification	16	What adverse outcomes are caused by exposure to PCDD/Fs and DL-PCBs in farm and companion animals?	Structured approach G
Hazard characterisation	17	What are the dose-response relationships between PCDD/Fs and DL-PCBs and relevant endpoints in farm and companion animals?	Structured approach G
Hazard characterisation	18	What is the ADME of the target compounds in the different farm and companion animal species?	Structured approach H
Hazard characterisation	19	What is the transfer of PCDD/Fs and DL-PCBs from feed to products of animal origin?	Structured approach H
Hazard characterisation	20	What levels in feed result in non-compliant levels in food?	Informed by sub-questions 18 and 19
Exposure assessment	21	What are the levels of PCDD/Fs and DL-PCBs in feed in Europe?	Structured approach E
Exposure assessment	22	What are the consumption levels of feeds among the farm and companion animals?	Narrative approach
Exposure assessment	23	What is the estimate of exposure to PCDD/Fs and DL-PCBs from the diet in the target farm and companion animal populations?	Informed by sub-questions 21 and 22

ADME: absorption, distribution, metabolism and excretion; DL-PCBs: dioxin-like polychlorinated biphenyls; PCDD/Fs: polychlorinated dibenzo-*p*-dioxins/dibenzofurans.

A.1.2. Method to address the hazard identification and characterisation sub-questions

A.1.2.1. Narrative approach to evidence identification, selection and appraisal

Sub-question 2 will be addressed narratively by a literature search carried out to identify review/meta-analysis/systematic review papers relevant for the hazard identification of PCDD/Fs and DL-PCBs in

experimental animals. These will be screened and evaluated by relevant domain experts from the Working Group. For details of the search strategy, see Table 4.

Table 4. Preliminary keywords for the narrative approach to address sub-question 2 (hazard identification all doses experimental animals)

Database	Web of Science™
Preliminary keywords	Dioxins, Tetrachlorodibenzodioxin, Polychlorinated Biphenyls, Dioxin-like, TEQ, Coplanar, PCBs, TCDD

Sub-question 4 will be addressed narratively. The genotoxicity of TCDD, as well as that of other PCDD/Fs and DL-PCBs, has been studied intensively (IARC, 1997; ATSDR 1998). The evidence for the genotoxicity of PCDD/Fs and DL-PCBs is negative or equivocal for a large range of *in vitro* and *in vivo* end points. Therefore, a literature search will be carried out to identify review/meta-analysis/systematic review papers relevant to the genotoxicity of the target compounds, as well as other peer-reviewed single studies published in the open literature that will be screened and evaluated by relevant domain experts from the Working Group. For details of the search strategy see Table 5.

Table 5. Preliminary search strings for the narrative approach to address sub-question 4 (genotoxicity)

Database	Web of Science™
Preliminary Keywords	Micronucleus, Gene mutations, Mutagenicity, Single strand breaks, DNA damage, Oxidative DNA damage, DNA repair, Chromosomal breaks/deletions/aberrations, Unscheduled DNA synthesis, Clastogenic, Polyploidy, nongenotoxicity, nongenotoxic, Epigenetic, Gene methylation, Transgenerational **AND** Dioxins, Tetrachlorodibenzodioxin, TCDD, Polychlorinated Biphenyls, Dioxin-like, TEQ, Coplanar, PCB

Sub-question 10 will be addressed narratively by a literature search to be carried out to identify review/meta-analysis/systematic review papers relevant to inform the modes of action of the target compounds, as well as other peer-reviewed single studies published in the open literature that will be screened and evaluated by relevant domain experts from the Working Group. This task will be performed by EFSA/Working Group members. For details of the literature search, see Table 6.

Table 6. Preliminary key words for the narrative approach to address sub-question 10 (mode of action)

Database	Web of Science™
Preliminary keywords	Ah receptor, aryl hydrocarbon receptor, AhR, structure, phylogenesis, signal transduction, gene regulation, response element, genomic pathway, non-genomic pathway, alternative pathway, nuclear receptor, protein-protein interactions, DNA-protein interactions, cross-talk, ARNT, AHRR, chaperone, co-activator, co-repressor, AhR-knockout, AhR-deficient **AND** Dioxins, Tetrachlorodibenzodioxin, Polychlorinated Biphenyls, Dioxin-like, TEQ, Coplanar, Polychlorinated biphenyls, PCBs, TCDD

For these narrative approaches, the scientific citation research platform interrogated will be Web Of Science™, encompassing the databases described in Section A.1.2.2.2 below and covering the vast majority of the published relevant studies. The output will be exported into a reference management software, i.e. Endnote X7 file.

A.1.2.2. Structured approach to evidence identification, selection and appraisal

Structured approach A will address sub-questions 1 and 8 on the adverse effects of the target compounds in humans by performing an extensive literature search (ELS) followed by a selection of relevant evidence based on eligibility criteria (see Table 7 below), and a structured appraisal and synthesis of the relevant evidence. This task will be carried out by an external contractor.

Structured approach B will address sub-questions 3 and 9 on the adverse effects of the target compounds in experimental animals at low doses, by performing an ELS and selection of relevant studies (see Table 8 below) to identify which are the adverse effects that occur following exposure to the target compounds in experimental animals at body burdens measured/estimated to be lower than 100 ng WHO_{2005}-TEQs/kg bw, i.e. at levels in the range of or lower than the body burdens previously used to derive HBGVs. The eligible studies will be appraised and synthesised following a structured approach. The outcome of this approach will also inform sub-question 2 in case effects not previously described are reported to occur at low levels (i.e. body burdens measured/estimated to be not higher than 100 ng WHO_{2005}-TEQ/kg bw). This task will be carried out by an external contractor.

Structured approach C and D will address sub-questions 5 and 6 related to the toxicokinetics of the target compounds in humans and experimental animals, respectively, by performing two ELS to define differences related to inter-species toxicokinetics, including inter-individual variability, that need to be taken into account when establishing a health-based guidance value (see Tables 9 and 10 below). This includes potential toxicokinetic models for experimental animals and humans. The evidence will be then appraised and described in a narrative way. This task will be performed by EFSA/Working Group members.

Structured approach G will address sub-questions 16 and 17 on the adverse effects of the target compounds in farm and companion animals, by performing an ELS, followed by a selection of relevant evidence (see Table 11 below), and a structured synthesis and appraisal of the relevant evidence. This task will be performed by EFSA/Working Group members.

Structured approach H will address sub-questions 18 and 19 by performing an ELS to identify information on the toxicokinetics of the target compounds in the farm and companion animals considered, and the transfer of these contaminants from feed to animal-derived food products (see **Table 12** below). Soil, as a possible source of the target compounds, will also be considered. The evidence will be described in a narrative way. This task will be performed by EFSA/Working Group members.

A.1.2.2.1. Review questions and eligibility criteria for study selection

The selection of the studies relevant to the sub-questions addressed by a structured approach will be performed using the eligibility criteria described in the Tables 7-12 below.

Table 7. Eligibility criteria for the **structured approach A** (sub-questions 1 and 8)

Sub-question 1 - **What adverse outcomes are associated with exposure to PCDD/Fs and DL-PCBs in humans?** Sub-question 8 - **What is the dose-response relationship between PCDD/Fs and DL-PCBs and relevant endpoints in humans?**		
Study design	In	Cross-sectional studies Cohort studies Case-control studies (retrospective and nested) Case series/Case reports[(d)]
	Out	Animal studies *In vitro* studies
Study characteristics:	In	Any study duration Any number of subjects
	Out	/
Population	In	All populations groups, all ages, males and females Study location: all countries
	Out	/
Exposure/ intervention	In	All routes of exposure (dietary, dermal, inhalation, transplacental exposure). Studies in which levels of the following target compounds have been measured in human tissues (including by bioassays), OR Studies in which the total dietary exposure to the following target compounds has been estimated [(a)], – 17 PCDD/Fs and 12 DL-PCBs

		– 17 PCDD/Fs – 12 DL-PCBs – 17 PCDD/Fs plus non-*ortho* PCBs, at least one PCB being PCB-126 – TCDD (when dominates the TEQs, as in the Seveso incident) or any of the individual target congeners that dominates the TEQs
	Out	Studies on mono-*ortho* PCBs only Studies on non dioxin-like (indicator) PCBs[(b)] Studies on mixtures in which the contribution from the target compounds does not allow the calculation of TEQs
Specific outcome of interest	In	All endpoints, including hormone levels
	Out	Studies on gene expression only Studies on drug metabolising enzyme activity/levels only
Language	In	English
Time	In	From 1998 onwards
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data) Systematic reviews, reviews and meta-analyses [(c)]
	Out	Expert opinions, editorials, and letters to the editor PhD Theses Extended abstracts, conference proceedings

DL-PCBs: dioxin-like polychlorinated biphenyls; PCB: dioxin-like polychlorinated biphenyl; PCDD/Fs: polychlorinated dibenzo-*p*-dioxins/dibenzofurans; TCDD: 2,3,7,8- tetrachlorodibenzo-*p*-dioxin; TEQ: toxic equivalents.
(a): Although these studies will not serve for the hazard characterisation, they are informative and serve as supporting information.
(b): Indicator PCBs: PCB-28, -52, -101, -138, -153, and -180.
(c): Systematic reviews, reviews and meta-analysis will be included and used as background information. These types of publications will not go through the data extraction process.
(d): Case series/case report studies will be included to inform the hazard identification. This type of studies will not go through the data extraction process.

Table 8. Eligibility criteria for the **structured approach B** (sub-questions 3 and 9)

Sub-question 3 **– Which adverse outcomes occur following exposure to PCDD/Fs and DL-PCBs in experimental animals at body burdens measured/estimated to be lower than 100 ng WHO_{2005}-TEQ/kg bw?** Sub-question 9 **- What is the dose-response relationship between PCDD/Fs and DL-PCBs and relevant endpoints in experimental animals at body burdens measured/estimated to be lower than 100 ng WHO_{2005}-TEQ/kg bw?**		
Study design	In	Experimental animal studies (e.g. rats, mice, monkeys, guinea pig, mini pigs, rabbit, hamster, dog, cat, mink) Including [(a)] TCDD-sensitive and resistant animals, and In relation to metabolic effects, including: • diabetic animal models, • animals on high/low fat diets, • lean/obese animals, In relation to immunotox endpoint, including: ☐Lupus-like autoimmune animals ☐Immunised animals ☐Pathogen infected animals
	Out	Studies on transgenic animals [(b)] Human studies *In vitro* studies
Study characteristics:	In	Any study duration Any number of animals
	Out	/
Population	In	Any experimental animal study, all ages, males and females
	Out	/
Exposure/ intervention	In	Route of administration: Oral (feeding, gavage studies), inhalation, *s.c.*, *i.p.*, *i.m.* Compounds: Levels measured in animal tissues (including by bioassays) of any of the 17 2,3,7,8-substituted PCDD/Fs and/or 12 DL-PCBs, administered individually or as mixtures OR Estimated exposure validated Number of doses: single or repeated administration Dose groups: ≥ 2 dose groups + control group Cut-off values: studies in which the lowest measured/estimated body burden is not

		higher than 100 ng WHO_{2005}-TEQ/kg bw
	Out	Dermal application Studies on non dioxin-like (indicator) PCBs[(c)] Studies on mixtures with compounds other than the target PCDD/Fs and DL-PCBs (e.g. organochlorinated compounds, brominated flame retardants, etc).
Specific outcome of interest	In	All endpoints
	Out	Studies on enzyme induction only (e.g. CYP modulation) Studies on gene expression only Studies on co-administration of pro-carcinogens (CON A, DMBA, NKK) only Studies on -omics profiles Studies on the protective effects of certain substances against PCDD/Fs and/or DL-PCB toxicity
Language	In	English
Time	In	From 1998 onwards
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data) Systematic reviews, reviews and meta-analyses [(d)]
	Out	Expert opinions, editorials, and letters to the editor. PhD Theses Extended abstracts, conference proceedings

bw: body weight; CYP: cytochrome P450; DL-PCBs: dioxin-like polychlorinated biphenyls; *i.m.*: intramuscular; *i.p.*: intraperitoneal; PCB: dioxin-like polychlorinated biphenyl; PCDD/Fs: polychlorinated dibenzo-*p*-dioxins/dibenzofurans; *s.c.*: subcutaneous; TCDD: 2,3,7,8- tetrachlorodibenzo-*p*-dioxin; TEQ: toxic equivalents.

(a): It is considered that these studies are informative, although they may not necessarily be directly used for hazard characterization.

(b): It is considered that studies on transgenic animals are helpful in terms of mechanism of action but these are not informative in terms of risk assessment.

(c): Indicator PCBs: PCB-28, -52, -101, -138, -153, and -180.

(d): Systematic reviews, reviews and meta-analysis will be included and used as background information. These types of publications will not go through the data extraction process.

Table 9. Eligibility criteria for the **structured approach C** (sub-question 5)

Sub-question 5 – **What is the ADME of the target compounds in humans?**		
Study design / Test system	In	*In vivo* studies in humans
	Out	*In vivo* studies in experimental animals *In vivo* studies in farm and companion animals *In vitro* studies in human culture cells/models
Exposure/ intervention	In	Any of the 17 2,3,7,8-substituted PCDD/Fs and/or 12 DL-PCBs, individually or as mixtures
	Out	Studies on mixtures with compounds other than the target PCDD/Fs and DL-PCBs (e.g. organochlorinated compounds, brominated flame retardants, etc)
Specific outcome of interest	In	Any outcome related to the ADME of the target compounds
Language	In	English
Time	In	From 1998 onwards
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data) Systematic reviews, reviews and meta-analyses
	Out	Expert opinions, editorials, and letters to the editor PhD Theses Extended abstracts, conference proceedings

ADME: absorption, distribution, metabolism and excretion; DL-PCBs: dioxin-like polychlorinated biphenyls; PCDD/Fs: polychlorinated dibenzo-*p*-dioxins/dibenzofurans.

Table 10. Eligibility criteria for the **structured approach D** (sub-question 6)

Sub-question 6 – **What is the ADME of the target compounds in experimental animals?**		
Study design / Test system	In	*In vivo* studies in experimental animals
	Out	*In vivo* studies in farm and companion animals *In vivo* studies in humans *In vitro* studies in experimental animals culture cells/models
Exposure/ intervention	In	Any of the 17 2,3,7,8-substituted PCDD/Fs and/or 12 DL-PCBs, individually or as mixtures
	Out	Studies on mixtures with compounds other than the target PCDD/Fs and DL-PCBs (e.g. organochlorinated compounds, brominated flame retardants, etc
Specific outcome of interest	In	Any outcome related to the ADME of the target compounds
Language	In	English
Time	In	From 1998 onwards
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data) Systematic reviews, reviews and meta-analyses
	Out	Expert opinions, editorials, and letters to the editor PhD Theses Extended abstracts, conference proceedings

ADME: absorption, distribution, metabolism and excretion; DL-PCBs: dioxin-like polychlorinated biphenyls; PCB: dioxin-like polychlorinated biphenyl; PCDD/Fs: polychlorinated dibenzo-*p*-dioxins/dibenzofurans.

Table 11. Eligibility criteria for the **structured approach G** (sub-questions 16 and 17)

Sub-question 16 - **Is there an association between dietary exposure to PCDD/Fs and DL-PCBs and adverse effects in the farm and companion animal target populations?** Sub-question 17 - **What are the dose-response relationships between PCDD/Fs and DL-PCBs and relevant endpoints in farm and companion animals?**		
Study design / Test system	In	Studies on adverse effects in the following species: – Ruminants: cows, sheep, goat, cattle, buffalo, bovine – Pigs: swine – Poultry: chicken, turkeys, goose, ducks, quails – Rabbits (*captured in the experimental animal search*) – Fish: trout, salmon, seabass, seabream, turbot, carp, eel, tilapia, cod, halibut, sturgeon – Horses – Companion animals (cats and dogs) (*captured in the experimental animal search*) – Fur animals (mink) (*captured in the experimental animal search*)
	Out	*In vitro* studies Human studies Studies in experimental animals Studies in experimental fish species (e.g. zebrafish, medaka)
Exposure/ intervention	In	Route of administration: oral, inhalation, *s.c.*, *i.p.*, *in ovo* Compounds: Levels measured in animal tissues (including by bioassays) of any of the 17 2,3,7,8-substituted PCDD/Fs and/or 12 DL-PCBs, administered individually or as mixtures OR Estimated exposure from feed (either reported or can be calculated) Number of doses: single or repeated exposure Dose groups: ≥ 1 dose groups + control group Field exposure studies in which the following target compounds have been analysed: – 17 PCDD/Fs and 12 DL-PCBs – 17 PCDD/Fs – 12 DL-PCBs – 17 PCDD/Fs plus non-*ortho* PCBs, at least one PCB being PCB-126 – TCDD (when dominates the TEQs) or any of the target congeners that dominates the TEQs
	Out	Studies on non dioxin-like (indicator) PCBs[(a)] Studies on mixtures with compounds other than the target PCDD/Fs and DL- PCBs (e.g. organochlorinated compounds, brominated flame retardants, etc).

Specific outcome of interest	In	Any outcome
	Out	Studies on enzyme induction only (e.g. EROD) Studies on gene expression only Studies on CYP modulation only
Language	In	English
Time	In	From 1950 onwards
Publication type	In	Peer reviewed primary research studies (i.e. studies generating new data) Systematic reviews, reviews and meta-analysis(b)
	Out	Expert opinions, editorials, letters to the editor PhD theses Extended abstracts, conference proceedings

CYP: cytochrome P450; DL-PCBs: dioxin-like polychlorinated biphenyls; *i.p.*: intraperitoneal; PCB: dioxin-like polychlorinated biphenyl; PCDD/Fs: polychlorinated dibenzo-*p*-dioxins/dibenzofurans; *s.c.*: subcutaneous; TCDD: 2,3,7,8- tetrachlorodibenzo-*p*-dioxin; TEQ: toxic equivalents.
(a): Indicator PCBs: PCB-28, -52, -101, -138, -153, and -180.
(b): Systematic reviews, reviews and meta-analysis will be included and used as background information. These types of publication will not go through the data extraction process.

Table 12. Eligibility criteria for the **structured approach H** (sub-question 18 and 19)

Sub-question 17 **– What is the ADME of PCDD/Fs and DL-PCBs in the different farm and companion animal species?** Sub-question 18 **– What is the transfer of PCDD/Fs and DL-PCBs from feed to products of animal origin?**		
Study design / Test system	In	*In vivo* studies in farm and companion animals
	Out	*In vivo* studies in experimental animals *In vivo* studies in humans *In vitro* studies in farm/companion animal culture cells/models
Exposure/ intervention	In	Any of the 17 2,3,7,8-substituted PCDD/Fs and/or 12 DL-PCBs, individually or as mixtures
	Out	Studies on non dioxin-like (indicator) PCBs[2] Studies on mixtures with compounds other than the target PCDD/Fs and DL-PCBs (e.g. organochlorinated compounds, brominated flame retardants, etc
Specific outcome of interest	In	Any outcome related to the ADME of the target compounds and their transfer from the feed to the products of animal origin
Language	In	English
Time	In	From 1950 onwards
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data) Systematic reviews, reviews and meta-analyses
	Out	Expert opinions, editorials, and letters to the editor PhD Theses Extended abstracts, conference proceedings

ADME: absorption, distribution, metabolism and excretion; DL-PCBs: dioxin-like polychlorinated biphenyls; PCB: dioxin-like polychlorinated biphenyl; PCDD/Fs: polychlorinated dibenzo-*p*-dioxins/dibenzofurans.

A.1.2.2.2. Literature searches

The ELSs will be performed searching the following bibliographic databases or scientific citation research platforms:

1. PubMed
2. Web of Science™, encompassing the following databases:
   - Web of Science™ Core Collection
   - BIOSIS Citation Index℠
   - CABI: CAB Abstracts®
   - Current Contents Connect®
   - Data Citation Index℠
   - FSTA® – the food science resource

[2] Indicator PCBs: PCB-28, -52, -101, -138, -153, and -180.

- MEDLINE®
- SciELO Citation Index
- Zoological Record®

For the structured approaches A and B, the ELS will be performed by an external contractor. The Working Group will agree on the draft preliminary keywords that will be provided to the external contractor (Table 13 for structured approach A and Table 14 for structured approach B) who will develop search strings. The final version of the search strings will, ultimately, be agreed by the Working Group.

Table 13. Databases and preliminary keywords for the ELS in **structured approach A** (sub-question 1 and 8, hazard identification and characterisation in humans)

Database	Web of Science™ PubMed
Preliminary Keywords	Dioxins, Tetrachlorodibenzodioxin, TCDD, Dioxin-like, TEQ, Coplanar, Polychlorinated biphenyls, PCBs **AND** Epidemiology, Cohort Studies, Case-Control Studies, adverse effects, Observational Study, Cross-Sectional Studies, case series/case reports

Table 14. Databases and preliminary keywords for the ELS in structured approach B (sub-questions 3 and 9, hazard identification and characterisation in experimental animal studies)

Database	Web of Science™ PubMed
Preliminary Keywords	Dioxins, Tetrachlorodibenzodioxin, Dioxin-like, TEQ, Coplanar, Polychlorinated biphenyls, PCBs **AND** Rats, Mice, Monkey, Guinea pigs, Mini pigs, Rabbits, Hamster, Dogs, Cats, Mink

For the **s**tructured approaches C (ADME in humans), D (ADME in experimental animals), G (HI/HC in farm and companion animals) and H (ADME and transfer in farm/companion animals), the ELS will be performed by the EFSA/Working Group. The preliminary keywords are reported in Table 15 for structured approach C, Table 16 for structured approach D, Table 17 for structured approach G and Table 18 for structured approach H.

Table 15. Preliminary search strings for **structured approach C** (sub-question 5, Toxicokinetics/ADME in humans)

Database	Web of Science™ PubMed
Preliminary keywords	Dioxins, Tetrachlorodibenzodioxin, Dioxin-like, TEQ, Coplanar, Polychlorinated biphenyls, PCBs **AND** Half-life, absorption, absorption rate, distribution, metabolism, excretion, elimination, bioconcentration, BCFs, PBPK, PBK, modelling, carry-over, transfer, placental transfer, human milk, **AND** Humans, child, infant

Table 16. Preliminary search strings for Structured approach D (sub-question 6, Toxicokinetics/ADME in experimental animals)

Database	Web of Science™ PubMed
Preliminary keywords	Dioxins, Tetrachlorodibenzodioxin, Dioxin-like, TEQ, Coplanar, Polychlorinated biphenyls, PCBs **AND** Half-life, absorption, absorption rate, distribution, metabolism, excretion, elimination, bioconcentration, BCFs, PBPK, PBK, modelling, carry-over, transfer, placental transfer **AND** Rats, mice, monkey guinea pigs, mini pigs, rabbits, hamster, dogs, cats, mink

Table 17. Preliminary search strings for **structured approach G** (sub-question 16 and 17, Hazard identification and characterisation in farm and companion animal studies)

Database	PubMed Web of Science™
Preliminary keywords	Dioxins, Tetrachlorodibenzodioxin, Dioxin-like, TEQ, Coplanar, Polychlorinated biphenyls, PCBs **AND** Ruminants, Cattle, cows, bovine, Sheep, goats, buffaloes, swine, pigs, poultry, chickens, turkeys, ducks, Quail, Goose, Rabbits, Fish, Trout, Salmon, Sea Bream, Sea Bass, sturgeon, Flatfish, Horses, Cats, Dogs, mink

Table 18. Preliminary search strings for **structured approach H** (sub-question 18 and 19, Toxicokinetics/ADME/transfer in farm and companion animals)

Database	Web of Science™ PubMed
Preliminary keywords	Dioxins, Tetrachlorodibenzodioxin, Dioxin-like, TEQ, Coplanar, Polychlorinated biphenyls, PCBs **AND** Half-life, absorption, absorption rate, distribution, metabolism, excretion, elimination, bioconcentration, BCFs, PBPK, PBK, modelling, carry-over, transfer, placental transfer, **AND** Ruminants, Cattle, cows, bovine, Sheep, goats, buffaloes, swine, pigs, poultry, chickens, turkeys, ducks, Quail, Goose, Rabbits, Fishes, Trout, Salmon, Sea Bream, Sea Bass, sturgeon, Flatfish, Zebrafish, Horses, Cats, Dogs, mink

The output from the searched databases, i.e. the bibliographic references including relevant information, e.g. title, authors, abstract, will be exported into separate Endnote X7 files, allowing a count of the individual hits per database. Files will then be combined and duplicate records will be removed.

The files obtained will be transferred into a web-based systematic review software, e.g. DistillerSR® (Evidence Partners, Ottawa, Canada), for the study selection procedure, see Section A.1.2.2.3.

A.1.2.2.3. Study selection process

The whole selection process will be performed in the same web-based systematic review software, e.g. with DistillerSR® (Evidence Partners, Ottawa, Canada). Studies to be included in the assessment will be selected by a two-step selection procedure applying the eligibility criteria described in Section A.1.2.2.1.:

1. **Screening of title and abstract** to identify potentially relevant studies that will be included for full text screening applying the eligibility criteria. If the information contained in the title or abstract is not relevant to the research objectives, the article is not selected for full text assessment. Articles that will be excluded during screening of title and abstract will be stored in DistillerSR®.

This step will be conducted in duplicate by an external contractor (for the **structured approach A** and **B**) or by the Working Group/EFSA (for the **structured approach C**, **D**, **G** and **H**).

For those cases where the relevance of the study is uncertain, a conservative approach will be taken and the article will proceed through the second step. In case of doubts or divergences between the two reviewers, the full article will be screened.

2. **Screening of full article** to assess whether the article is relevant to the risk assessment for the references that have passed the first step.

This step will be conducted in duplicate by an external contractor or by the Working Group/EFSA, depending on the structured approach. When conducted by the external contractor, interaction between the external contractor and the Working Group/EFSA will be ensured, e.g. in case possible divergences arise, and in case these would highlight the need for amendments to the inclusion/exclusion criteria.

Previous to the outsourcing to the external contractor, the eligibility criteria were pilot tested by the Working Group members on a subset of records, and were refined if prone to misinterpretation.

The results of the different phases of the study selection process will be reported in a flowchart as recommended in the PRISMA statement on preferred reporting items for systematic reviews and meta-analyses (Moher et al., 2009).

A.1.2.2.4. Data extraction from included studies

For the structured approaches C, D and H related to the toxicokinetics (ADME) of the target compounds in humans, experimental animals and farm/companion animals (including transfer), respectively, the eligible studies will be considered and described in a narrative way by the relevant domain experts from the Working Group.

For the structured approach A, B and G the studies that will be considered eligible for inclusion will undergo data extraction and pre-defined information on e.g. the study design, intervention/exposure, methodology and results will be retrieved to allow an appraisal of their reliability and a descriptive synthesis of their results.

Outlines of the data extraction forms for structured approach A (epidemiological studies, Table 19), structured approach B (experimental animal studies, Table 20) and structured approach G (farm and companion animal studies, Table 21) will be used for collecting the data from the included studies.

This process will be carried out either by the external contractor (for structured approach A and B) or by the Working Group/EFSA (for structured approach G) based on the outlines of the data extraction forms developed by the Working Group members. Previously, the data extraction forms will be pilot tested in a subset of studies by the Working Group members. The data extraction forms will be set up into a web-based systematic review software, e.g. DistillerSR® (Evidence Partners, Ottawa, Canada), and data extraction will be performed. Instructions for extracting data will be made available to data extractors. Interaction between the external contractor and EFSA/the Working Group will be ensured in case of missing data, and a decision will be taken by the Working Group on how to proceed for inclusion of the study or whether to exclude it.

Table 19. Outline of the data extraction form for structured approach A (human studies, sub-questions 1 and 8)

Study ID	Reference [(a)]:
	Trial/study name and acronym (if applicable):
	Total number of subjects:
Funding	Funding source(s):
Study design	Type: Cross-sectional studies, Cohort studies, Case control studies, Meta-analysis
	Type of blinding:
	Year the study was conducted (start):
	Duration/length of follow-up:
	Dates of sampling (when relevant):
	Dates of analysis of the target compounds in the samples:
Subjects	Number of participants in the present study: Participation rates (%): Number of subject with measured levels:
	Number of subjects per group: Follow-up rates by group (%):
	Sex (male/female):
	Geography (country, region, state, etc.):
	Race and ethnicity, socioeconomic background, other variables (e.g. age, BMI, parity) as reported:
	Age at exposure and outcome assessment (e.g. mean, median, measures of variance as presented in paper such as SD, SEM, 75th/90th/95th percentile, minimum/maximum):
	Inclusion and exclusion criteria:
Intervention/exposure	Compounds (e.g. PCDD/Fs and/or DL-PCBs): Exposure: - Measured levels in tissues (e.g. breast milk, blood, fat): Lipid adjusted: - Estimated dietary exposure:

	Method for assessing the dietary exposure: Validation of the method:
	Levels measured in human tissues:
	Dietary intake (pg WHO-TEQ/kg bw per day):
	TEF scheme (NATO, WHO_{1998}, WHO_{2005}, other, no TEF scheme applied):
Methods: health outcome assessment	End-point health category[(b)]:
	Parameters measured:
	Diagnostic or method to measure health outcome (including self-reporting):
	Were sub-groups analyses predefined (yes/no, if not, how was it justified?):
	Confounders (other exposures), modifying factors, or other potential sources of bias considered in the analysis, and how they were considered:
Results: Main findings as reported by the authors and statistically significant findings	Measures of effect and confidence interval at each exposure level as reported in the paper, and for each sub-group when applicable:
	Statistical test used:
	How were the variables treated (continuous or transformed or categorical):
	Shape of dose-response if reported by the authors (e.g. description of whether shape appears to be monotonic, non-monotonic, *p* value, according to the study authors):

ADME: absorption, distribution, metabolism and excretion; BMI: body mass index; DL-PCBs: dioxin-like polychlorinated biphenyls; PCB: dioxin-like polychlorinated biphenyl; PCDD/Fs: polychlorinated dibenzo-*p*-dioxins/dibenzofurans; SD: standard deviation; SEM: Standard error of the mean; TEF: toxicity equivalency factor; TEQ: toxic equivalents; WHO: World Health Organization.

(a): Relevant information on the particular study/trial not provided in the paper can be retrieved from the references provided therein.

(b): Reproductive effects (including organs), hepatotoxicity/gastrointestinal effects, immunotoxicity, cardiovascular effects, behavioural effects, neurotoxicity, carcinogenicity, metabolic effects (diabetes, thyroid function, obesity), effects on other hormone levels, teeth, musculoskeletical/bones, other (more than one option should be possible).

Table 20. Outline of the data extraction form for structured approach B (experimental animal studies, sub-question 3 and 9)

Study ID	Reference[(c)]:
	Year the study was conducted (start, if available):
Funding	Funding source(s):
Animal model	Species/(sub-)strain/line:
	Disease models (e.g. infection, diabetes, allergy, obesity, autoimmune disease):
Type of study and guideline	Type of study[(a)]:
	Guideline compliance[(b)]: GLP (yes/no): Non-GLP, but consistent with guideline study (yes/no):
Exposure	Compounds or mixture administered:
	Dose regimen (dose level or concentration of compounds or mixtures per group, and frequency):
	Duration of the exposure:
	Route of administration (diet, gavage, *i.p.*, *s.c.*):
	Compound purity (if available, specify impurities identified):
	Vehicle used:
Diet	Diet name and source:
	Control of background levels of contaminants in the diet (type and levels):
Study design	Sex and age of the initially exposed animals:
	Number of groups/ number of animals per group:
	Total doses applied during the study period (per kg bw)[(e)]:
	TEF scheme (NATO, WHO_{1998} , WHO_{2005}, other, no TEF scheme applied):
	Randomization procedures at start of the study:
	Reducing (culling) of litters and method:
	Number of pups per litter for next generation and methodology:
	Number of pups per litter/animals for certain measurements and methodology:
	Period (premating, gestation, lactation):
	End-point health category[(d)]:
	Parameters measured:
	Methods to measure outcome :
Statistical analysis	Statistical method used:

Results: Main findings as reported by the authors and statistically significant finding	Concentration of the test compound in vehicle (analysed, stated, unclear):
	Documentation of details for dose conversion when conducted:
	Level of test compound(s) in tissue or blood:
	Main findings per dose or concentration (e.g., mean, median, frequency, measures of precision or variance):
	NOEL, LOEL, BMD/BMDL, and statistical significance of other dose levels (author's interpretation):
	Shape of dose response if reported by the authors (e.g., description of whether shape appears to be monotonic, non-monotonic, NA for single exposure or treatment group studies)

BMD: benchmark dose; BMDL: benchmark dose lower confidence limit; bw: body weight; GLP: Good Laboratory Practice; *i.p.*: intraperitoneal; LOEL: lowest-observed-effect level; NA: not applicable; NOEL: no-observed-effect level; *s.c.*: subcutaneous; TEF: toxicity equivalency factor.

(a): e.g. acute, sub-acute (i.e. 4 weeks), subchronic (i.e. 13 weeks), chronic (i.e. 104 weeks), multigenerational, developmental, carcinogenicity.

(b): i.e. use of Environmental Protection Agency (EPA), Organisation for Economic Co-Operation (OECD), Food and Drug Administration (FDA) or other guideline for study design.

(c): Relevant information on the particular study/trial not provided in the paper can be retrieved from the references provided therein.

(d): Reproductive effects (including organs), hepatotoxicity/gastrointestinal effects, immunotoxicity, cardiovascular effects, behavioural effects, neurotoxicity, carcinogenicity, metabolic effects (diabetes, thyroid function, obesity), effects on other hormone levels, teeth, musculoskeletical/bones, others (more than one option should be possible).

(e): Total dose applied during the study period, estimated using default values (EFSA Scientific Committee, 2012a) if feed consumption not provided.

Table 21. Outline of the data extraction form for structured approach G (farm and companion animal studies, sub-questions 16 and 17)

Study ID	Reference:
	Year the study was conducted (start, if available):
Funding	Funding source(s):
Animal model	Species:
	Strain/breed:
	Disease models (e.g. infection, diabetes, allergy, obesity, autoimmune disease):
Type of study and guidelines	Type of study[(a)]
	Guideline compliance[(b)]: GLP (yes/no): Non-GLP but consistent with guideline study (yes/no):
Exposure	Compounds or mixture administered/exposed to:
	Source in case of contamination incident:
	Dose regime (dose level or concentration of compounds or mixtures per group, and frequency):
	Duration of exposure:
	Route of administration (diet, gavage, *i.p.*, *s.c.*, *in ovo*):
	Compound purity (if available, specify impurities identified):
	Vehicle used:
Diet	Diet name and source:
	Control of background levels of contaminants in the diet (type and levels):
Study design	Sex and age of the initially exposed animals:
	Number of groups / number of animals per group:
	TEF scheme (NATO, WHO_{1998} or WHO_{2005}):
	Randomization procedures at start of study:
	Period (premating, mating, gestation, lactation):
	Frequency of exposure (e.g. daily, 5 days per week, 7 days per week):
	End-point health category[(c)]:
	Parameters measured:
	Method to measure outcome:
	Quality assurance system:
Statistical analysis	Statistical methods used:
Results: Main findings as reported by the authors and statistically significant findings	Concentration of the test compound in vehicle:
	Documentation of details for dose conversion when conducted:
	Levels of test compound(s) in tissue or blood:
	Main findings per dose or concentration (e.g., mean, median, frequency, measures of precision or variance):

	Feed intake:
	NOEL, LOEL, BMD/BMDL, and statistical significance of other dose levels (author's interpretation):
	Shape of dose response, if reported by the authors (e.g., description of whether shape appears to be monotonic, non-monotonic, NA for single exposure or treatment group studies):

BMD: benchmark dose; BMDL: benchmark dose lower confidence limit; bw: body weight; GLP: Good Laboratory Practice; *i.p.*: intraperitoneal; LOEL: lowest-observed-effect level; NA: not applicable; NOEL: no-observed-effect level; *s.c.*: subcutaneous; TEF: toxicity equivalency factor.

(a): Acute, sub-acute (i.e. up to 4 weeks), subchronic (i.e. up to 13 weeks), chronic (i.e. up to 104 weeks), multigenerational, developmental, *in ovo.*

(b): i.e. use of EPA, OECD, NTP, EFSA or other guideline for study design.

(c): Reproductive effects (including organs), hepatotoxicity/gastrointestinal effects, immunotoxicity, cardiovascular effects, behavioural effects, carcinogenicity, metabolic effects (diabetes, thyroid function, obesity), effects on other hormone levels, others.

A.1.2.2.5. Assessment of reliability of included studies

The studies retrieved to inform the human risk assessment (structured approach A, human studies, and structured approach B, experimental animal studies), and the farm and companion animal risk assessment (structured approach G) will be appraised for reliability.

The studies retrieved and data extracted by each structured approach will be sorted as follows:

- The human studies (structured approach A, addressing sub-questions 1 and 8) will be sorted by: (i) endpoint, (ii) target compound(s) analysed and (iii) study design.

- The experimental animal studies (structured approach B, addressing sub-questions 3 and 9) will be sorted by: (i) animal species, (ii) endpoint, (iii) target compound(s) applied and (iii) study duration (e.g. acute, subchronic, chronic, multigenerational, developmental, carcinogenicity).

  Once sorted, the studies performed in animal models (e.g. diabetic models, animals on high/low fat diets, lean/obese animals, TCDD-sensitive and -resistant animals) will be identified and it will be decided whether they are informative to address the corresponding sub-questions. If they are, they will be appraised as described below, otherwise they will be excluded from the process.

- The farm and companion animal studies (structured approach G, addressing sub-questions 16 and 17) will be sorted as the experimental animal studies above.

The reliability of the individual studies will be appraised by considering the internal validity or risk of bias, defined as 'the extent to which the design and conduct of a study are likely to have prevented bias', i.e. non-random error (Higgins and Green, 2011).

The elements that will be considered for appraising the reliability of each individual study are illustrated in the critical appraisal tools (CATs) reported below for human, experimental animal and farm/companion animal studies, respectively. These tools have been developed by tailoring the current OHAT Risk of Bias Tool as included in the NTP-OHAT Approach for Systematic Review (Rooney et al., 2014). Specific forms will be implemented in the web-based systematic review software (e.g. DistillerSR®) by the external contractor to allow the study appraisal by the Working Group.

The appraisal of the studies will be done independently by two reviewers (experts from the Working Group) and possible discrepancies will be discussed by the whole Working Group.

For each element considered in the appraisal, expert judgement will be translated into the rating scale shown in Table 22.

Table 22. Proposed rating scale for appraising the studies

Rating	Internal validity	Explanation
+ +	Definitively low risk of bias	There is direct evidence of low risk-of-bias practices
+	Probably low risk of bias	There is indirect evidence of low risk-of-bias practices OR it is deemed that deviations from low risk-of-bias practices for these criteria during the study would not appreciably bias results, including consideration of direction and magnitude of bias
-/NR	Probably high risk of bias/Not reported	There is indirect evidence of high risk-of-bias practices OR there is insufficient information (e.g., not reported or 'NR') provided about relevant risk-of-bias practices
- -	Definitively high risk of bias	There is direct evidence of high risk-of-bias practices
NA	Not applicable	/

A.1.2.2.6. Study allocation to different tiers of reliability

Once the individual studies have been appraised for internal validity, they will be assigned to tiers of reliability, with an explanation for their allocation. This will then be considered for the analysis (see Section A.1.2.3. above).

For the purpose of creating a classification of the reliability of the evidence, the Working Group identified 3 key questions among the elements that need to be considered for the appraisal of internal validity of the studies (see Tables 23, 24, 25 and 26).

Human studies

The 3 key questions for the appraisal of human studies are the following:

- **Key question A**: Did the study design or analysis account for important confounding and modifying variables?
- **Key question B**: Can we be confident in the exposure characterisation?
- **Key question C**: Can we be confident in the outcome assessment?

Each study will be assigned to Tier-1 or Tier-2 or Tier-3 of reliability using the method described below:

- A human study is classified in Tier-1 if: it is rated as 'definitely low' or 'probably low' for the three key questions A-B-C **AND** it has at least half of the other three applicable questions answered 'definitely low' or 'probably low' risk of bias (see Table 23);

- A study is classified in Tier-3 if: it is rated as 'definitely high' or 'probably high' for the three key questions A-B-C **AND** it has at least half of the other three applicable questions answered 'definitely high' or 'probably high' risk of bias (see Table 23),

- A study is classified in the Tier-2 if it falls neither in Tier-1 nor Tier-3.

Experimental animal studies

The 3 key questions for the appraisal of experimental animal studies are the following:

- **Key question A:** Was allocation to study groups adequately randomised (including selection of groups during the study)?
- **Key question B**: Can we be confident in the exposure characterisation?
- **Key question C:** Can we be confident in the outcome Assessment? Are we confident that valid, reliable and sensitive methods to assess the outcome have been consistently applied across groups?

Each study will be assigned to Tier-1 or Tier-2 or Tier-3 of reliability using the method described below:

- A study is classified in the Tier-1 if: it is rated as 'definitely low' or 'probably low' for the three key questions A-B-C **AND** it has at least half of the other six applicable questions answered 'definitely low' or 'probably low' risk of bias (see Table 24);

- A study is classified in the Tier-3 if: it is rated as 'definitely high' or 'probably high' for the three key questions A-B-C **AND** it has at least half of the other six applicable questions answered 'definitely high' or 'probably high' risk of bias (see Table 24),

- A study is classified in Tier-2 if it falls neither in Tier-1 nor Tier-3.

Farm and companion animal studies

The key questions for the appraisal of farm and companion animal studies are the following based on the study type:

For studies following an experimental design with controlled exposure:

- **Key question A:** Was allocation to study groups adequately randomised (including selection of groups during the study)?
- **Key question B**: Can we be confident in the exposure characterisation?
- **Key question C:** Can we be confident in the outcome Assessment? Are we confident that valid, reliable and sensitive methods to assess the outcome have been consistently applied across groups?

For field exposure studies:

- **Key question D**: Did the study design or analysis account for important confounding and modifying variables?
- **Key question E**: Can we be confident in the exposure characterisation?
- **Key question F**: Can we be confident in the outcome assessment?

Each study will be assigned to Tier-1 or Tier-2 or Tier-3 of reliability using the method described below:

- A farm or companion animal study is classified in the Tier-1 if: it is rated as 'definitely low' or 'probably low' for the three key questions A-B-C or D-E-F depending on the study design (see **Tables 25** and **26**, respectively);

- A study is classified in the Tier-3 if: it is rated as 'definitely high' or 'probably high' for the three key questions A-B-C or D-E-F depending on the study design (see **Tables 25** and **26, respectively**);

- A study is classified in Tier-2 if it falls neither in Tier-1 nor Tier-3.

A.1.2.2.7. Summary of the results from individual studies

The results of the studies for the human hazard identification sub-questions (structured approach A and B) and the farm and companion animal hazard identification sub-question (structured approach G) will be presented in a tabulated format considering the following characteristics as a minimum set. The Working Group may identify additional aspects at a later stage:

- Lines of evidence (i.e. human studies, experimental animal studies, or farm/companion animal studies),
- Type of study (e.g. cohort, cross-sectional, case-control or acute, subchronic, chronic, multigenerational, developmental, carcinogenicity, other, or field exposure)
- Species
- Compound(s) analysed
- Doses (or dietary exposure)

- Direct exposure or indirect via the dams
- Levels in tissues
- End-point(s), e.g. developmental effects, reproductive organs/effects, hepatotoxicity/gastrointestinal effects, immunotoxicity, cardiovascular effects, behavioural effects, carcinogenicity, metabolic effects (diabetes, thyroid function, obesity), effects on other hormone levels[3].
- Internal validity or risk of bias (see Sections A.1.2.2.5 and A.1.2.2.6)

[3] Hormones of the oestrogen, androgen, thyroid, or steroidogenesis (EATS) modalities.

Table 23. Appraisal tool for human observational studies (adapted from NTP Risk of Bias tool)

Q	Target organ: Endpoint: Intervention/Exposure:	Rating	Explanation for expert judgement
1	**Selection bias:** Did selection of study participants result in appropriate comparison groups?	++	There is direct evidence that subjects (both exposed and non-exposed) were similar (e.g. recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates. *For case-control studies*: There is direct evidence that cases and controls were similar (e.g. recruited from the same eligible population including being of similar age, gender, ethnicity, and eligibility criteria other than outcome of interest as appropriate), recruited within the same time frame, and controls are described as having no history of the outcome. *Note: A study will be considered low risk of bias if baseline characteristics of groups differed but these differences were considered as potential confounding or stratification variables.*
		+	There is indirect evidence that subjects (both exposed and non-exposed) were similar (e.g., recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates **OR** differences between groups would not appreciably bias results. For case-control studies: There is indirect evidence that cases and controls were similar (e.g., recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age), recruited within the same time frame, and controls are described as having no history of the outcome **OR** differences between cases and controls would not appreciably bias results.
		-	There is indirect evidence that subjects (both exposed and non-exposed) were not similar, recruited within very different time frames, or had the very different participation/response rates **OR** there is insufficient information provided about the comparison group including a different rate of non-response without an explanation. *For case-control studies*: There is direct evidence that controls were drawn from a very dissimilar population than cases or recruited within very different time frames **OR** there is insufficient information provided about the appropriateness of controls including rate of response reported for cases only.
		--	There is direct evidence that subjects (both exposed and non-exposed) were not similar, recruited within very different time frames, or had very different participation/response rates. *For case-control studies*: There is direct evidence that controls were drawn from a very dissimilar population than cases or recruited within very different time frames.
		NA	Not applicable

Q	Target organ: Endpoint: Intervention/Exposure:	Rating	Explanation for expert judgement
2	**Confounding bias:** Did the study design or analysis account for important confounding and modifying variables? **KEY QUESTION A**	++	There is direct evidence that appropriate adjustments or explicit considerations were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research-specific bias including standardization, matching, adjustment in multivariate model, stratification, propensity scoring, or other methods that were appropriately justified. Acceptable consideration of appropriate adjustment factors includes cases when the factor is not included in the final adjustment model because the author conducted analyses that indicated it did not need to be included, **AND** there is direct evidence that primary covariates and confounders were assessed using valid and reliable measurements, **AND** there is direct evidence that other exposures anticipated to bias results were not present or were appropriately measured and adjusted for. In occupational studies or studies of contaminated sites, other chemical exposures known to be associated with those settings were appropriately considered. *For case-control studies*: There is direct evidence that appropriate adjustments were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research specific bias including standardization, matching of cases and controls, adjustment in multivariate model, stratification, propensity scoring, or other methods were appropriately justified, AND there is direct evidence that primary covariates and confounders were assessed using valid and reliable measurements, AND there is direct evidence that other exposures anticipated to bias results were not present or were appropriately measured and adjusted for.
		+	There is indirect evidence that appropriate adjustments were made, OR it is deemed that not considering or only considering a partial list of covariates or confounders in the final analyses would not appreciably bias results. AND there is evidence (direct or indirect) that primary covariates and confounders were assessed using valid and reliable measurements, OR it is deemed that the measures used would not appreciably bias results (i.e., the authors justified the validity of the measures from previously published research), AND there is evidence (direct or indirect) that other co-exposures anticipated to bias results were not present or were appropriately adjusted for, OR it is deemed that co-exposures present would not appreciably bias results. *Note: As discussed above, this includes insufficient information provided on co-exposures in general population studies.*
		-	There is indirect evidence that the distribution of primary covariates and known confounders differed between the groups and was not appropriately adjusted for in the final analyses, OR there is insufficient information provided about the distribution of known confounders (record 'NR' as basis for answer), OR there is indirect evidence that primary covariates and confounders were assessed using measurements of unknown validity, OR there is insufficient information provided about the measurement techniques used to assess primary covariates and confounders (record 'NR' as basis for answer), OR there is indirect evidence that there was an unbalanced provision of additional co-exposures across the primary study groups, which were not appropriately adjusted for, OR there is insufficient information provided about co-exposures in occupational studies or studies of contaminated sites where high exposures to other chemical exposures would have been reasonably anticipated (record 'NR' as basis for answer). *For case-control studies*: There is indirect evidence that the distribution of primary covariates and known confounders differed between cases and controls and was not investigated further, OR there is insufficient information provided about the distribution of known confounders in cases and controls (record 'NR' as basis for answer), OR there is indirect evidence that

Q	Target organ: Endpoint: Intervention/Exposure:	Rating	Explanation for expert judgement
			primary covariates and confounders were assessed using measurements of unknown validity, OR there is insufficient information provided about the measurement techniques used (record 'NR' as basis for answer), OR there is indirect evidence that there was an unbalanced provision of additional co-exposures across cases and controls, which were not appropriately adjusted for, OR there is insufficient information provided about co-exposures in occupational studies or studies of contaminated sites where high exposures to other chemical exposures would have been reasonably anticipated (record 'NR' as basis for answer).
		--	There is direct evidence that the distribution of primary covariates and known confounders differed between the groups, confounding was demonstrated, and was not appropriately adjusted for in the final analyses, OR there is direct evidence that primary covariates and confounders were assessed using non valid measurements, OR there is direct evidence that there was an unbalanced provision of additional co-exposures across the primary study groups, which were not appropriately adjusted for. *For case-control studies*: There is direct evidence that the distribution of primary covariates and known confounders differed between cases and controls, confounding was demonstrated, but was not appropriately adjusted for in the final analyses, OR there is direct evidence that primary covariates and confounders were assessed using non valid measurements, OR there is direct evidence that there was an unbalanced provision of additional co-exposures across cases and controls, which were not appropriately adjusted for.
		NA	Not applicable
3	**Attrition/exclusion bias:** Were outcome data completely reported without attrition or exclusion from analysis?	++	There is direct evidence that loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study. Acceptable handling of subject attrition includes: very little missing outcome data; reasons for missing subjects unlikely to be related to outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across study groups, with similar reasons for missing data across groups, OR missing data have been imputed using appropriate methods and characteristics of subjects lost to follow up or with unavailable records are described in identical way and are not significantly different from those of the study participants. *For case-control and cross sectional studies*: There is direct evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
		+	There is indirect evidence that loss of subjects (i.e. incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study **OR** it is deemed that the proportion lost to follow-up would not appreciably bias results. This would include reports of no statistical differences in characteristics of subjects lost to follow up or with unavailable records from those of the study participants. Generally, the higher the ratio of participants with missing data to participants with events, the greater potential there is for bias. For studies with a long duration of follow-up, some withdrawals for such reasons are inevitable. *For case-control and cross sectional studies*: There is indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from

Q	Target organ: Endpoint: Intervention/Exposure:	Rating	Explanation for expert judgement
			analyses.
		-	There is indirect evidence that loss of subjects (i.e. incomplete outcome data) was unacceptably large and not adequately addressed **OR** there is insufficient information provided about numbers of subjects lost to follow-up. *For case-control and cross sectional studies*: There is indirect evidence that exclusion of subjects from analyses was not adequately addressed, **OR** there is insufficient information provided about why subjects were removed from the study or excluded from analyses.
		--	There is direct evidence that loss of subjects (i.e. incomplete outcome data) was unacceptably large and not adequately addressed. Unacceptable handling of subject attrition includes: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across study groups; or potentially inappropriate application of imputation. *For case-control and cross sectional studies*: There is direct evidence that exclusion of subjects from analyses was not adequately addressed. Unacceptable handling of subject exclusion from analyses includes: reason for exclusion likely to be related to true outcome, with either imbalance in numbers or reasons for exclusion across study groups.
		NA	Not applicable
4	**Detection bias:** Can we be confident in the exposure characterisation? **KEY QUESTION B**	++	There is direct evidence that exposure was consistently assessed (i.e. under the same method and time-frame) using well-established methods that directly measure exposure (e.g., measurement of the chemical in air or measurement of the chemical in blood, plasma, urine, etc.), OR exposure was assessed using less-established methods that directly measure exposure and are validated against well-established methods.
		+	There is indirect evidence that the exposure was consistently assessed using well-established methods that directly measure exposure, OR exposure was assessed using indirect measures (e.g., questionnaire or occupational exposure assessment by a certified industrial hygienist) that have been validated or empirically shown to be consistent with methods that directly measure exposure (i.e., inter-methods validation: one method vs. another) .
		-	There is indirect evidence that the exposure was assessed using poorly validated methods that directly measure exposure, OR there is direct evidence that the exposure was assessed using indirect measures that have not been validated or empirically shown to be consistent with methods that directly measure exposure (e.g., a job-exposure matrix or self-report without validation) (record 'NR' as basis for answer), OR there is insufficient information provided about the exposure assessment, including validity and reliability, but no evidence for concern about the method used (record 'NR' as basis for answer).
		--	There is direct evidence that the exposure was assessed using methods with poor validity, OR evidence of exposure misclassification (e.g., differential recall of self-reported exposure).
		NA	Not applicable

Q	Target organ: Endpoint: Intervention/Exposure:	Rating	Explanation for expert judgement
5	**Detection bias:** Can we be confident in the outcome assessment? **KEY QUESTION C**	++	*For cohort studies*: There is direct evidence that the outcome was assessed using well-established methods (e.g. the 'gold standard'), AND subjects had been followed for the same length of time in all study groups. Acceptable assessment methods will depend on the outcome, but examples of such methods may include: objectively measured with diagnostic methods, measured by trained interviewers, obtained from registries. *For case-control studies*: There is direct evidence that the outcome was assessed in cases (i.e., case definition) and controls using well-established methods (the gold standard), AND subjects had been followed for the same length of time in all study groups, AND there is direct evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the exposure level when outcome was assessed in cases (i.e., case definition) and controls. *For cross-sectional studies*: There is direct evidence that the outcome was assessed using well-established methods (the gold standard), AND there is direct evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the exposure level, and it is unlikely that they could have broken the blinding prior to reporting outcomes.
		+	*For cohort studies*: There is indirect evidence that the outcome was assessed using acceptable methods (i.e. deemed valid and reliable but not the gold standard) AND subjects had been followed for the same length of time in all study groups [Acceptable, but not ideal assessment methods will depend on the outcome, but examples of such methods may include proxy reporting of outcomes and mining of data collected for other purposes], OR it is deemed that the outcome assessment methods used would not appreciably bias results, AND there is indirect evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes, OR it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, which is more likely to apply to objective outcome measures. *For case-control studies*:. There is indirect evidence that the outcome was assessed in cases (i.e., case definition) and controls using acceptable methods, AND subjects had been followed for the same length of time in all study groups, OR it is deemed that the outcome assessment methods used would not appreciably bias results, AND there is direct evidence that the outcome assessors were adequately blinded to the exposure level when reporting outcomes, OR it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (including that subjects self-reporting outcomes were likely not aware of reported links between the exposure and outcome or lack of blinding is unlikely to bias a particular outcome). *For cross-sectional studies*: There is indirect evidence that the outcome was assessed using acceptable methods, OR it is deemed that the outcome assessment methods used would not appreciably bias results, AND there is indirect evidence that the outcome assessors were adequately blinded to the exposure level, and it is unlikely that they could have broken the blinding prior to reporting outcomes, OR it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (including that subjects self-reporting outcomes were likely not aware of reported links between the exposure and outcome lack of blinding is unlikely to bias a particular outcome).

Q	Target organ: Endpoint: Intervention/Exposure:	Rating	Explanation for expert judgement
		-	*For cohort studies*: There is indirect evidence that the outcome assessment method is an insensitive instrument (e.g., a questionnaire used to assess outcomes with no information on validation), OR the length of follow up differed by study group, OR there is indirect evidence that it was possible for outcome assessors (including study subjects if outcomes were self-reported) to infer the study group prior to reporting outcomes, OR there is insufficient information provided about blinding of outcome assessors (record 'NR' as basis for answer). *For case-control studies*:. There is indirect evidence that the outcome was assessed in cases (i.e., case definition) using an insensitive instrument, OR there is insufficient information provided about how cases were identified (record 'NR' as basis for answer), OR there is indirect evidence that it was possible for outcome assessors to infer the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were likely aware of reported links between the exposure and outcome), OR there is insufficient information provided about blinding of outcome assessors (record 'NR' as basis for answer). *For cross-sectional studies*: There is indirect evidence that the outcome assessment method is an insensitive instrument, OR there is indirect evidence that it was possible for outcome assessors to infer the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were likely aware of reported links between the exposure and outcome), OR there is insufficient information provided about blinding of outcome assessors (record 'NR' as basis for answer).
		--	*For cohort studies*: There is direct evidence that the outcome assessment method is an insensitive instrument, OR the length of follow up differed by study group, OR there is direct evidence for lack of adequate blinding of outcome assessors (including study subjects if outcomes were self-reported), including no blinding or incomplete blinding. *For case-control studies*: There is direct evidence that the outcome was assessed in cases (i.e., case definition) using an insensitive instrument, OR there is direct evidence that outcome assessors were aware of the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were aware of reported links between the exposure and outcome). *For cross-sectional studies*: There is direct evidence that the outcome assessment method is an insensitive instrument, OR there is direct evidence that outcome assessors were aware of the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were aware of reported links between the exposure and outcome).
		NA	Not applicable
6	**Selective reporting:** Were all measured outcomes reported?	++	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported. This would include outcomes reported with sufficient detail to be included in meta-analysis or fully tabulated during data extraction and analyses had been planned in advance.

Q	Target organ: Endpoint: Intervention/Exposure:	Rating	Explanation for expert judgement
		+	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported **OR** analyses that had not been planned in advance (i.e. retrospective unplanned subgroup analyses) are clearly indicated as such and it is deemed that the unplanned analyses were appropriate and selective reporting would not appreciably bias results (e.g. appropriate analyses of an unexpected effect). This would include outcomes reported with insufficient detail such as only reporting that results were statistically significant (or not).
		-	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported **OR** there is indirect evidence that unplanned analyses were included that may appreciably bias results. OR there is insufficient information provided about selective outcome reporting (record 'NR' as basis for answer).
		--	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the methods, abstract, and/or introduction (that are relevant for the evaluation) have not been reported. In addition to not reporting outcomes, this would include reporting outcomes based on composite score without individual outcome components or outcomes reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified or reporting outcomes not pre-specified, or that unplanned analyses were included that would appreciably bias results.
		NA	Not applicable

++: definitely low risk of bias, +: probably low risk of bias, -: probably high risk of bias, --: definitely high risk of bias.

Table 24. Appraisal tool for experimental animal studies (adapted from NTP Risk of Bias tool)

Question	Target organ: Endpoint: Intervention/Exposure:	Rating	Explanation for expert judgement
1	**Selection bias:** Was administered dose or exposure level adequately randomised? (including selection of groups during the study)? **KEY QUESTION A**	++	There is direct evidence that animals were allocated to any study group including controls using a method with a random component, **AND** there is direct evidence that the study used a concurrent control group as an indication that randomization covered all study groups. **Note**: Acceptable methods of randomization include: referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, or drawing of lots (Higgins and Green 2011). Restricted randomization (e.g., blocked randomization) to ensure particular allocation ratios will be considered low risk of bias. Similarly, stratified randomization and minimization approaches that attempt to minimize imbalance between groups on important prognostic factors (e.g., body weight) will be considered acceptable. This type of approach is used by NTP, i.e., random number generator with body weight as a covariate. **Note**: Investigator-selection of animals from a cage is not considered random allocation because animals may not have an equal chance of being selected, e.g., investigator selecting animals with this method may inadvertently choose healthier, easier to catch, or less aggressive animals.
		+	There is indirect evidence that animals were allocated to any study group including controls using a method with a random component (i.e., authors state that allocation was random, without description of the method used), **AND** there is direct or indirect evidence that the study used a concurrent control group as an indication that randomization covered all study groups, **OR** it is deemed that allocation without a clearly random component during the study would not appreciably bias results. For example, approaches such as biased coin or urn randomization, replacement randomization, mixed randomization, and maximal randomization may require consultation with a statistician to determine risk-of-bias rating (Higgins and Green, 2011).
		-	There is indirect evidence that animals were allocated to study groups using a method with a non-random component, **OR** there is indirect evidence that there was a lack of a concurrent control group, **OR** there is insufficient information provided about how subjects were allocated to study groups (record 'NR' as basis for answer). **Note**: Non-random allocation methods may be systematic, but have the potential to allow researchers to anticipate the allocation of animals to study groups (Higgins and Green 2011). Such 'quasi-random' methods include investigator-selection of animals from a cage, alternation, assignment based on shipment receipt date, date of birth, or animal number.
		--	There is direct evidence that animals were allocated to study groups using a non-random method including judgment of the investigator, the results of a laboratory test or a series of tests (Higgins and Green 2011), **OR** there is direct evidence that there was a lack of a concurrent control group, indicating that randomization did not cover all study groups.
		NA	Not applicable
2	**Confounding bias:**	++	There is direct evidence that appropriate adjustments or explicit considerations were made for primary covariates and confounders (e.g. unintended chemical co-exposures)in the final analyses.
		+	There is indirect evidence that appropriate adjustments or explicit considerations were made for primary covariates and

Question	Target organ: Endpoint: Intervention/Exposure:	Rating	Explanation for expert judgement
	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?		confounders (e.g. unintended chemical co-exposures) in the final analyses, **OR** it is deemed that confounding would not appreciably bias results.
		-	There is indirect evidence that no appropriate adjustments or explicit considerations were made for primary covariates and confounders (e.g. unintended chemical co-exposures)in the final analyses, **OR** there is insufficient information provided about confounding.
		--	There is direct evidence that no appropriate adjustments or explicit considerations were made for primary covariates and confounders (e.g. unintended chemical co-exposures) in the final analyses.
		NA	Not applicable
3	**Performance bias:** Were experimental conditions identical across study groups?	++	There is direct evidence that same vehicle was used in control and experimental animals, **AND** there is direct evidence that non-treatment-related experimental conditions were identical across study groups (i.e., the study report explicitly provides this level of detail).
		+	There is indirect evidence that the same vehicle was used in control and experimental animals, **OR** it is deemed that the vehicle used would not appreciably bias results, **AND** as described above, identical non-treatment-related experimental conditions are assumed if authors did not report differences in housing or husbandry.
		-	There is indirect evidence that the vehicle differed between control and experimental animals, **OR** authors did not report the vehicle used (record 'NR' as basis for answer), OR there is indirect evidence that non-treatment-related experimental conditions were not comparable between study groups.
		--	There is direct evidence from the study report that control animals were untreated, or treated with a different vehicle than experimental animals, **OR** there is direct evidence that non-treatment-related experimental conditions were not comparable between study groups.
		NA	Not applicable
4	**Performance bias:** Were the outcome assessors blinded to study group or exposure level?	++	There is direct evidence that the research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study. Methods used to ensure blinding include central allocation; sequentially numbered treatment containers of identical appearance; sequentially numbered animal cages; or equivalent methods.
		+	There is indirect evidence that the research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study, **OR** it is deemed that lack of adequate blinding during the study would not appreciably bias results. This would include cases where blinding was not possible but research personnel took steps to minimize potential bias, such as restricting the knowledge of study group to veterinary or supervisory personnel monitoring for overt toxicity, or randomized husbandry or handling practices (e.g., placement in the animal room, necropsy order, etc.).
		-	There is indirect evidence that the research personnel were not adequately blinded to study group, **OR** there is insufficient information provided about blinding to study group during the study (record 'NR' as basis for answer).
		--	There is direct evidence that the research personnel were not adequately blinded to study group.
		NA	Not applicable

Question	Target organ: Endpoint: Intervention/Exposure:	Rating	Explanation for expert judgement
5	**Attrition/exclusion bias:** Were outcome data completely reported without attrition or exclusion from analysis?	++	There is direct evidence that loss of animals was adequately addressed and reasons were documented when animals were removed from a study. Acceptable handling of attrition includes: very little missing outcome data; reasons for missing animals unlikely to be related to outcome (or for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across study groups, with similar reasons for missing data across groups; missing outcomes is not enough to impact the effect estimate, OR missing data have been imputed using appropriate methods (ensuring that characteristics of animals are not significantly different from animals retained in the analysis).
		+	There is indirect evidence that loss of animals was adequately addressed and reasons were documented when animals were removed from a study, OR it is deemed that the proportion lost would not appreciably bias results. This would include reports of no statistical differences in characteristics of animals removed from the study from those remaining in the study.
		-	There is indirect evidence that loss of animals was unacceptably large and not adequately addressed, OR there is insufficient information provided about loss of animals (record 'NR' as basis for answer).
		--	There is direct evidence that loss of animals was unacceptably large and not adequately addressed. Unacceptable handling of attrition or exclusion includes: reason for loss is likely to be related to true outcome, with either imbalance in numbers or reasons for loss across study groups.
		NA	Not applicable
6	**Detection bias:** Can we be confident in the exposure characterisation? **KEY QUESTION B**	++	There is direct evidence that the exposure (including purity and stability of the test substance and compliance with the treatment, if applicable) was independently characterized and purity confirmed generally as ≥99% for single substance or non-mixture evaluations.
		+	There is indirect evidence that the exposure (including purity and stability of the test substance and compliance with the treatment, if applicable) was independently characterized and purity confirmed generally as ≥99% (i.e., the supplier of the chemical provides documentation of the purity of the chemical), **OR** direct evidence that purity was independently confirmed as ≥98% it is deemed that impurities of up to 2% would not appreciably bias results, **AND** there is indirect evidence that exposure was consistently administered (i.e., with the same method and time-frame) across treatment groups.
		-	There is indirect evidence that the exposure (including purity and stability of the test substance and compliance with the treatment, if applicable) was assessed using poorly validated methods, **OR** there is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern (record 'NR' as basis for answer).
		--	There is direct evidence that the exposure (including purity and stability of the test substance and compliance with the treatment, if applicable) was assessed using poorly validated methods.
		NA	Not applicable
7	**Detection bias:** Can we be confident in the outcome Assessment?	++	There is direct evidence that the outcome was assessed using well-established methods (the gold standard), **AND** assessed at the same length of time after initial exposure in all study groups, **AND** there is direct evidence that the outcome assessors were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes.
		+	There is indirect evidence that the outcome was assessed using acceptable methods (i.e., deemed valid and reliable but not the gold standard), **AND** assessed at the same length of time after initial exposure in all study groups, **OR** it is deemed that the outcome assessment methods used would not appreciably bias results, **AND** there is indirect evidence that the outcome

Question	Target organ: Endpoint: Intervention/Exposure:	Rating	Explanation for expert judgement
	(Are we confident that valid, reliable and sensitive methods to assess the outcome have been consistently applied across groups?) **KEY QUESTION C**		assessors were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes, **OR** it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, which is more likely to apply to objective outcome measures. For some outcomes, particularly histopathology assessment, outcome assessors are not blind to study group as they require comparison to the control to appropriately judge the outcome, but additional measures such as multiple levels of independent review by trained pathologists can minimize this potential bias.
		-	There is indirect evidence that the outcome assessment method is an insensitive instrument, **OR** the length of time after initial exposure differed by study group, **OR** there is indirect evidence that it was possible for outcome assessors to infer the study group prior to reporting outcomes without sufficient quality control measures, **OR** there is insufficient information provided about blinding of outcome assessors (record 'NR' as basis for answer).
		--	There is direct evidence that the outcome assessment method is an insensitive instrument, **OR** the length of time after initial exposure differed by study group, **OR** there is direct evidence for lack of adequate blinding of outcome assessors, including no blinding or incomplete blinding without quality control measures.
		NA	Not applicable
8	**Selective reporting bias:** Were all measured outcomes reported?	++	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported. This would include outcomes reported with sufficient detail to be included in meta-analysis or fully tabulated during data extraction and analyses had been planned in advance.
		+	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported, OR analyses that had not been planned in advance (i.e., retrospective unplanned subgroup analyses) are clearly indicated as such and it is deemed that the unplanned analyses were appropriate and selective reporting would not appreciably bias results (e.g., appropriate analyses of an unexpected effect). This would include outcomes reported with insufficient detail such as only reporting that results were statistically significant (or not).
		-	There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported, OR and there is indirect evidence that unplanned analyses were included that may appreciably bias results, OR there is insufficient information provided about selective outcome reporting (record 'NR' as basis for answer).
		--	There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have not been reported. In addition to not reporting outcomes, this would include reporting outcomes based on composite score without individual outcome components or outcomes reported using measurements, analysis methods or subsets of the data (e.g., subscales) that were not pre-specified or reporting outcomes not pre-specified, or that unplanned analyses were included that would appreciably bias results.
		NA	Not applicable
9	**Other bias:**	++	There is direct evidence that statistical methods were appropriate.

Question	Target organ: Endpoint: Intervention/Exposure:	Rating	Explanation for expert judgement
	Were statistical methods appropriate? One of the common statistical issues identified has been reporting of statistical tests that require normally distributed data (e.g., t-test or ANOVA) without reporting that the homogeneity of variance was tested or confirmed.	+	There is indirect evidence that statistical methods were appropriate.
		-	There is indirect evidence that no statistical methods were appropriate.
		--	There is direct evidence that no statistical methods were appropriate.
		NA	Not applicable

[++: definitely low risk of bias, +: probably low risk of bias, -: probably high risk of bias, --: definitely high risk of bias].

Table 25. Appraisal tool for farm and companion animal studies (controlled exposure) (adapted from NTP Risk of Bias tool)

Question	Target organ: Endpoint: Intervention/Exposure:	Rating	Explanation for expert judgement (wording taken from the original OHAT document)
1	**Selection bias:** Was allocation to study groups adequately randomised (including selection of groups during the study)? **KEY QUESTION A**	++	There is direct evidence that at the time of assigning study groups the research personnel did not know what group animals were allocated to, and it is unlikely that they could have broken the blinding of allocation until after assignment was complete and irrevocable. Acceptable methods used to ensure allocation concealment include sequentially numbered treatment containers of identical appearance or equivalent methods.
		+	There is indirect evidence that at the time of assigning study groups the research personnel did not know what group animals were allocated to and it is unlikely that they could have broken the blinding of allocation until after assignment was complete and irrevocable, **OR** it is deemed that lack of adequate allocation concealment would not appreciably bias results.
		-	There is indirect evidence that at the time of assigning study groups it was possible for the research personnel to know what group animals were allocated to, or it is likely that they could have broken the blinding of allocation before assignment was complete and irrevocable, **OR** there is insufficient information provided about allocation to study groups (record 'NR' as basis for answer).
		--	There is direct evidence that at the time of assigning study groups it was possible for the research personnel to know what group animals were allocated to, or it is likely that they could have broken the blinding of allocation before assignment was complete and irrevocable.
		NA	Not applicable
2	**Detection bias:** Can we be confident in the exposure characterisation? **KEY QUESTION B**	++	There is direct evidence that the exposure (including purity and stability of the test substance and compliance with the treatment, if applicable) was independently characterized and purity confirmed generally as ≥99% for single substance or non-mixture evaluations.
		+	There is indirect evidence that the exposure (including purity and stability of the test substance and compliance with the treatment, if applicable) was independently characterized and purity confirmed generally as ≥99% (i.e., the supplier of the chemical provides documentation of the purity of the chemical), **OR** direct evidence that purity was independently confirmed as ≥98% it is deemed that impurities of up to 2% would not appreciably bias results, **AND** there is indirect evidence that exposure was consistently administered (i.e., with the same method and time-frame) across treatment groups.
		-	There is indirect evidence that the exposure (including purity and stability of the test substance and compliance with the treatment, if applicable) was assessed using poorly validated methods, **OR** there is insufficient information provided about the validity of the exposure assessment method, but no evidence for concern (record 'NR' as basis for answer).
		--	There is direct evidence that the exposure (including purity and stability of the test substance and compliance with the treatment, if applicable) was assessed using poorly validated methods.
		NA	Not applicable
3	**Detection bias:** Can we be confident in the	++	There is direct evidence that the outcome was assessed using well-established methods (the gold standard), **AND** assessed at the same length of time after initial exposure in all study groups, **AND** there is direct evidence that the outcome assessors were adequately blinded to the study group, and it is unlikely that they could have

Question	Target organ: Endpoint: Intervention/Exposure:	Rating	Explanation for expert judgement (wording taken from the original OHAT document)
	outcome Assessment? Are we confident that valid, reliable and sensitive methods to assess the outcome have been consistently applied across groups? **KEY QUESTION C**		broken the blinding prior to reporting outcomes.
		+	There is indirect evidence that the outcome was assessed using acceptable methods (i.e., deemed valid and reliable but not the gold standard), **AND** assessed at the same length of time after initial exposure in all study groups, **OR** it is deemed that the outcome assessment methods used would not appreciably bias results, **AND** there is indirect evidence that the outcome assessors were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes, **OR** it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, which is more likely to apply to objective outcome measures. For some outcomes, particularly histopathology assessment, outcome assessors are not blind to study group as they require comparison to the control to appropriately judge the outcome, but additional measures such as multiple levels of independent review by trained pathologists can minimize this potential bias.
		-	There is indirect evidence that the outcome assessment method is an insensitive instrument, **OR** the length of time after initial exposure differed by study group, **OR** there is indirect evidence that it was possible for outcome assessors to infer the study group prior to reporting outcomes without sufficient quality control measures, **OR** there is insufficient information provided about blinding of outcome assessors (record 'NR' as basis for answer).
		--	There is direct evidence that the outcome assessment method is an insensitive instrument, **OR** the length of time after initial exposure differed by study group, **OR** there is direct evidence for lack of adequate blinding of outcome assessors, including no blinding or incomplete blinding without quality control measures.
		NA	Not applicable

[++: definitely low risk of bias, +: probably low risk of bias, -: probably high risk of bias, --: definitely high risk of bias].

Table 26. Appraisal tool for **farm and companion animal studies** (field exposure) (adapted from NTP Risk of Bias tool)

1	**Confounding bias:** Did the study design or analysis account for important confounding and modifying variables? **KEY QUESTION D**	++	There is direct evidence that appropriate adjustments or explicit considerations were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research-specific bias including standardization, matching, adjustment in multivariate model, stratification, propensity scoring, or other methods that were appropriately justified. Acceptable consideration of appropriate adjustment factors includes cases when the factor is not included in the final adjustment model because the author conducted analyses that indicated it did not need to be included, **AND** there is direct evidence that primary covariates and confounders were assessed using valid and reliable measurements, **AND** there is direct evidence that other exposures anticipated to bias results were not present or were appropriately measured and adjusted for. In occupational studies or studies of contaminated sites, other chemical exposures known to be associated with those settings were appropriately considered. For case-control studies: There is direct evidence that appropriate adjustments were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research specific bias including standardization, matching of cases and controls, adjustment in multivariate model, stratification, propensity scoring, or other methods were appropriately justified, AND there is direct evidence that primary covariates and confounders were assessed using valid and reliable measurements, AND there is direct evidence that other exposures anticipated to bias results were not present or were appropriately measured and adjusted for.
		+	There is indirect evidence that appropriate adjustments were made, OR it is deemed that not considering or only considering a partial list of covariates or confounders in the final analyses would not appreciably bias results. AND there is evidence (direct or indirect) that primary covariates and confounders were assessed using valid and reliable measurements, OR it is deemed that the measures used would not appreciably bias results (i.e., the authors justified the validity of the measures from previously published research), AND there is evidence (direct or indirect) that other co-exposures anticipated to bias results were not present or were appropriately adjusted for, OR it is deemed that co-exposures present would not appreciably bias results. Note: As discussed above, this includes insufficient information provided on co-exposures in general population studies.
		-	There is indirect evidence that the distribution of primary covariates and known confounders differed between the groups and was not appropriately adjusted for in the final analyses, OR there is insufficient information provided about the distribution of known confounders (record 'NR' as basis for answer), OR there is indirect evidence that primary covariates and confounders were assessed using measurements of unknown validity, OR there is insufficient information provided about the measurement techniques used to assess primary covariates and confounders (record 'NR' as basis for answer), OR there is indirect evidence that there was an unbalanced provision of additional co-exposures across the primary study groups, which were not appropriately adjusted for, OR there is insufficient information provided about co-exposures in occupational studies or studies of contaminated sites where high exposures to other chemical exposures would have been reasonably anticipated

			(record 'NR' as basis for answer). For case-control studies: There is indirect evidence that the distribution of primary covariates and known confounders differed between cases and controls and was not investigated further, OR there is insufficient information provided about the distribution of known confounders in cases and controls (record 'NR' as basis for answer), OR there is indirect evidence that primary covariates and confounders were assessed using measurements of unknown validity, OR there is insufficient information provided about the measurement techniques used (record 'NR' as basis for answer), OR there is indirect evidence that there was an unbalanced provision of additional co-exposures across cases and controls, which were not appropriately adjusted for, OR there is insufficient information provided about co-exposures in occupational studies or studies of contaminated sites where high exposures to other chemical exposures would have been reasonably anticipated (record 'NR' as basis for answer).
		--	There is direct evidence that the distribution of primary covariates and known confounders differed between the groups, confounding was demonstrated, and was not appropriately adjusted for in the final analyses, OR there is direct evidence that primary covariates and confounders were assessed using non valid measurements, OR there is direct evidence that there was an unbalanced provision of additional co-exposures across the primary study groups, which were not appropriately adjusted for. For case-control studies: There is direct evidence that the distribution of primary covariates and known confounders differed between cases and controls, confounding was demonstrated, but was not appropriately adjusted for in the final analyses, OR there is direct evidence that primary covariates and confounders were assessed using non valid measurements, OR there is direct evidence that there was an unbalanced provision of additional co-exposures across cases and controls, which were not appropriately adjusted for.
		NA	Not applicable
2	**Detection bias:** Can we be confident in the exposure characterisation? **KEY QUESTION E**	++	There is direct evidence that exposure was consistently assessed (i.e. under the same method and time-frame) using well-established methods that directly measure exposure (e.g., measurement of the chemical in air or measurement of the chemical in blood, plasma, urine, etc.), OR exposure was assessed using less-established methods that directly measure exposure and are validated against well-established methods.
		+	There is indirect evidence that the exposure was consistently assessed using well-established methods that directly measure exposure, OR exposure was assessed using indirect measures (e.g., questionnaire or occupational exposure assessment by a certified industrial hygienist) that have been validated or empirically shown to be consistent with methods that directly measure exposure (i.e., inter-methods validation: one method vs. another).
		-	There is indirect evidence that the exposure was assessed using poorly validated methods that directly measure exposure, OR there is direct evidence that the exposure was assessed using indirect measures that have not been validated or empirically shown to be consistent with methods that directly measure exposure (e.g., a job-exposure matrix or self-report without validation) (record 'NR' as basis for answer), OR there is insufficient information provided about the exposure assessment, including validity and reliability, but no evidence for concern about the method used (record 'NR' as basis for answer).
		--	There is direct evidence that the exposure was assessed using methods with poor validity, OR evidence of exposure misclassification (e.g., differential recall of self-reported exposure).

		NA	Not applicable
3	**Detection bias:** Can we be confident in the outcome assessment? **KEY QUESTION F**	++	For cohort studies: There is direct evidence that the outcome was assessed using well-established methods (e.g. the 'gold standard'), AND subjects had been followed for the same length of time in all study groups. Acceptable assessment methods will depend on the outcome, but examples of such methods may include: objectively measured with diagnostic methods, measured by trained interviewers, obtained from registries. For case-control studies: There is direct evidence that the outcome was assessed in cases (i.e., case definition) and controls using well-established methods (the gold standard), AND subjects had been followed for the same length of time in all study groups, AND there is direct evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the exposure level when outcome was assessed in cases (i.e., case definition) and controls. For cross-sectional studies: There is direct evidence that the outcome was assessed using well-established methods (the gold standard), AND there is direct evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the exposure level, and it is unlikely that they could have broken the blinding prior to reporting outcomes.
		+	For cohort studies: There is indirect evidence that the outcome was assessed using acceptable methods (i.e. deemed valid and reliable but not the gold standard) AND subjects had been followed for the same length of time in all study groups [Acceptable, but not ideal assessment methods will depend on the outcome, but examples of such methods may include proxy reporting of outcomes and mining of data collected for other purposes], OR it is deemed that the outcome assessment methods used would not appreciably bias results, AND there is indirect evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes, OR it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, which is more likely to apply to objective outcome measures For case-control studies: There is indirect evidence that the outcome was assessed in cases (i.e., case definition) and controls using acceptable methods, AND subjects had been followed for the same length of time in all study groups, OR it is deemed that the outcome assessment methods used would not appreciably bias results, AND there is direct evidence that the outcome assessors were adequately blinded to the exposure level when reporting outcomes, OR it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (including that subjects self-reporting outcomes were likely not aware of reported links between the exposure and outcome or lack of blinding is unlikely to bias a particular outcome). For cross-sectional studies: There is indirect evidence that the outcome was assessed using acceptable methods, OR it is deemed that the outcome assessment methods used would not appreciably bias results, AND there is indirect evidence that the outcome assessors were adequately blinded to the exposure level, and it is unlikely that they could have broken the blinding prior to reporting outcomes, OR it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (including that subjects self-reporting outcomes were likely not aware of reported links between the exposure and outcome lack of blinding is unlikely to bias a

			particular outcome).
		-	For cohort studies: There is indirect evidence that the outcome assessment method is an insensitive instrument (e.g., a questionnaire used to assess outcomes with no information on validation), OR the length of follow up differed by study group, OR there is indirect evidence that it was possible for outcome assessors (including study subjects if outcomes were self-reported) to infer the study group prior to reporting outcomes, OR there is insufficient information provided about blinding of outcome assessors (record 'NR' as basis for answer). For case-control studies: There is indirect evidence that the outcome was assessed in cases (i.e., case definition) using an insensitive instrument, OR there is insufficient information provided about how cases were identified (record 'NR' as basis for answer), OR there is indirect evidence that it was possible for outcome assessors to infer the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were likely aware of reported links between the exposure and outcome), OR there is insufficient information provided about blinding of outcome assessors (record 'NR' as basis for answer). For cross-sectional studies: There is indirect evidence that the outcome assessment method is an insensitive instrument, OR there is indirect evidence that it was possible for outcome assessors to infer the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were likely aware of reported links between the exposure and outcome), OR there is insufficient information provided about blinding of outcome assessors (record 'NR' as basis for answer).
		-	For cohort studies: There is direct evidence that the outcome assessment method is an insensitive instrument, OR the length of follow up differed by study group, OR there is direct evidence for lack of adequate blinding of outcome assessors (including study subjects if outcomes were self-reported), including no blinding or incomplete blinding. For case-control studies: There is direct evidence that the outcome was assessed in cases (i.e., case definition) using an insensitive instrument, OR there is direct evidence that outcome assessors were aware of the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were aware of reported links between the exposure and outcome). For cross-sectional studies: There is direct evidence that the outcome assessment method is an insensitive instrument, OR there is direct evidence that outcome assessors were aware of the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were aware of reported links between the exposure and outcome).
		NA	Not applicable

[++: definitely low risk of bias, +: probably low risk of bias, -: probably high risk of bias, --: definitely high risk of bias].

A.1.2.3. Evaluating the confidence in the body of evidence[4]

Once the individual studies have been appraised for internal validity, the Working Group experts will evaluate the overall confidence in the evidence (i.e. group of studies addressing the same endpoint in experimental animal studies or in human studies or farm/companion animal studies) considering[5]:

(i) Presence of effects at low doses, per line of evidence (human studies, experimental animal studies and farm/companion animal studies).

(ii) Factors that can decrease the confidence in the evidence, such as unexplained inconsistency, indirectness, imprecision, publication bias, risk of bias.

(iii) Factors that can increase the confidence in the evidence, such as large magnitude effects, dose response, residual confounding, cross-species/population/study consistency.

A.1.2.4. Integration of the lines of evidence for hazard identification

Human hazard identification

The final critical endpoints will be identified by integrating evidence from both human and experimental animal lines of evidence considering the respective level of confidence (see Section A.1.2.3).

Farm and companion animal hazard identification

The critical endpoints will be identified considering the level of confidence described in Section A.1.2.3 above.

A.1.2.5. Method to perform hazard characterisation

For each endpoint, dose-response assessment will be performed on relevant adverse effects for the identification of reference points (e.g. a no-observed-adverse-effect level (NOAEL) or a benchmark dose (BMD) and its lower confidence limit (BMDL) for a particular incidence of effect). The lowest reference point will be considered for the possible derivation of a health-based guidance value, such as a tolerable intake.

For the human hazard characterisation, data on the toxicokinetics (ADME and toxicokinetic modelling) will support the extrapolation of results from experimental animal studies and human studies to the general population. This information is also important to determine which uncertainty factors related to inter-species difference and inter-individual variability need to be taken into account when establishing a HBGV.

Information on mode of action of the target compounds and endpoints will also support this step. Mode of action studies in laboratory animals can establish the key events and their relationships required for the various adverse outcomes as a result of PCDD/Fs and DL-PCBs exposure.

[4] A body of scientific evidence is a collection of pieces of evidence that is identified and evaluated to answer one or a set of scientific question(s).

[5] The evaluation of the confidence in the body of evidence will be carried out considering the conceptual framework developed by the NTP Office of Health Assessment and Translation (OHAT), without necessarily following the same structured methodology (NTP, 2015)

A.1.3. Method to address the exposure assessment sub-questions

A.1.3.1. Human dietary exposure assessment

To address sub-question 11 on the levels of PCDD/Fs and DL-PCBs in food in Europe, a structured approach will be followed to collect and evaluate the evidence (structured approach E). The available occurrence data on PCDD/Fs and DL-PCBs in food will be extracted from the EFSA database by the EFSA DATA Unit. Occurrence data are collected through the continuous annual call for data issued by EFSA requesting data on a list of prioritised chemical contaminants[6]. National food authorities and also research institutions, academia, food business operators and other stakeholders are invited to submit data occurrence by the 1st of October of each year. The data submission to EFSA must follow the requirements of the EFSA Guidance on Standard Sample Description for Food and Feed (EFSA, 2010c); occurrence data will be managed following the EFSA standard operating procedures (SOPs) on 'Data collection and validation' and on 'Data analysis and reporting'.

For this risk assessment all occurrence data received before the end of April 2016 will be considered. As the analytical methodology to measure PCDD/Fs and DL-PCBs as well as the reporting of congeners has been improved in recent years, only the occurrence data collected from 2010 onwards will be included in the final dataset.

TEFs established in 2005 (van den Berg et al., 2006) will be applied to the occurrence data (food and feed).

In addition and to guarantee an appropriate quality of the food data used in the exposure assessment, the initial dataset will be evaluated carefully before being used to estimate dietary exposure. Among the steps that will be followed, it is worth mentioning the re-codification of samples under FoodEx classification, the application of the substitution method to left-censored data, the exclusion of suspect samples or those samples for with incomplete information (e.g. absence of particular congeners) is given and the grouping at the appropriate FoodEx level, among others. These steps will be carried out by the EFSA DATA Unit in close collaboration with the members of the Working Group.

Sub-question 13 on the consumption levels of foods among the target European population will be addressed by a structured approach to collect and analyse the evidence available (structured approach F). The EFSA Comprehensive European Food Consumption Database (Comprehensive Database) will be the source of the food consumption information. This database provides a compilation of existing national information on food consumption at individual level. It was first built in 2010 (EFSA, 2011b; Huybrechts et al., 2011; Merten et al., 2011) and then updated in 2015[7]. Details on how the Comprehensive Database is used are published in the Guidance of EFSA (EFSA, 2011b).

The Comprehensive Database contains data of dietary surveys from different European countries. Consumption data are available for 'Infants' (< 12 months old), 'Toddlers' (≥ 12 months to < 36 months old), 'Other children' (≥ 36 months to < 10 years old), 'Adolescents' (≥ 10 years to < 18 years old), 'Adults' (≥ 18 years to < 65 years old), the 'Elderly' (≥ 65 years to < 75 years old) and the 'Very elderly' (≥ 75 years old). As indicated by the EFSA Working Group on Food Consumption and Exposure (EFSA, 2011c), dietary surveys with only one day per subject will only be considered for acute exposure as they are not adequate to assess repeated exposure. Similarly, subjects who participated only one day in the dietary studies, when the protocol prescribed more reporting days per individual, will also be excluded for the chronic exposure assessment.

To estimate the human dietary exposure (sub-question 14), both occurrence and consumption data will be codified and classified according to the FoodEx classification system (EFSA, 2011d). FoodEx is a food classification system developed by the former EFSA DCM Unit in 2009 with the objective of simplifying the linkage between occurrence and food consumption data when assessing the exposure to hazardous substances. It contains 20 main food groups (first level), which are further divided into subgroups having 140 items at the second level, 1,261 items at the third level and reaching about

[6] http://www.efsa.europa.eu/en/data/call/datex101217
[7] http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb

1,800 end-points (food names or generic food names) at the fourth level. The EFSA DATA Unit will verify the correct application of FoodEx classification to the data before dietary exposure is estimated.

The CONTAM Panel considered that only chronic dietary exposure to PCDD/Fs and DL-PCBs was to be assessed for the general population. Two scenarios will be used to estimate chronic dietary exposure. Scenario A will only use food samples that reported the 29 target congeners (the seventeen 2,3,7,8-substituted PCDD/Fs and the 12 DL-PCBs) while in the scenario B dietary exposure will be estimated considering only the food samples that reported the 17 target PCDD/Fs congeners.

For calculating chronic dietary exposure to PCDD/Fs and DL-PCBs, food consumption and body weight data at the individual level will be accessed in the Comprehensive Database. Food occurrence data and consumption data will be linked at the least possible aggregated FoodEx level. In addition, the different food commodities will be grouped within each food category to better explain their contribution to the total dietary exposure to PCDD/Fs and DL-PCBs. Exposure estimates will be calculated per dietary survey and age class. The mean and the high (95th percentile) chronic dietary exposures will be calculated by combining PCDD/Fs and DL-PCBs mean occurrence values for food samples collected in different countries (pooled European occurrence data) with the average daily consumption for each food at individual level in each dietary survey. When occurrence data on the target PCDD/Fs and DL-PCBs are reported on fat content basis, consumption levels will be converted into amount of fat before dietary exposure is estimated. When the fat content of consumed foods is not available for specific eating occasions, an average value will be derived according to the different levels of hierarchy of the FoodEx1 catalogue from the available consumption data.

The estimates will be performed by the EFSA data Unit. All analyses will be run using the SAS Statistical Software (SAS enterprise guide 5.1).

Sub-question 12 on the effects of processing in food on the levels of the target compounds will be addressed narratively. A literature search will be carried out to identify reviews as well as other peer-reviewed single studies published in the open literature that will be screened and evaluated by relevant domain experts from the Working Group. For details of the preliminary search strategy see Table 27. When possible, it will be complemented with the data submitted to EFSA, in case this information is available.

Sub-question 15 on the concentrations of PCDD/Fs and DL-PCBs in human tissues (e.g. blood, breast milk, adipose tissue, placenta) in the target European population will be addressed narratively. Also in this case, a literature search will be carried out to identify reviews as well as peer-reviewed studies published in the open literature that will be screened and evaluated by relevant domain experts from the Working Group. For details of the preliminary search strategy see Table 28.

Table 27. Preliminary search strings for Narrative approach D (sub-question 12, effects of processing)

Database	Web Of Science™
Preliminary keywords	Dioxins, Tetrachlorodibenzodioxin, TCDD, Dioxin-like, TEQ, Coplanar, Polychlorinated biphenyls, PCBs **AND** Processing, cooking procedures, cooking technique, cooking practices

Table 28. Preliminary search strings for Narrative approach E (sub-question 15, levels in human tissues)

Database	Web Of Science™
Preliminary search string	Dioxins, Tetrachlorodibenzodioxin, Dioxin-like, TEQ, Coplanar, Polychlorinated biphenyls, PCBs **AND** Blood, breast milk, adipose tissue, placenta

A.1.3.2. Farm and companion animal dietary exposure assessment

To address sub-question 21 on the levels of PCDD/Fs and DL-PCBs in feed in Europe, the same approach as to address sub-question 11 related to food will be used (structured approach E). As done for the occurrence data in food (see above), available occurrence data on PCDD/Fs and DL-PCBs in feed will be extracted from the EFSA database by the EFSA DATA Unit. The feed occurrence data are

also collected through the continuous annual call for data issued by EFSA requesting data on a list of prioritised chemical contaminants[16]. As for food, WHO_{2005}-TEFs will be applied to the feed occurrence data. The initial dataset will be evaluated carefully by the EFSA DATA Unit before being used to estimate dietary exposure.

Sub-question 22 on the consumption levels of feeds among the farm and companion animals, will be addressed narratively. In contrast to the situation for the human food consumption data (see structured approach F) there is no comprehensive database on what or how much feed livestock in the EU consume. Therefore, general estimates of feeds consumed for each of the main categories of farm livestock and companion animals will be used. These will be based on published guidelines on nutrition and feeding (e.g. AFRC, 1993; Carabano and Piquer, 1998; NRC, 2007a,b; Leeson and Summers, 2008; EFSA, 2009c; OECD, 2009; McDonald et al., 2011), expert knowledge of production systems in Europe, and data on EU manufacture of compound feeds (FEFAC, 2009). As a result, the composition of diets for each of the major farm livestock species used for the exposure assessment are estimates of the CONTAM Panel, but are in agreement with common practice.

To estimate farm and companion animal dietary exposure (sub-question 23) the feed will be classified based on the catalogue of feed materials as last specified in the corresponding Commission Regulation creating the Catalogue of feed materials. If possible, compound feedingstuffs will be classified in groups based on the species/production categories for which the feed is intended. This step will be performed by the EFSA DATA Unit.

As for the human risk assessment, the CONTAM Panel considered that only chronic dietary exposure to PCDD/Fs and DL-PCBs was to be assessed. It will be estimated by combining the mean occurrence data with the species specific feed mean consumption data. Two scenarios will be used to estimate chronic dietary exposure, one using food samples that reported the 29 target congeners (the seventeen 2,3,7,8-substituted PCDD/Fs and the 12 DL-PCBs) and another considering only the food samples that reported the 17 target PCDD/Fs congeners. These estimates will be performed by the Working Group.

A.1.4. Method to address the uncertainties in the risk assessment

The evaluation of the inherent uncertainties in the risk assessment on PCDD/Fs and DL-PCBs will be performed following the guidance of the Opinion of the Scientific Committee related to Uncertainties in Dietary Exposure Assessment (EFSA, 2006). Furthermore, the report on 'Characterizing and Communicating Uncertainty in Exposure Assessment' (WHO/IPCS, 2008) will be considered. According to the guidance provided by the EFSA opinion (2006) the following sources of uncertainties are to be considered: assessment objectives, exposure scenario, exposure model, and model input (parameters).

A.1.5. Approach for reaching risks characterisation conclusions

The general principles of the risk characterisation for chemicals in food as described by WHO/IPCS (2009) will be applied as well as the different EFSA guidance documents relevant to this step of the risk assessment (see Section A.1.1.5 above). For the animal risk characterisation, the same principles will be applied.

A.1.6. Plans for updating the literature searches and dealing with newly available evidence

The literature searches performed for the structured approaches will be repeated approximately 7 and 4 months before the planned date of adoption of the opinion. The scientific papers retrieved by these additional searches will be screened for relevance, applying the same inclusion/exclusion criteria as detailed in this Annex. These tasks will be performed by the members of the Working Group and EFSA staff.

Relevant studies will be reviewed narratively by the Working Group experts and in case of controversial issues are identified (e.g. conflicting conclusions) these will be discussed in the Working Group which will prepare a proposal on how to deal with the issues. The controversial issues and the

proposed solution will be brought to the attention of the CONTAM Panel which will take the final decision.

A.1.7. Human resource, software and timeline for performing the risk assessment

Tasks for performing the different steps in the risk assessment are shown in Table 29.

Table 29. Allocation of task for performing the assessment

What	Who	Software[(a)]	Timeline (planned)
Hazard identification and characterisation (human and farm/companion animal risk assessment)			
Structured approach A Search process, study selection for relevance, and data extraction for sub-questions 1 and 8 (human studies)	External contractor	EndNote DistillerSR®	June 2016
Structured approach A Appraisal of relevant studies for sub-questions 1 and 8 (human studies)	Members of the Working Group	DistillerSR®	November 2016
Structured approach B Search process, study selection for relevance, and data extraction for sub-questions 3 and 9 (experimental animal studies)	External contractor	EndNote DistillerSR®	June 2016
Structured approach B Appraisal of relevant studies for sub-questions 3 and 9 (experimental animal studies)	Members of the Working Group	DistillerSR®	November 2016
Structured approach C Search process and narrative review and analysis of data for sub-question 5 (ADME humans)	Working Group and EFSA (BIOCONTAM Unit)	EndNote DistillerSR®	July 2016
Structured approach D Search process and narrative review and analysis of data for sub-question 6 (ADME experimental animals)	Working Group and EFSA (BIOCONTAM Unit)	EndNote DistillerSR®	July 2016
Structured approach G Search process, study selection for relevance, and data extraction for sub-questions 16 and 17 (farm and companion animal studies)	Working Group and EFSA (BIOCONTAM Unit)	EndNote DistillerSR®	June 2016
Structured approach G Appraisal of relevant studies for sub-questions 16 and 17 (farm and companion animals)	Members of the Working Group	DistillerSR®	November 2016
Structured approach H Search process and narrative review and analysis of data for sub-question 18 and 19 (ADME and transfer in farm and companion animals)	Working Group and EFSA (BIOCONTAM Unit)	EndNote DistillerSR®	July 2016
Referee in case of doubt and divergences	Working Group members	DistillerSR®	n.a.
Narrative approach - Review and analysis of data for sub-question 2 (HI experimental animals at all doses)	Working Group and EFSA (BIOCONTAM Unit)	EndNote	June 2016
Narrative approach - Review and analysis of data for sub-question 4 (genotoxicity)	Members of the Working Group	EndNote	June 2016
Narrative approach - Review and analysis of data for sub-question 10 (Mode of action)	Members of the Working Group	EndNote	June 2016
Dietary exposure assessment (human and farm/companion animal risk assessment)			
Structured approach E Collection and analysis of the occurrence data on food and feed submitted to EFSA for sub-questions 11 and 21	EFSA (DATA Unit)	SAS	September 2016
Structured approach F Collection and analysis of the food consumption data available at EFSA for sub-question 13	EFSA (DATA Unit)	SAS	September 2016
Narrative approach - Review and analysis of data for sub-	Working Group and	EndNote	November

What	Who	Software[(a)]	Timeline (planned)
question 12 (effects of food processing)	EFSA (BIOCONTAM Unit)		2016
Narrative approach - Review and analysis of data for sub-question 15 (concentrations in human samples)	Working Group and EFSA (BIOCONTAM Unit)	EndNote	July 2016
Narrative approach - Collection and analysis of the feed consumption data for sub-question 22.	Working Group and EFSA (BIOCONTAM Unit)	SAS	September 2016
Literature check for background data on occurrence and dietary exposure to dioxins and DL-PCBs published in the literature	EFSA (BIOCONTAM Unit)	EndNote	December 2016
Estimation of the human dietary intake and scenarios for sub-question14	EFSA (DATA Unit)	SAS	December 2016
Estimation of the farm and companion animal dietary intake and scenarios for sub-question 23.	Working Group and EFSA (DATA and BIOCONTAM Units)	xls	December 2016
Plans for updating the literature searches			
Update of the searches	Working Group and EFSA (BIOCONTAM Unit)	EndNote	
Select studies for relevance	Working Group members	DistillerSR®	
Narrative review of relevant additional studies	Working Group members	/	
Finalisation of the draft opinion: May 2017[8]			

(a): Reference management software or web-based review software or data management software.

A.1.8. History of the amendments

The following amendments to the protocol were applied due to time and resources constraints:

Section A.1.2.2.4: In July 2016, it was decided that the data extraction of the relevant farm and companion animal studies would be done using a simplified data extraction form based on Table 12. It was also decided that the risk of bias appraisal for the studies in farm and companion animals would be done in a qualitative way.

Section A.1.2.2.5: In May 2017, it was decided that the risk of bias appraisal of the studies in humans would be done in duplicate for some endpoints only, including the critical endpoint 'effects on reproduction' (both male and female). Similarly for the experimental animals, only some studies were appraised in duplicate. Whether a study has been appraised in duplicate or by one expert is indicated where appropriate. Appraisals were performed in Distiller or in word files.

Section A.1.2.2: In November 2017 it was decided that Structured approach C and D to address sub-questions 5 and 6 related to the toxicokinetics of the target compounds in humans and experimental animals, respectively, would be addressed narratively. A literature search would be carried out to identify previous assessment and studies relevant to inform these sub-questions published in the open literature. The studies would be screened and evaluated by relevant domain experts from the Working Group. This task would be performed by EFSA/Working Group members.

Section A.1.2.2.3: In February 2018, it was decided to exclude animal studies with exposure to PCDD/Fs and DL-PCBs other than TCDD, or with exposure to mixtures. Body burdens estimated from some of these studies would be associated with higher uncertainty, as TEFs are weighted factors based on a range of relative potencies from various studies and endpoints, and determined to discrete points on a log scale.

Section A.1.3.1: For this risk assessment it was decided to extend the period to include occurrence data from April 2016 to December 2016.

[8] An extension until 30 June 2018 was agreed with EC.

Section A.1.6: In October 2017, it was agreed that only one update of the literature search would be performed. This literature update would target the section on observations in humans and studies in experimental animals.

ANNEX A.2. DATA AND METHODOLOGIES – SEARCH STRINGS

A.2.1. Supporting information for the risk assessment

The references resulting from the literature search presented in the tables below were imported to EndNote[9].

Table 30. Search strings used to retrieve studies to inform the section on occurrence data in food and feed published in the open literature and previously reported exposure assessments

Database	**Web of Science™**	
Search strategy	**#1**	TS = (*dioxin OR tetrachlorodibenzo* OR TCDD OR dioxin-like OR TEQ OR coplanar OR polychlorinated biphenyl OR PCBs OR PCDD* OR PCDF*)
	#2	**A**: TS = ("food occur"* OR "food" OR "foodstuffs" OR "food-stuffs" OR "food occurrence") **B**: TS=(feed occur"* OR "feed" OR "feedstuffs" OR "feed-stuffs" OR "feed occurrence" OR "grains" OR " barley" OR "wheat" OR "maize" OR "oat" OR "rice" OR "rye" OR "spelt" OR "compound feed" OR "seeds" OR "complete feed")
	#3	(#1) AND (#2)
	#4	(#3) AND Refined by: [excluding] Databases: (KJD OR CSCD) AND LANGUAGES: (ENGLISH) Timespan: 1998-2016
	#5	#4 AND Refined by COUNTRIES/TERRITORIES**:** (LITHUANIA OR ROMANIA OR BULGARIA OR ITALY OR SPAIN OR GERMANY OR CROATIA OR NORWAY OR BELGIUM OR SWEDEN OR NETHERLANDS OR FRANCE OR ENGLAND OR HUNGARY OR DENMARK OR POLAND OR FINLAND OR ESTONIA OR CZECH REPUBLIC OR WALES OR SLOVENIA OR UK OR GREECE OR UNITED KINGDOM OR SLOVAKIA OR LATVIA OR PORTUGAL OR AUSTRIA OR LUXEMBOURG OR SCOTLAND OR IRELAND)
	#6	(#5) AND Refined by: DOCUMENT TYPES: (REVIEW)
Number of Hits: **A**: 40, **B**: 22. Date of search: 29.05.2016		

Table 31. Search string used to retrieve studies ion of studies relevant to inform the section on effects on processing in the levels of PCDD/Fs and DL-PCBs in food and feed

Database	**Web of Science™**	
Search Strategy	**#1**	TS = (*dioxin OR tetrachlorodibenzo* OR TCDD OR dioxin-like OR TEQ OR coplanar OR polychlorinated biphenyl OR PCBs OR PCDD* OR PCDF*)
	#2	TS=("food processing" OR cooking OR "cooking procedures" OR "cooking technique" OR "cooking practices" OR frying OR smoking OR drying)
	#3	(#1) AND (#2)
	#4	#3 AND TS=(food OR feed)
	#5	#4 - Refined by: [excluding] Databases: (Korean JD OR Chinese SCD OR Russian SCI) LANGUAGES: (ENGLISH) Timespan=1950-2016
Number of Hits: 1,068 Date of search: 13.04.2016		

[9] EndNote X5, Thomson Reuters. Available online: http://endnote.com/

Table 32. Search string used for the identification of studies relevant to inform the section on levels in humans

Database	Web of Science™	
Search Strategy	**#1**	TS = (*dioxin OR tetrachlorodibenzo* OR TCDD OR dioxin-like OR TEQ OR coplanar OR polychlorinated biphenyl OR PCBs OR PCDD* OR PCDF*)
	#2	TS=(blood OR "breast milk" OR "human milk" OR "placenta" OR "Adipose Tissue" OR "Human adipose tissue" OR "Human fatty tissue" OR liver)
	#3	(#1) AND (#2)
	#4	(#3) AND TS=(human)
	#5	#4 - Refined by: [excluding] Databases: (Korean JD OR Chinese SCD OR Russian SCI) DOCUMENT TYPES: (REVIEW) LANGUAGES: (ENGLISH) Timespan=1950-2016
Number of Hits: 589 Date of search: 13.04.2016		

A.2.2. Adverse effects in farm and companion animals

The search strings used for the identification of studies relevant to inform the adverse effects of PCDD/Fs and DL-PCBs in farm and companion animals (sub-questions 16 and 17) are shown in Tables 33 to 37 for the different animal species (ruminants, pigs, poultry, fish and horses).

The studies were transferred from the databases to EndNote where a first check for duplicates was carried out. The references where then transferred to the web-based systematic review software Distiller[SR]. A second duplicate check was done, followed by a two-step selection for relevance by two independent reviewers according to the eligibility criteria set in Annex A.1. The outcome of this selection is discussion in Section 3.1.5 of the scientific opinion.

Table 33. Search strings used to retrieve studies on the adverse effects in **ruminants**

Database	Web of Science™	
Search strategy	**#1**	TS=(TCDD OR dioxins OR *dioxin OR dioxin-like* OR coplanar OR PCB* OR polychlorinated biphenyl* OR PCDD* OR PCDF*)
	#2	TS=(ruminant OR ruminants OR cattle OR cow OR cows OR bovine OR sheep OR goat OR goats OR buffalo OR buffaloes)
	#3	TS=(*toxic* OR adverse OR effect OR effects OR "adverse effects" OR fertility OR disease* OR diseases)
	#4	(#1) AND (#2) AND (#3)
	#5	#4 NOT TS=(rat OR rats OR mice OR mouse OR monkey OR monkeys OR "guinea pig" OR guinea-pig OR guineapig OR "mini pig" OR minipig OR rabbit OR rabbits OR hamster OR hamsters OR dog OR dogs OR cat OR cats OR mink OR minks)
	#6	#5 NOT TI=(zebrafish OR medaka OR "human milk" OR birds OR "in vitro" OR transfer OR "carry over" OR carry-over OR carryover)
	#7	#6 AND PY=(1950-18/04/2016)
	#8	#7 *Refine by* LANGUAGE=(English)
	#9	#8 *Refine by* DOCUMENT TYPES: (article OR review)
	#10	#9 *Refine by* DATABASE: exclude Chinese and Korean an Russian (if appear)
Database	**PubMed**	
Search Strategy	**#1**	"dioxins"[MeSH Terms] OR "Tetrachlorodibenzodioxin"[Mesh]) OR ("polychlorinated biphenyls"[MeSH Terms]
	#2	((((("ruminants"[MeSH Terms] OR "ruminants"[All Fields] OR "ruminant"[All Fields]) OR ("cattle"[MeSH Terms] OR "cattle"[All Fields]) OR ("cattle"[MeSH Terms] OR "cattle"[All Fields] OR "cow"[All Fields]) OR ("cattle"[MeSH Terms] OR "cattle"[All Fields] OR "bovine"[All Fields]) OR ("sheep, domestic"[MeSH Terms] OR ("sheep"[All Fields] AND "domestic"[All Fields]) OR "domestic sheep"[All Fields] OR "sheep"[All Fields] OR "sheep"[MeSH Terms]) OR ("goats"[MeSH Terms] OR "goats"[All Fields] OR "goat"[All Fields]) OR ("buffaloes"[MeSH Terms] OR "buffaloes"[All Fields] OR "buffalo"[All Fields]))

	#3	"adverse effects" [Subheading]
	#4	#1 AND #2 AND #3
	#5	#4 NOT (mice[Title] OR rat[Title] OR rats[Title] OR "in vitro"[Title])
	#6	#5 AND ("1950"[Date - Publication] : "3000"[Date - Publication])
	#7	#6 AND "english"[Language]
HITS combined WOS + pubMED = 880 (w/o duplicate in EndNote) Date of search: 19.04.2016		

Table 34. Search strings used to retrieve studies on the adverse effects in **pigs**

Database	**Web of Science™**	
Search strategy	**#1**	TS=(TCDD OR dioxins OR *dioxin OR dioxin-like* OR coplanar OR PCB* OR polychlorinated biphenyl* OR PCDD* OR PCDF*)
		TS=(swine OR pig OR pigs)
	#3	TS=(*toxic* OR adverse OR effect OR effects OR "adverse effects" OR fertility OR disease* OR diseases)
	#4	(#1) AND (#2) AND (#3)
	#5	#4 NOT TS=(rat OR rats OR mice OR mouse OR monkey OR monkeys OR "guinea pig" OR guinea-pig OR guineapig OR "mini pig" OR minipig OR rabbit OR rabbits OR hamster OR hamsters OR dog OR dogs OR cat OR cats OR mink OR minks)
	#6	#5 NOT TI=(zebrafish OR medaka OR "human milk" OR birds OR "in vitro" OR transfer OR "carry over" OR carry-over OR carryover OR pigment OR pigments OR pigeon)
	#7	#6 AND PY=(1950-date of the search)
	#8	#7 *Refine by* LANGUAGE=(English)
	#9	#8 *Refine by* DOCUMENT TYPES: (article OR review OR correction)
	#10	#9 *Refine by* DATABASE: exclude Chinese and Korean an Russian (if appear)
Database	**PubMed**	
Search Strategy	**#1**	"dioxins"[MeSH Terms] OR "Tetrachlorodibenzodioxin"[Mesh]) OR ("polychlorinated biphenyls"[MeSH Terms]
	#2	"swine"[MeSH Terms] OR "swine"[All Fields] OR "pig"[All Fields] OR "pigs"[All Fields]
	#3	"adverse effects" [Subheading]
	#4	#1 AND #2 AND #3
	#5	NOT (mice[Title] OR rat[Title] OR rats[Title] OR "in vitro"[Title])
	#6	#6 AND ("1950"[Date - Publication] : "3000"[Date - Publication])
	#7	#5 AND "english"[Language]
HITS combined WOS + pubMED = 367 (w/o duplicate in EndNote) Date of search:19.04.2016		

Table 35. Search strings used to retrieve studies on the adverse effects in **poultry**

Database	**Web of Science™**	
Search strategy	**#1**	TS=(TCDD OR dioxins OR *dioxin OR dioxin-like* OR coplanar OR PCB* OR polychlorinated biphenyl* OR PCDD* OR PCDF*)
	#2	TS=(poultry OR chicken OR chickens OR turkey OR turkeys OR duck OR ducks OR quail OR quails OR goose OR geese)
	#3	TS=(*toxic* OR adverse OR effect OR effects OR "adverse effects" OR fertility OR disease* OR diseases)
	#4	(#1) AND (#2) AND (#3)
	#5	#4 NOT TS=(rat OR rats OR mice OR mouse OR monkey OR monkeys OR "guinea pig" OR guinea-pig OR guineapig OR "mini pig" OR minipig OR rabbit OR rabbits OR hamster OR hamsters OR dog OR dogs OR cat OR cats OR mink OR minks)
	#6	#5 NOT TI=(zebrafish OR medaka OR "human milk" OR birds OR "in vitro" OR transfer OR "carry over" OR carry-over OR carryover)

	#7	#6 AND PY=(1950-date of the search)
	#8	#7 *Refine by* LANGUAGE=(English)
	#9	#8 *Refine by* DOCUMENT TYPES: (article OR review OR correction)
	#10	#9 *Refine by* DATABASE: exclude Chinese and Korean an Russian (if appear)
Database	**PubMed**	
Search Strategy	**#1**	"dioxins"[MeSH Terms] OR "Tetrachlorodibenzodioxin"[Mesh]) OR ("polychlorinated biphenyls"[MeSH Terms]
	#2	((("Chickens"[Mesh]) OR "chicken"[All Fields] OR "Poultry"[Mesh]) OR "poultry"[All Fields] OR "Ducks"[Mesh]) OR "ducks"[All Fields] OR "Quail"[Mesh]) OR "quails"[All Fields] OR "Coturnix"[Mesh]) OR "Geese"[Mesh] OR "geese"[All Fields]))
	#3	"adverse effects" [Subheading]
	#4	#1 AND #2 AND #3
	#5	NOT (mice[Title] OR rat[Title] OR rats[Title] OR "in vitro"[Title])
	#6	#6 AND ("1950"[Date - Publication] : "3000"[Date - Publication])
	#7	#5 AND "english"[Language]
HITS combined WOS + pubMED = 1,015 (w/o duplicate in EndNote) Date of search:19.04.2016		

Table 36. Search strings used to retrieve studies on the adverse effects in **fish**

Database	**Web of Science™**	
Search strategy	**#1**	TS=(TCDD OR dioxins OR *dioxin OR dioxin-like* OR coplanar OR PCB* OR polychlorinated biphenyl* OR PCDD* OR PCDF*)
	#2	TS=(trout OR trouts OR salmon OR "sea bream" OR seabream OR "sea bass" OR seabass OR turbot OR carp OR sturgeon OR eel OR eels OR tilapia OR cod OR halibut OR cobia OR "milk fish" OR tuna OR "tuna fish" OR tunafish)
	#3	TS=(*toxic* OR adverse OR effect OR effects OR "adverse effects" OR fertility OR disease* OR diseases)
	#4	(#1) AND (#2) AND (#3)
	#5	#4 NOT TS=(rat OR rats OR mice OR mouse OR monkey OR monkeys OR "guinea pig" OR guinea-pig OR guineapig OR "mini pig" OR minipig OR rabbit OR rabbits OR hamster OR hamsters OR dog OR dogs OR cat OR cats OR mink OR minks)
	#6	#5 NOT TS=(zebrafish OR "zebra fish" OR medaka OR "Danio rerio" OR "Oryzias latipes" OR mummichog* OR killifish OR "Fundulus heteroclitus" OR fundulus OR minnows OR "Pimephales promelas" OR "human milk" OR birds OR "in vitro" OR transfer OR "carry over" OR carry-over OR carryover)
	#7	#6 NOT TI=(survey OR monitoring OR trend)
	#8	#7 AND PY=(1950-date of the search)
	#9	#8 *Refine by* LANGUAGE=(English)
	#10	#9 *Refine by* DOCUMENT TYPES: (article OR review OR correction) (exclude the remaining)
	#11	#10 *Refine by* DATABASE: exclude Chinese and Korean an Russian (if appear)
Database	**PubMed**	
Search Strategy	**#1**	"dioxins"[MeSH Terms] OR "Tetrachlorodibenzodioxin"[Mesh]) OR ("polychlorinated biphenyls"[MeSH Terms]
	#2	("trout"[MeSH Terms] OR "trout"[All Fields]) OR ("salmon"[MeSH Terms] OR "salmon"[All Fields] OR "salmo salar"[MeSH Terms] OR ("salmo"[All Fields] AND "salar"[All Fields]) OR "salmo salar"[All Fields]) OR "sea bream"[All Fields] OR "sea bass"[All Fields] OR "turbot"[All Fields] OR ("carps"[MeSH Terms] OR "carps"[All Fields] OR "carp"[All Fields]) OR sturgeon$[All Fields] OR eel$[All Fields] OR ("tilapia"[MeSH Terms] OR "tilapia"[All Fields]) OR cod$[All Fields] OR ("flounder"[MeSH Terms] OR "flounder"[All Fields] OR "halibut"[All Fields]) OR cobia[All Fields] OR "milk fish"[All Fields] OR "Tuna"[Mesh]
	#3	"adverse effects" [Subheading]
	#4	#1 AND #2 AND #3
	#5	NOT (mice[Title] OR rat[Title] OR rats[Title] OR "in vitro"[Title] OR zebrafish[Title] OR "zebra fish" [Title] OR medaka[Title] OR "Danio rerio" [Title] OR "Oryzias latipes" [Title] OR mummichog$[Title] OR killifish[Title] OR "Fundulus heteroclitus" [Title] OR fundulus[Title] OR minnow$[Title] OR "Pimephales promelas"[Title]) NOT (survey[Title] OR monitoring[Title] OR trend[Title])
	#6	#6 AND ("1950"[Date - Publication] : "3000"[Date - Publication])
	#7	#5 AND "english"[Language]
HITS combined WOS + pubMED = 1,860 (w/o duplicate in EndNote)		

Date of search: 02.05.2016

Table 37. Search strings used to retrieve studies on the adverse effects in **horses**

Database	**Web of Science™**	
Search strategy	**#1**	TS=(TCDD OR dioxins OR *dioxin OR dioxin-like* OR coplanar OR PCB* OR polychlorinated biphenyl* OR PCDD* OR PCDF*)
		TS=(horse OR horses)
	#3	TS=(*toxic* OR adverse OR effect OR effects OR "adverse effects" OR fertility OR disease* OR diseases)
	#4	(#1) AND (#2) AND (#3)
	#5	#4 NOT TS=(rat OR rats OR mice OR mouse OR monkey OR monkeys OR "guinea pig" OR guinea-pig OR guineapig OR "mini pig" OR minipig OR rabbit OR rabbits OR hamster OR hamsters OR dog OR dogs OR cat OR cats OR mink OR minks)
	#6	#5 NOT TI=(zebrafish OR medaka OR "human milk" OR birds OR "in vitro" OR transfer OR "carry over" OR carry-over OR carryover)
	#7	#6 AND PY=(1950-date of the search)
	#8	#7 *Refine by* LANGUAGE=(English)
	#9	#8 *Refine by* DOCUMENT TYPES: (article OR review OR correction)
	#10	#9 *Refine by* DATABASE: exclude Chinese and Korean an Russian (if appear)
Database	**PubMed**	
Search Strategy	**#1**	"dioxins"[MeSH Terms] OR "Tetrachlorodibenzodioxin"[Mesh]) OR ("polychlorinated biphenyls"[MeSH Terms]
	#2	"Horses"[Mesh] OR "horse"[All Fields] OR "horses"[All Fields]
	#3	"adverse effects"[Subheading]
	#4	#1 AND #2 AND #3
	#5	#4 AND ("1950"[Date - Publication] : "3000"[Date - Publication])
	#6	#5 AND "english"[Language]
HITS combined WOS + pubMED = 60 (w/o duplicate in EndNote) Date of search: 19.04.2016		

A.2.3. Toxicokinetics and transfer

The search strings used for the identification of studies relevant to inform the section on toxicokinetics in farm animals and transfer of PCDD/Fs and DL-PCBs from food producing animals (sub-questions 18 and 19) are shown in Table 38 for the different animal species (ruminants, pigs, poultry, fish and horses).

The studies were transferred from the databases to EndNote where a first check for duplicates was carried out. The references where then transferred to the web-based systematic review software DistillerSR. A second duplicate check was done, followed by a two-step selection for relevance by two independent reviewers according to the eligibility criteria set in Annex A.1 to this scientific opinion. The outcome of this selection is discussion in Section 3.1.1 of the scientific opinion.

Table 38. Search strings used to retrieved studies on the **toxicokinetics and transfer in livestock**

Database	**Web of Science™**	
Search strategy	**#1**	TS=(TCDD OR dioxins OR *dioxin OR dioxin-like* OR coplanar OR PCB* OR polychlorinated biphenyl* OR PCDD* OR PCDF*)
	#2	TS=(administration OR absorption OR distribution OR "tissue distribution" OR bioavailab* OR metaboli* OR biotransform* OR activat* OR half-li* OR excret* OR clearance OR eliminat* OR bioconcentrat* OR *kinetic* OR PBPK OR PBK OR transfer OR carry-over OR carryover OR "carry over")
	#3	**A** - TS=(ruminant* OR cattle OR cow* OR bovine* OR sheep* OR goat* OR buffal*) **B** - TS=(swine OR pig*) **C** - TS=(poultry OR chicken* OR turkey* OR duck* OR quail* OR goose*) **D** - TS=(trout OR trouts OR salmon OR "sea bream" OR seabream OR "sea bass" OR seabass OR turbot OR carp OR sturgeon OR eel OR eels OR tilapia OR cod OR halibut OR cobia OR "milk fish" OR tuna OR tunafish OR "tuna fish") **E** - TS=(horse*) **F -** TS=(ostrich OR ostriches)
	#4	(#1) AND (#2) AND (#3)
	#5	#4 NOT TS=(rat* OR mice* OR mouse OR monkey* OR "guinea pig" OR "mini pig" OR rabbit* OR hamster* OR dog* OR cat* OR mink*) For **B**-PIGS: NOT=TS=(*pigment*) For **D**-FISH: NOT TS=(zebrafish OR "zebra fish" OR "Danio rerio" OR medaka OR "Oryzias latipes" OR mummichog* OR killifish OR "Fundulus heteroclitus" OR fundulus OR minnows OR "Pimephales promelas" OR "model fish") NOT TI=(survey OR monitoring OR trend)
	#6	#5 AND PY=(1998-date of the search)
	#7	#6 *Refine by* LANGUAGE=(English)
	#8	#7 *Refine by* DOCUMENT TYPES: (article OR review)
	#9	#8 *Refine by* DATABASE
Database	**PubMed**	
Search Strategy	**#1**	All fields (TCDD OR dioxins OR *dioxin OR dioxin-like* OR coplanar OR PCB* OR polychlorinated biphenyl* OR PCDD* OR PCDF*)
	#2	All fields (administration OR absorption OR distribution OR "tissue distribution" OR bioavailab* OR metaboli* OR biotransform* OR activat* OR half-li* OR excret* OR clearance OR eliminat* OR bioconcentrat* OR *kinetic* OR PBPK OR PBK OR transfer OR carry-over OR carryover OR "carry over")
	#3	**A** – (ruminant* OR cattle OR cow* OR bovine* OR sheep* OR goat* OR buffal*) **B** - (swine OR pig*) **C** - (poultry OR chicken* OR turkey* OR duck* OR quail* OR goose*) **D** - (trout OR trouts OR salmon OR "sea bream" OR seabream OR "sea bass" OR seabass OR turbot OR carp OR sturgeon OR eel OR eels OR tilapia OR cod OR halibut OR cobia OR "milk fish" OR tuna OR tunafish OR "tuna fish") **E** - (horse*) **F** – (ostrich OR ostriches OR "Struthioniformes"[Mesh])
	#4	#1 AND #2 AND #3
	#5	#4 NOT (rat* OR mice* OR mouse OR monkey* OR guinea pig OR mini pig OR rabbit* OR hamster* OR dog* OR cat* OR mink*) For **D** – FISH: NOT (zebrafish OR "zebra fish" OR "Danio rerio" OR medaka OR "Oryzias latipes" OR mummichog* OR killifish OR "Fundulus heteroclitus" OR fundulus OR minnows OR "Pimephales promelas" OR "model fish") NOT tittle (survey OR monitoring OR trend)
	#6	#5 AND ("1998"[Date - Publication] : "3000"[Date - Publication])
	#7	#6 AND "english"[Language]

A – Ruminants WOS+PUBMED = 336 hits (w/o duplicates in EndNote). Date of search:10.05.2016
B – Pigs. WOS+PUBMED = 178 hits (w/o duplicates in EndNote). Date of search:07.06.2016
C – Poultry. WOS+PUBMED = 440 hits (w/o duplicates in EndNote). Date of search: 03.06.2016
D – Fish. WOS+PUBMED = 1,073 hits (w/o duplicates in EndNote). Date of search: 19.06.2016
E – Horse. WOS+PUBMED = 48 hits (w/o duplicates in EndNote). Date of search: 12.04.2016
F – Ostriches. WOS+PUBMED = 2 hits (w/o duplicates in EndNote). Date of search: 28.04.2016

ANNEX A.3. FEED INTAKES AND DIET COMPOSITION FOR LIVESTOCK AND COMPANION ANIMALS

This Annex A.3 gives details of the feed intakes, live weights and diet compositions for different livestock, fish and companion animals which were used as the basis to estimate exposures. These are based on published guidelines on nutrition and feeding (e.g. Carabano and Piquer, 1998; NRC 2000, 2007a,b; Ewing, 2002; Leeson and Summers, 2008; OECD, 2009; McDonald et al., 2011; EBLEX, 2008, 2012; EFSA FEEDAP Panel, 2012) and information provided by European feed manufacturers. They are therefore estimates of the EFSA Scientific Panel on Contaminants in the Food Chain (CONTAM Panel), but agree with common practice.

In Table 39 the concentrations of PCDD/Fs and DL-PCBs in feeds used to estimate exposure are presented.

Table 39. Levels of the sum of PCDD/Fs and DL-PCBs (29 congeners) and the sum of PCDD/Fs (17 congeners) (pg WHO_{2005}-TEQ/kg DM) in species-specific compound/complementary feeds and feed materials used to estimate exposure by farmed livestock and companion animals

	Sum of PCDD/Fs and DL-PCBs (29 congeners)				Sum of PCDD/Fs (17 congeners)			
	Mean		P95		Mean		P95	
	LB	UB	LB	UB	LB	UB	LB	UB
Compound/complementary feeds								
Horses			95.4	96.6			36.3	50.4
Pig: growing/fattening			143	168			60.9	66.2
Pig: breeding			186	217			186	190
Poultry (starter diet)	17.3	31.7	32.6	68.2	6.8	19.5	20.5	40.5
Fattening chickens			297	323			297	299
Salmonids	609	660	1,345	1,348	144	194	411	476
Rabbits			94.0	107			58.6	76.2
Dogs			488	501			462	467
Feed materials								
Wheat	37.5	60.2	239	304	10.2	31.0	81.9	173
Barley	16.9	28.5	45.5	54.0	4.5	14.9	14.5	32.6
Maize (corn)	37.3	54.2	174	189	27.9	42.5	99.9	116
Soybean meal	21.1	33.2	204	205	13.2	24.8	171	171
Rapeseed meal	12.1	27.4	30.2	52.6	4.8	19.7	10.9	48.5
Sunflower meal	20.1	46.7	99.6	145	4.7	28.4	25.7	71.4
Fishmeal	676	743	1,762	1,763	239	304	719	756
Minerals	40.2	149	180	248	28.4	131	23.1	150
Forages								
Forages [(a)]	128	149	372	372	65.9	85.9	231	240
Maize silage	58.1	77.3	139	142	32.4	50.1	105	112

(a): Forages and roughages and products thereof.

A.3.1. Feed intakes

A.3.1.1. Cattle, sheep, goats and horses

Dairy cows

The amounts of feed given to lactating dairy cows vary according to the quantity and quality of forages and other feeds available, the weight of the cow, its physiological status (e.g. pregnancy) and its milk yield. In this Opinion, it is assumed that non-forage feeds are fed at the rate of 0.3 kg/kg of milk produced (Nix, 2010). Exposures to the sum of PCDD/Fs and DL-PCBs (29 congeners) and to the sum of PCDD/Fs (17 congeners) have been estimated for a 650-kg dairy cow, with a milk yield of 40 kg per day. Assumptions on the amounts of forages and non-forage feeds for dairy cows fed on grass and maize silage are given in Table 40.

Beef cattle

There are a wide variety of beef production and husbandry systems in Europe. They may be categorised broadly as forage-based or cereal-based systems, although combinations of these systems are commonly found. In this Opinion, four feeding systems are considered, in which the forages are: (1) grass hay, (2) maize silage, and (3) cereal straw with, in each case, appropriate supplementation with non-forage feed materials. A fourth system, commonly known as 'cereal beef', is also considered. For exposure estimates, live weights of 300 or 400 kg, and feed intakes of between 6.6 and 10 kg dry matter (DM) per day have been assumed, depending on the feeding regime, based on guidelines published by EBLEX (2008, 2012), and details are given in Table 40.

Sheep and goats

Many breeds and systems of management have been developed for sheep and goats to suit the land, climate and husbandry conditions in the EU. As for other ruminants, forages may be the only feeds used after weaning (NRC, 2007a). Common exceptions to this are pregnant and lactating animals, whose feed is usually supplemented with non-forage feeds or commercial compound (complementary) feeds (AFRC, 1993; NRC, 2007a).

In this Opinion, exposure estimates have been made for lactating sheep and goats. The CONTAM Panel has used a daily dry matter intake of 2.8 kg for an 80-kg lactating sheep feeding twin lambs to estimate the exposures. For lactating goats, the CONTAM Panel has used daily dry matter intakes of 3.4 kg for a 60-kg goat for milking (4 kg milk/day); for fattening goats, a body weight of 40 kg and feed intake of 1.5 kg DM/day has been assumed, of which 60% is forage.

Horses

Horses are non-ruminant herbivores. They generally consume 2–3.5 % of their body weight in feed (DM) each day, of which a minimum of 50% should be as forage (pasture grass or hay) (NRC, 2007b). Assumed intakes are given in Table 40.

Table 40. Live weights, growth rate/productivity, dry matter intake for cattle, sheep, goats and horses, and the proportions of the diet as non-forage

	Live weight (kg)	Growth rate or productivity	Dry matter intake (kg/day)	% of diet as non-forage feed	Reference
Dairy cows, lactating [(a)]	650	40 kg milk/day	20.7	40	OECD (2009)
Fattening cattle: beef [(b)]	400	1 kg/day	9.6	15	AFRC (1993)
Fattening cattle: maize silage-based ration	300	1.4 kg/day	6.6	25	Browne et al. (2004)
Fattening cattle: cereal beef	400	1.4 kg/day	10.0	85	EBLEX (2012)
Sheep: lactating	80	Feeding twin lambs	2.8	50	OECD (2009)
Goats: lactating	60	6 kg milk/day	3.4	65	NRC (2007a)
Goats: fattening	40		1.5	40	
Horses	450	Moderate activity	9.0	50	NRC (2007b)

(a): Months 2–3 of lactation. The same levels of feed intake and productivity have been applied for both grass and maize silage-based diets
(b): Housed castrate cattle, medium maturing breed.

A.3.1.2. Non-ruminant animals

Pigs

Although there is a considerable range of pig production systems in Europe, exposure estimates have been made for piglets (pig starter), finishing pigs and lactating sows (using feed intakes proposed by EFSA FEEDAP Panel, 2012). Details are given in Table 41.

Poultry

The CONTAM Panel applied the live weights and feed intakes reported for fattening chickens (broilers), laying hens and fattening turkeys proposed by EFSA (2009) and for fattening ducks by Leeson and Summers (2008) (Table 41).

Farmed fish (salmonids and carp)

Commercially reared species include Atlantic salmon, rainbow trout, sea bass, sea bream, cod, halibut, tuna, eel and turbot. In this Scientific Opinion exposures to PCDD/Fs and DL-PCBs have been made for farmed salmon and carp. Details of the body weights and feed intakes used are given in Table 41.

Table 41. Live weights and feed intake for pigs, poultry (EFSA FEEDAP Panel, 2012), ducks (Leeson and Summers, 2008) and fish

	Live weight (kg)	Feed intake (kg dry matter/day)	Reference
Pigs: starter	20	1.0	EFSA (2012)
Pigs: finishing	100	3.0	EFSA (2012)
Pigs: lactating sows	200	6.0	EFSA (2012)
Poultry: broilers [(a)]	2	0.12	EFSA (2012)
Poultry: laying hens	2	0.12	EFSA (2012)
Turkeys: fattening turkeys	12	0.40	EFSA (2009)
Ducks: fattening ducks	3	0.14	Leeson and Summers (2008)
Salmonids	2	0.04	EFSA (2012)
Carp	1	0.02	Schultz et al. (2012)

(a): Fattening chickens.

Rabbits

Feed intakes of 65–80 g/kg bw per day have been reported (Carabano and Piquer, 1998). For the exposure estimates, the CONTAM Panel have assumed a live weight of 2 kg, and a daily feed intake of 75 g/kg bw (derived from Carabano and Piquer, 1998).

Farmed mink

For estimating exposure, the CONTAM Panel have assumed a live weight of 2.07 kg for a male mink at pelting, and with a feed intake of 227 g fresh weight per day (75 g DM) (NRC, 1982).

Companion animals: dogs and cats

The amount of food consumed is largely a function of the mature weight of the animal, level of activity, physiological status (e.g. pregnancy or lactation) and the energy content of the diet. In this Scientific Opinion, the CONTAM Panel assumed body weights (kg) and feed intakes (g DM/day) for dogs and cats of 25/360 and 4/60, respectively (derived from NRC, 2006).

A.3.2. Diet composition

Many livestock in the European countries are fed proprietary commercial compound feeds. Where sufficient data have been provided on species-specific compound feeds, estimates of exposure have been made using these data (given in Table 39) together with estimated intakes given in this Annex A.3.1. Where data on proprietary compound feeds were not available, or were available but in insufficient numbers, estimates of exposure have been made using dietary inclusion rates of feed materials given in this section. Levels of PCDD/Fs and DL-PCBs in species-specific compound/complementary feeds or feed materials used to estimate exposure are given in Table 39.

A.3.2.1. Cattle, sheep, goats and horses

For most ruminants and horses, forages (either fresh or conserved as silage or hay) are important ingredients in their diet, but they are normally supplemented with non-forage feeds such as cereals, cereal by-products, oilseed meals and by-products of human food production. These may be fed

either as individual feeds, mixtures of feed materials, or as species-specific complementary feeds in the form of compound feeds. In some situations, however, forages may represent the total diet.

The data submitted to EFSA were predominantly in the general category of 'Forages and roughages and products thereof' (n = 57), and these were used to estimate exposure for lactating dairy cows, lactating sheep, and lactating and fattening goats. Data were also provided on levels of PCDD/Fs and DL-PCBs in 'Maize silage' (n = 18), and these have been used to estimate mean LB and UB exposure in dairy and beef systems where maize silage is the main forage. Insufficient data were available for grass hay or cereal straws, and therefore no estimates of exposure have been possible for those livestock for which these are the predominant forages.

In the absence of data on the levels of PCDD/Fs and DL-PCBs (29 congeners) or of PCDD/Fs (17 congeners) in species-specific compound feeds for dairy cows, beef cattle, lactating sheep, and milking or fattening goats, example rations (Table 42) have been used, together with the sum of PCDD/Fs and DL-PCBs (29 congeners) or the sum of PCDD/Fs (17 congeners) in the individual ingredients to estimate exposure.

Maize silage is widely used in diets for lactating dairy cows and beef cattle. AFSSA (2009) have provided example intakes of dairy cows fed maize silage supplemented with maize grain and soybean meal, while example diets of beef cattle on maize silage diets are taken from EBLEX (2012), and these are given in Table 43.

For lactating sheep and goats, and for fattening goats, levels of PCDD/Fs and DL-PCBs in species-specific compound feed data were not available and therefore example diets (Table 42) and levels of the sum of PCDD/Fs and DL-PCBs (29 congeners) or the sum of PCDD/Fs (17 congeners) in individual feeds (Table 39) have been used, together with levels in 'Forages and roughages and products thereof' to estimate exposure.

Horses are non-ruminant herbivores, and consequently their diet should contain a minimum of 50% forages. In this Opinion, the CONTAM Panel have used data available on levels of PCDD/Fs and DL-PCBs in complementary feeds for horses (Table 39) to estimate exposure.

Table 42. Assumed diet compositions (%) for lactating sheep, goats and cows, and fattening goats

Non-forage feed materials	Lactating dairy cows	Lactating sheep	Lactating goats	Fattening goats
% of non-forage feeds in the diet	40	50	75	40
Composition of the non-forage feeds				
Wheat (%)	15	14	ni	ni
Barley (%)	20	18	25	20
Oats (%)	ni	ni	35	40
Soybean meal (%)	5	5	10	10
Rapeseed meal (%)	20	10	10	10
Sunflower meal (%)	ni	5	ni	ni
Beans (%)[(a)]	5	10	ni	ni
Maize gluten feed (%)	10	ni	ni	ni
Wheat feed (%)[(a)]	10	15	10	10
Oat feed (%)[(a)]	ni	ni	ni	ni
Sugar beet pulp (%)[(a)]	7	14	1	1
Molasses (%)[(a)]	3	4	4	4
Vegetable oils (%)[(a)]	3	5	5	5
Minerals, vitamins etc (%)[(a)]	2	ni	ni	ni

ni: not included in the diet formulations.

(a): No data for the sum of PCDD/Fs and DL-PCBs (29 congeners) and to the sum of PCDD/Fs (17 congeners) were available, and therefore no contribution from these feeds has been assumed.

Table 43. Assumed diet compositions and feed intake of lactating dairy cows (40 litres/day) and fattening beef cattle fed diets based on different forages

Animal species	Forage	Maize grain	Soybean meal	Barley grain	Rapeseed meal	Reference
Lactating dairy cows: maize silage-based diet	15.0	9.5	2.8	ni	ni	AFSSA (2009)
Fattening beef cattle: maize silage-based diet	4.9	ni	ni	ni	1.5	EBLEX (2012)

ni: not included in the diet formulations.

A.3.2.2. Pigs and poultry

Sufficient data for species-specific compound feeds for pigs, and for most categories of poultry (fattening chickens, ducks and turkeys, and for laying hens), were provided (see Table 39) together with assumed live weights and feed intakes (see Table 41) were used to estimate exposure to the sum of PCDD/Fs and DL-PCBs (29 congeners) and to the sum of PCDD/Fs (17 congeners).

A.3.2.3. Rabbits

Rabbits are usually fed a pelleted diet (in the form of complete feedingstuffs) consisting of dried forages, cereals and vegetable proteins supplemented with minerals, vitamins and trace elements. Lebas and Renouf (2009) reviewed diet formulations used in experimental studies: in 58 diets, cereals and cereal by-products (mostly wheat bran) accounted for up to 40% of all ingredients. In these studies, maize was a major cereal grain and was included in more than one-third of all diets. In northern Europe, however, maize may be replaced by barley and wheat. In this opinion, the feed ingredients used in a typical French commercial rabbit compound, as provided by T. Gidenne, (Personal communication, 2011) have been used, details of which are given in Table 44.

A.3.2.4. Farmed fish (salmonids and carp)

In this Opinion, exposure to PCDD/Fs and DL-PCBs by salmonids has been derived from data provided to EFSA on levels in complementary or complete feeds for fish. Although the species to which these were intended to be fed has not been defined, the data have been used for salmonids, since this accounts for the majority of fish food manufactured in the EU.

In contrast to salmonids, common carp (*Cyprinus cardio*) have a greater ability to utilise carbohydrates. As a result, diets for this species typically contain more cereals and vegetable proteins. The CONTAM Panel have used the ingredients of commercial compound feeds for carp reported by Schultz et al. (2012) to estimate exposure to PCDD/Fs and DL-PCBs in Table 44.

A.3.2.5. Farmed mink

Mink are carnivorous animals and are fed high protein diets consisting mainly of meat and meat by-products. Commercially manufactured mink feed consists largely of fish and land animal by-products, with lesser amounts of cereals and cereal by-products, and supplemented with mineral/vitamin premixtures. Mink are fed diets high in protein, although their nutritional requirements vary according to the animal's physiological stage (e.g. gestating, lactating and growing) and climatic conditions, particularly temperature. The proportions of cereal grains, their products and by-products used in estimating the exposure are given in Table 44.

A.3.2.6. Companion animals (dogs and cats)

Most small companion animals derive their nutritional needs from processed food, and in 2010 EU annual sales of pet food products was approximately 8.3 million tonnes.[10] Although a wide range of ingredients is used in commercial diets, most dog and cat diets contain at least some animal protein. Other ingredients include cereals (predominantly wheat, rice or maize), cereal by-products, vegetable

[10] Available online: www.Fediaf.org

proteins and by-products of human food production. The ingredients will vary depending both on the availability of feed materials and the nutrient requirements of the animals.

The European Pet Food Industry Federation (FEDIAF) has provided information on typical inclusion levels of cereals, cereal by-products and other feed materials in dry cat food[11]. In the absence of sufficient data on species-specific manufactured complete feedingstuffs, the CONTAM Panel has used example diets based on information provided by FEDIAF[11] (details given in Table 44).

Table 44. Assumed diet composition (%) for farmed fish (salmonids and carp), farmed rabbits, farmed mink and companion animals (cats and dogs)

Inclusion levels in the diet	Farmed fish		Farmed rabbits	Farmed mink [(b)]	Companion animals	
	Salmon	Carp			Cats	Dogs
Compound feed (%)	100	0	0	0	0	100
Wheat (%)		24	ni	6	10	
Barley (%)		ni	ni	1	ni	
Maize (%)		10	17.6	6	5	
Oats (%)		ni	ni	ni	1	
Soybean meal (%)		32.4	ni	ni	8	
Rapeseed meal (%)		12.5	ni	ni	ni	
Maize gluten meal (%)		ni	ni	ni	17	
Sunflower meal (%)[(a)]		ni	20.0	ni	ni	
Lucerne meal (%)[(a)]		ni	19.1	ni	ni	
Beans (%)[(a)]		ni	10.4	ni	1	
Peas (%)		7.5	ni	ni	ni	
Wheat feed (%)		ni	18.3	ni	12	
Sugar beet pulp (%)		ni	11.9	ni	ni	
Fishmeal (%)		6.7	ni	ni	6	
Meat meal (%)[(a)]		ni	ni	40	38	
Molasses (%)[(a)]		ni	ni	ni	ni	
Fish and vegetable oils (%)[(a)]		3.6	ni	8	ni	
Other feeds (unspecified) (%)[(a)]		1.3	ni	ni	ni	
Minerals, vitamins, etc (%)[(a)]		2.0	2.7	3	2.0	

ni: not included in the diet formulations.

(a): No data sum of PCDD/Fs and DL-PCBs (29 congeners) or the sum of PCDD/Fs (17 congeners) were available, and therefore no contribution from these feeds has been assumed

(b): Diet formulation based on data provided by the Finnish Fur Breeders Association in 2015 and translated from Finnish to English, www.profur.fi

[11] The European Pet Food Industry Federation (FEDIAF), Personal communication by email, May 2016

ANNEX A.4. STUDIES ON THE TRANSFER OF PCDD/FS AND DL-PCBS IN FOOD PRODUCING ANIMALS

A.4.1. Studies in ruminants

Table 45. Studies retrieved in the literature search and selection for relevance to inform about toxicokinetics and transfer in **cows and buffaloes**

Reference	Species	Compounds	Comments
Thomas et al. (1999). Metabolism and body-burden of PCBs in lactating dairy cows.	Dairy Cows	PCB-105, PCB-118	PCB-105 and -118. Background exposure. *Study not useful for transfer.*
Fries et al. (1999). A congener specific evaluation of transfer of PCDDs and PCDFs to milk of cows following ingestion of pentachlorophenol-treated wood.	Dairy Cows	Mixtures of PCDD/Fs	
Malisch (2000). Increase of the PCDD/F-contamination of milk, butter and meat samples by use of contaminated citrus pulp.	Dairy Cows	Mixture of PCDD/Fs	Follow-up of citrus pulp incident
Feil et al. (2000). Chlorinated dibenzo-*p*-dioxin and dibenzofuran concentrations in beef animals from a feeding study.	Beef Cows	Mixtures PCDD/Fs, DL-PCBs	No data in tissues. Also PCP contamination stable. study useful but only for Tetra- and Penta-CDD/Fs congeners
Thorpe et al. (2001). Concentration changes for 5 PCDD/F congeners after administration in beef cattle.	Beef Cows	TCDD, 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF	Study useful for some congeners
Fries et al. (2002). Complete mass balance of dietary PCDDs and PCDFs in dairy cattle and characterization of the apparent synthesis of hepta- and octachlorodioxins.	Dairy Cows	Mixtures of PCDD/Fs	
Huwe et al. (2004). Levels of PCDDs and PCDFs in cattle raised at agricultural research facilities across the USA and the influence of PCP-treated wood.	Beef Cows	Mixtures PCDD/Fs	Only levels in meat from different farms. No intake studied. *Study not useful for transfer.*
Hirako et al. (2005). Comparison of the concentrations of PCDDs, PCDFs, and DL-PCBs in maternal and fetal blood, amniotic and allantoic fluids in cattle.	Beef Cows	Mixtures PCDD/Fs, DL-PCBs	No data on intake. Only comparison of non-edible tissues. *Study not useful for transfer.*
Huwe and Smith (2005). Laboratory and on-farm studies on the bioaccumulation and elimination of dioxins from a contaminated mineral supplement fed to dairy cows.	Dairy Cows	Mixtures of PCDD/Fs + DL-PCBs	Both exposure and elimination period
Hirako (2008a). Transfer and accumulation of persistent organochlorine compounds from bovine dams to newborn and suckling calves.	Beef Cows	Mixtures PCDD/Fs, DL-PCBs	Exposure to low background levels; levels in milk and blood dams and calves. *Study not useful for transfer.*
Hirako (2008b). Distribution of PCDDs, PCDFs and dioxin-like PCBs in the blood, testis and adipose tissue of suckling beef calves.	Beef Cows	Mixtures PCDD/Fs, DL-PCBs	Field study. No information on on exposure. Only very young calves and only data in testes and adipose tissue. *Study not useful for*

Reference	Species	Compounds	Comments
			transfer.
Hoogenboom et al. (2010). Kaolinic clay derived PCDD/Fs in the feed chain from a sorting process for potatoes.	Dairy Cows	Mixtures of PCDD/Fs	Only elimination period
Petro et al. (2010). Occurrence of endocrine disrupting compounds in tissues and body fluids of Belgian dairy cows and its implications for the use of the cow as a model to study endocrine disruption.	Dairy Cows	PCB-105, PCB-118, PCB-156, PCB-167	*Study not useful for transfer*
Rossi et al. (2010). Monitoring of the declining trend of Polychlorobifenyls concentration in milk of contaminated dairy cows.	Dairy Cows	PCB-118	Only depletion. *Study not useful for transfer.*
De Filippis et al. (2013). PCDD/Fs and DL-PCBs distribution in tissues and dairy products of dairy buffaloes.	Buffaloes	Mixtures PCDD/Fs, DL-PCBs	Comparison of milk and tissue levels at 1 time-point
Hoogenboom et al. (2015a). Carry-over of PCDD/Fs and PCBs in dairy cows fed smoke contaminated maize silage or sugar beet pulp.	Dairy Cows	Mixtures PCDD/Fs, DL-PCBs	Both exposure and elimination period

Table 46. Studies retrieved in the literature search and selection for relevance to inform about the toxicokinetics and transfer in **sheep**

Reference	Species	Compounds	Comments
Jan et al. (1999). Tissue distribution of planar and non-planar chlorobiphenyls, 4,4'-DDE and hexachlorobenzene in sheep and lambs.	Sheep	PCB-169	i.m injection; not oral. Blood, adipose tissue, brain and liver analysed; liver sequestration of PCB 169. *Study not useful for transfer.*
Jan et al. (2001). Bioconcentration of lipophilic organochlorines in ovine dentine.	Sheep	PCB-169	i.m injection, not oral. Co-exposure with HCB/DDT. Adipose tissue and teeth analysed. *Study not useful for transfer.*
Vrecl et al. (2005). Excretion pattern of co-planar and non-planar tetra- and hexa-chlorobiphenyls in ovine milk and faeces.	Sheep	PCB-169	PCB-169, single injection; not oral. *Study not useful for transfer.*
Jan et al. (2006). Distribution of organochlorine pollutants in ovine dental tissues and bone.	Sheep	PCB-169	i.m. injection (not oral). No edible tissues analysed. *Study not useful for transfer.*
Rhind et al. (2009). Accumulation of endocrine disrupting compounds in sheep fetal and maternal liver tissue following exposure to pastures treated with sewage sludge.	Sheep	PCB-118	*Study not useful for PCDD/Fs and DL-PCBs relevant for TEQ.*
Rhind et al. (2010). Maternal and fetal tissue accumulation of selected endocrine disrupting compounds (EDCs) following exposure to sewage sludge-treated pastures before or after conception.	Sheep	PCB-118	*Study not useful for PCDD/Fs and DL-PCBs relevant for TEQ*
Berg et al. (2010). Distribution of PCB 118 and PCB 153 and hydroxylated PCB metabolites (OH-CBs) in maternal, fetal and lamb tissues of sheep exposed during gestation and lactation.	Sheep	PCB-118	*Study not useful for PCDD/Fs and DL-PCBs relevant for TEQ*
Rhind et al. (2011). Effect of duration of exposure to sewage sludge-treated pastures on liver tissue accumulation of persistent endocrine disrupting compounds (EDCs) in sheep.	Sheep	PCB-118	*Study not useful for PCDD/Fs and DL-PCBs relevant for TEQ*
Panton et al. (2013). Transfer and uptake of dioxins and polychlorinated biphenyls (PCBs) into sheep: a case study.	Sheep	Mixtures PCDD/Fs, DL-PCBs	Review including field data. levels in feed low and too few animals per time point. *Study less suitable for transfer.*

Reference	Species	Compounds	Comments
Jan et al. (2013). Levels and distribution of organochlorine pollutants in primary dental tissues and bone of lamb.	Sheep	PCB-169	*i.m.* injection, not oral.; no data on edible tissues. *Study not suitable for transfer.*
Hoogenboom et al. (2015b). Accumulation of polychlorinated dibenzo-*p*-dioxins, dibenzofurans, and biphenyls in livers of young sheep.	Sheep	Mixtures PCDD/Fs, DL-PCBs	
Brambilla et al. (2016). Potential impact on food safety and food security from persistent organic pollutants in top soil improvers on Mediterranean pasture.	Sheep	Mixtures PCDD/Fs, DL-PCBs	Modelled data on soil improvers. No specific data on levels in sheep. *Study not useful for transfer*

Table 47. Studies retrieved in the literature search and selection for relevance to inform about the toxicokinetics and transfer in **goats**

Reference	Species	Compounds	Comments
Grova et al. (2002). C-14 Milk, urine and faeces excretion kinetics in lactating goats after an oral administration of C-14 polycyclic aromatic hydrocarbons.	Goats	TCDD	Only TCDD but still useful
Lyche et al. (2004a). Levels of PCB 126 and PCB 153 in plasma and tissues in goats exposed during gestation and lactation.	Goats	PCB-126	Only one congener, PCB-126 but co-exposure to PCB-153. *Study not useful for transfer.*
Fouzy and Ruoff (2006). Distribution of PCDDs/PCDFs into milk and organs of Egyptian Baladi goats after oral supplementation of dioxins.	Goats	Mixtures PCDD/Fs	Exposure poorly described with unlikely low levels in milk, not very different from controls. *Study not useful for transfer.*
Costera et al. (2006). PCDD/F and PCB transfer to milk in goats exposed to a long-term intake of contaminated hay.	Goats	Mixtures PCDD/Fs, DL-PCBs	
Ounnas et al. (2010). Polychlorinated biphenyl and low polybrominated diphenyl ether transfer to milk in lactating goats chronically exposed to contaminated soil.	Goats	Mixtures DL-PCBs	Both DL- and NDL-PCBs
Fournier et al. (2013). Polychlorinated biphenyl (PCB) decontamination kinetics in lactating goats (*Capra hircus*) following a contaminated corn silage exposure.	Goats	Mixtures PCDD/Fs, DL-PCBs	
Feidt et al. (2013). Relative bioavailability of soil-bound polychlorinated biphenyls in lactating goats.	Goats	PCB-118	Only PCB-118. Less relevant for TEQ. *Study not useful for transfer.*

A.4.2. Studies in poultry

Table 48. Studies retrieved in the literature search and selection for relevance to inform about the toxicokinetics and transfer in **poultry**

Reference	Species	Compounds	Comments
Zabik et al. (1998). Tissue residues in male chickens fed a 50 ng/kg dietary concentration of 2,3,7,8-TCDD.	Broilers	TCDD	Only TCDD at high level and only liver analysed. *Not useful for transfer.*
Bargar et al. (2001a). Maternal transfer of contaminants: case study of the excretion of three PCB congeners and technical-grade endosulfan into eggs by white Leghorn chickens (*Gallus domesticus*).	Laying hens	PCB-105 PCB-156 PCB-189	*i.m.* treatment, not oral. *Study not useful for transfer.*
Bargar et al. (2001b). Uptake and distribution of three PCB congeners and endosulfan by	Broilers	PCB-105 PCB-156	*s.c.* injection. *In ovo* exposure only embryos studied. *Study*

Reference	Species	Compounds	Comments
developing white leghorn chicken embryos (*Gallus domesticus*).		PCB-189	*not useful for transfer.*
Sucman et al. (2001). Studies on the transfer of harmful substances from feed to chicken tissues.	Broilers	PCB-118	No info on uptake. *Not useful for tasnfer.*
De Vos et al (2003). PCBs in broiler diets: their digestibility and incorporation in body tissues.	Broilers	PCB-118	Only PCB 118; less relevant for PCBs contributing to TEQ
Iben et al. (2003). Dioxin residues in the edible tissue of broiler chicken.	Broilers	Mixtures PCDD/Fs	Possibly useful for transfer
Maervoet et al. (2004). Accumulation and tissue distribution of selected polychlorinated biphenyl congeners in chickens.	Chicken	PCB-118	+ indicator PCBs. Only PCB 118; less relevant for PCBs contributing to TEQ
Maervoet et al. (2005). Uptake and tissue-specific distribution of selected polychlorinated biphenyls in developing chicken embryos.	Broilers	PCB-77	+ PCB-153 and -180. *In ovo* exposure. *Study not useful for transfer*
De Vos et al. (2005). Digestibility, retention and incorporation of low-level dietary PCB contents in laying hens.	Laying hens	PCB-118	Only PCB 118; less relevant for congeners contributing to TEQ levels
Nishimura et al. (2005). Dioxin concentrations in body tissues and egg of female chicken.	Laying hens	Mixtures PCDD/Fs, DL-PCBs	Field study with background levels and no increase in egg levels. *Levels too low for transfer study*.
Pirard and De Pauw (2005). Uptake of PCDDs, PCDFs and coplanar PCBs in chickens.	Laying hens	Mixtures PCDD/Fs, DL-PCBs	Laying hens; egg production decreased for no obvious reason. *Study not suitable for transfer.*
Zhao et al. (2006). Evidence for the transfer of PCBs and PCDD/Fs from soil into biota.	Chicken	Mixtures PCDD/Fs, DL-PCBs	Very few samples analyzed. *Study not suitable for transfer*.
Van Eijkeren et al. (2006). A toxicokinetic model for the carry-over of dioxins and PCBs from feed and soil to eggs.	Laying hens	Mixtures PCDD/Fs, DL-PCBs	PBPK model. Data from Hoogenboom et al. (2006).
Pirard and De Pauw (2006). Toxicokinetic study of dioxins and furans in laying chickens.	Laying hens	Mixtures PCDD/Fs	
Hoogenboom et al. (2006). Carry-over of dioxins and PCBs from feed and soil to eggs at low contamination levels - influence of mycotoxin binders on the carry-over from feed to eggs.	Laying hens	Mixtures PCDD/Fs, DL-PCBs	
Traag et al. (2006). Residues of dioxins (PCDD/Fs) and PCBs in eggs, fat and livers of laying hens following consumption of contaminated feed.	Laying hens	Mixtures PCDD/Fs, DL-PCBs	
Parera et al. (2008). Occurrence and bioaccumulation study of PCDD and PCDF from mineral feed additives.	Chicken	Mixtures PCDD/Fs	Exposure from clay; only livers examined. To some extent useful.
Brambilla et al. (2009). PCP, PCDDs and PCDFs in eggs from hens exposed to contaminated wood shavings.	Laying hens	Mixtures PCDD/Fs	
Shih et al. (2009). Uptake of PCDD/Fs in laying ducks.	Ducks	Mixtures of PCDD/Fs	Study shows BCFs for PCDD/Fs in duck eggs and meat.
Menotta et al. (2010). Depletion study of PCDD/Fs and dioxin-like PCBs concentrations in contaminated home-produced eggs: Preliminary study.	Laying hens	Mixtures PCDD/Fs, DL-PCBs	Only depletion studied and no intake levels determined. *Study not suitable for transfer*.
Fournier et al. (2012). Relative bioavailability to laying hens of indicator polychlorobiphenyls present in soil.	Laying hens	PCB-118	Only PCB-118. Study not useful for PCDD/Fs and DL-PCBs contributing most to TEQ**.**
Lin et al. (2012a). Coexposure of dioxin-like PCBs and PCDD/Fs in free-range hens and	Laying hens	Mixtures PCDD/Fs,	Study on levels on farms; some feed and soil analysed.

Reference	Species	Compounds	Comments
implications derived from congener profile analysis.		DL-PCBs	*Not a transfer study, so not suitable*.
Piskorska-Pliszczynska et al. (2014). Soil as a source of dioxin contamination in eggs from free-range hens on a Polish farm.	Laying hens	Mixtures PCDD/Fs, DL-PCBs	Ingestion of contaminated soil. *Study not useful for transfer feed to eggs.*
Zheng et al. (2015). Contaminant sources, gastrointestinal absorption, and tissue distribution of organohalogenated pollutants in chicken from an e-waste site.	Chicken	PCB-118	Limited information and only on PCB-118. *Study not useful for transfer.*

A.4.3. Studies in pigs

Table 49. Studies retrieved in the literature search and selection for relevance to inform about the toxicokinetics and transfer in **pigs**

Reference	Species	Compounds	Comments
Qiao and Riviere (2001). Enhanced systemic tissue distribution after dermal versus intravenous 3,3',4,4'-tetrachlorobiphenyl exposure: limited utility of radiolabel blood area under the curve and excretion data in dermal absorption calculations and tissue exposure assessment.	Swine	PCB-77	Dermal vs iv exposure. Not oral. *Study not useful for transfer*
Rychen et al. (2002). Milk-arterial plasma transfer of PCDDs and PCDFs in pigs.	Swine	Mixtures PCDD/Fs	Only plasma, no tissues. *Study not useful for transfer.*
Cavret et al. (2003). Intestinal absorption of 14C from 14C-phenanthrene, 14C-benzo[a]pyrene and 14C-tetrachlorodibenzo-para-dioxin: approaches with the Caco-2 cell line and with portal absorption measurements in growing pigs.	Swine	TCDD	Only plasma levels. *Study not useful for transfer.*
Spitaler et al. (2005). Dioxin residues in the edible tissue of finishing pigs after dioxin feeding.	Swine	Mixtures PCDD/Fs	
Hoogenboom et al. (2007). A novel source for dioxins present in recycled fat from gelatin production.	Swine	Mixtures PCDD/Fs	Gelatin incident and use of PBPK model
Wittsiepe et al. (2007). Bioavailability of PCDD/F from contaminated soil in young Goettingen minipigs.	Swine	Mixtures PCDD/Fs	Study with soil, not feed; showing relatively poor bioavailability. *Study not suitable for estimating BCFs.*
Watanabe et al. (2010). Dioxin-like and perfluorinated compounds in pigs in an Indian open waste dumping site: toxicokinetics and effects on hepatic cytochrome P450 and blood plasma hormones.	Swine	Mixture PCDD/Fs, DL-PCBs	Exposure unknown; relevant information on liver sequestration.
Brambilla et al. (2011a). Bioaccumulation of dioxin-like substances and selected brominated flame retardant congeners in the fat and livers of black pigs farmed within the Nebrodi Regional Park of Sicily.	Swine	Mixture PCDD/Fs, DL-PCBs	Farmed and wild pigs; no data on exposure.
Rose et al. (2012). Transfer and uptake of polychlorinated dibenzo-*p*-dioxins and furans (PCDD/Fs) and polychlorinated biphenyls (PCBs) into meat and organs of indoor and outdoor reared pigs.	Swine	Mixtures PCDD/Fs, DL-PCBs	Few animals; low levels, most below LOQ. *Study less suitable for transfer.*
Shen et al. (2012a). Physiologically based persistent organic pollutant accumulation in pig tissues and their edible safety differences: an *in vivo* study.	Swine	Mixture of TCDD, PCDD, 1,2,3,4,78-HxCDD,	11 weeks exposure, 10 week elimination; biopsies at wk 11, 16 and 21. Other tissues at week 21

Reference	Species	Compounds	Comments
		1,2,3,4,6,7,8-HpCDD, OCDD, TCDF, PCDF, OCDF, PCB-126	
Shen et al. (2012b). The predictive power of the elimination of dioxin-like pollutants from pigs: an *in vivo* study.	Swine	Mixtures PCDD/Fs, DL-PCBs	
Adolphs et al. (2013). A probabilistic model for the carry-over of PCDD/Fs from feed to growing pigs.	Swine	Mixtures PCDD/Fs	

A.4.4. Studies in several species (ruminants, pigs, poultry)

Table 50. Studies retrieved in the literature search and selection for relevance to inform about the toxicokinetics and transfer in **several species**

Reference	Species	Compounds	Comments
Hoogenboom et al. (2004). Residues of dioxins and PCBs in fat of growing pigs and broilers fed contaminated feed.	Chiken Pigs	Mixtures PCDD/Fs, DL-PCBs	
Hirai et al. (2004). Congener-specific intake fractions for PCDDs/DFs and Co-PCBs: modeling and validation.	Cow Chicken Fish	Mixtures PCDD/Fs, DL-PCBs	Full chain model but no new data on transfer. *Not suitable for transfer, since no additional information*
Feidt et al. (2005). Evaluation of the risk of PAHs and dioxins transfer to humans via the dairy ruminant.	Goats Pigs	TCDD	Data from other studies, already described above.
Schulz et al. (2005). Dioxin concentration in milk and tissues of cows and sheep related to feed and soil contamination.	Cow Sheep	Mixtures PCDD/Fs, DL-PCBs	No data on intake levels. *Study les useful for transfer*
Fernandes et al. (2011). The assimilation of dioxins and PCBs in conventionally reared farm animals: occurrence and biotransfer factors.	Sheep Chicken Pigs	Mixtures PCDD/Fs, DL-PCBs	*Study useful for transfer*
Fierens et al. (2014). Modelling the environmental transfer of phthalates and polychlorinated dibenzo-*p*-dioxins and dibenzofurans into agricultural products: The EN-forc model.	Ruminants Poultry Pigs	TCDD TCDF 1,2,3,6,7,8-HxCDD 1,2,3,6,7,8-HxCDF	Model on food chain, using data from other studies; no new data on transfer
Åberg et al. (2015). Performance of the CalTOX fate and exposure model in a case study for a dioxin-contaminated site.	Cow Poultry	Mixtures PCDD/Fs	Chain model; no new data on transfer in animals.

A.4.5. Studies in fish

Table 51. Studies retrieved in the literature search and selection for relevance to inform the toxicokinetics and transfer in **salmonids** - **salmon**

Reference	Species	Compounds	Exposure Elimination period	Comments
Isosaari et al. (2004). Accumulation and distribution of polychlorinated dibenzo-*p*-dioxin, dibenzofuran, and polychlorinated biphenyl congeners in Atlantic salmon (*Salmo salar*).	Atlantic salmon	Mixtures PCDD/Fs, DL-PCBs	Multiple exposure No	Dietary exposure. PCDD/F + PCB-77, -81, -126, -169 (and other PCBs). TEQs provided.
Berntssen et al. (2011). Carry-over of dietary organochlorine pesticides, PCDD/Fs, PCBs, and brominated flame retardants to Atlantic salmon (*Salmo salar* L.) fillets.	Atlantic salmon	Mixtures PCDD/Fs, DL-PCBs	Multiple exposure No	Mixture of POPs including OCPs and BFRs. WHO-TEQs provided
Berntssen et al. (2010a). Chemical contaminants in aquafeeds and Atlantic salmon (*Salmo salar*) following the use of traditional- versus alternative feed ingredients.	Atlantic salmon	Mixtures PCDD/Fs, DL-PCBs	Multiple exposure No	17 + 12 target congeners. Mixture of POPs found in commercial fish feed.
Bell et al. (2012). Complete replacement of fish oil with a blend of vegetable oils affects dioxin, dioxin-like polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) in 3 Atlantic salmon (*Salmo salar*) families differing in flesh adiposity.	Atlantic salmon	Mixtures PCDD/Fs, DL-PCBs	Multiple exposure No	
Lundebye et al. (2004). Dietary uptake of dioxins (PCDD/PCDFs) and dioxin-like PCBs in Atlantic salmon (*Salmo salar*).	Atlantic salmon	Mixtures PCDD/Fs, DL-PCBs	Multiple exposure No	Dietary exposure. WHO-TEQs. Levels in fish muscle.
Sprague et al. (2010). Effects of decontaminated fish oil or a fish and vegetable oil blend on persistent organic pollutant and fatty acid compositions in diet and flesh of Atlantic salmon (*Salmo solar*).	Atlantic salmon	Mixtures PCDD/Fs, DL-PCBs	Multiple exposure No	
Friesen et al. (2015). Influence of terrestrial lipid and protein sources and activated carbon-treated fish oil on levels of persistent organic pollutants and fatty acids in the flesh of Atlantic salmon.	Atlantic salmon	Mixtures PCDD/Fs, DL-PCBs	Multiple exposure Unclear	
Berntssen et al. (2007). Predicting World Health Organization toxic equivalency factor dioxin and dioxin-like polychlorinated biphenyl levels in farmed Atlantic salmon (*Salmo salar*) based on known levels in feed.	Atlantic salmon	Mixtures PCDD/Fs, DL-PCBs	Multiple exposure No	
Sprague et al. (2015). Replacement of fish oil with a DHA-rich algal meal derived from Schizochytrium sp on the fatty acid and persistent organic pollutant levels in diets and flesh of Atlantic salmon	Atlantic salmon	Mixtures PCDD/Fs, DL-PCBs	Multiple exposure No	'Indirect' study. Levels in the diets and in the salmon fillet.

Reference	Species	Compounds	Exposure Elimination period	Comments
(*Salmo salar*, L.) post-smolts.				
Bell et al. (2005). Dioxin and dixon-like polychlorinated biphenyls (PCBS) in Scottish farmed salmon (*Salmo salar*): effects of replacement of dietary marine fish oil vegetable oils.	Atlantic salmon	Mixtures PCDD/Fs, DL-PCBs	Multiple exposure Yes	TEQs
Berntssen et al. (2016). Modelling scenarios on feed-to-fillet transfer of dioxins and dioxinlike PCBs in future feeds to farmed Atlantic salmon (*Salmo salar*)	Atlantic salmon	Mixtures PCDD/Fs, DL-PCBs	Multiple exposure Unclear	Feed experiment. WHO-TEQs.
Karjalainen et al. (2006). Tissue-specific and whole-fish accumulation of polychlorinated biphenyls by juvenile Baltic salmon (*Salmo salar* L.) after oral gavage exposure.	Salmon	PCB-169	Single exposure Unclear	Exposure of fish through gelatine capsules. Levels in gonads, muscle, liver and intestine

Table 52. Studies retrieved in the literature search and selection for relevance to inform the toxicokinetics and transfer in **salmonids** - **trout**

Reference	Species	Compounds	Exposure Elimination period	Comments
Jones et al. (2001). Accumulation of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin by rainbow trout (*Onchorhynchus mykiss*) at environmentally relevant dietary concentrations.	Rainbow trout	TCDD	Single exposure No	Dietary exposure. Levels in muscle, liver and ovaries.
Tietge et al. (1998). Reproductive toxicity and disposition of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in adult brook trout (*Salvelinus fontinalis*) following a dietary exposure.	Brook trout	TCDD	Multiple exposure Yes	
Sherman et al. (1992). Reevaluation of dioxin bioconcentration and bioaccumulation factors for regulatory purposes.	Lake trout	TCDD	Unclear No	
Branson et al. (1985). Bioconcentration kinetics of 2,3,7,8-tetrachlorodibenzo-para-dioxin in rainbow-trout.	Rainbow trout	TCDD	Unclear Unclear	
Kleeman et al. (1986). Metabolism and disposition of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in rainbow trout.	Rainbow trout	TCDD	Multiple exposure Yes	
Brambilla et al. (2007). Depletion of selected polychlorinated biphenyl, dibenzodioxin, and dibenzofuran congeners in farmed rainbow trout (*Oncorhynchus mykiss*): A hint for safer fish farming.	Rainbow trout	TCDD, TCDF, 1,2,3,7,8-PeCDD, 1,2,3,7,8-PeCDF, OCDD, OCDF	Multiple exposure Yes	
Servos et al. (1989). The effect of dissolved organic-matter on the	Rainbow trout	TCDD, 1,2,3,4,7,8-	Multiple exposure	Transfer water/fish. Aquatic exposure (detritus)

Reference	Species	Compounds	Exposure Elimination period	Comments
bioavailability of polychlorinated dibenzo-para-dioxins.		HxCDD, 1,2,3,4,6,7,8 -HpCDD, OCDD	No	
Sijm et al. (1990). Biotransformation and tissue distribution of 1,2,3,7-tetrachlorodibenzo-para-dioxin, 1,2,3,4,7-pentachlorodibenzo-para-dioxin and 2,3,4,7,8-pentachlorodibenzofuran in rainbow-trout.	Rainbow trout	23478-PeCDF	Single exposure Yes	Administration via gelatine capsules
Sijm et al. (1993). The influence of temperature on the uptake rate constants of hydrophobic compounds determined by the isolated perfused gills of rainbow-trout (*oncorhynchus-mykiss*).	Rainbow trout	OCDD	Single exposure No	Water-fish transfer. OCDD not detected in the gill studies
Koponen et al. (2000). Accumulation pattern and biotransformation enzyme induction in rainbow trout embryos exposed to sublethal aqueous concentrations of 3,3',4,4'-tetrachlorobiphenyl.	Rainbow trout	PCB-77	Single exposure No	Aquatic exposure of embryos
Koponen et al. (1998). Chemical accumulation and biotransformation enzyme activities of rainbow trout embryos in waterborne exposure to PCB-77.	Rainbow trout	PCB-77	Unclear No	Accumulation in eggs
Brown et al. (2002). Dietary accumulation and biochemical responses of juvenile rainbow trout (*Oncorhynchus mykiss*) to 3,3 ',4,4 ',5-pentachlorobiphenyl (PCB 126).	Rainbow trout	PCB-126	Multiple exposure Yes	
Huuskonen et al. (1996). Effects of non-*ortho*-substituted polychlorinated biphenyls (Congeners 77 and 126) on cytochrome P4501A and conjugation activities in rainbow trout (*Oncorhynchus mykiss*).	Rainbow trout	PCB-77, -126	Single exposure No	*i.p.* injection
Buckman et al. (2007a). Role of temperature and enzyme induction in the biotransformation of polychlorinated biphenyls and bioformation of hydroxylated polychlorinated biphenyls by rainbow trout (*Oncorhynchus mykiss*).	Trout	PCB-77, -126, -169	Single exposure Yes	Spiked fish food.
Buckman et al. (2004). Toxicokinetics of three polychlorinated biphenyl technical mixtures in rainbow trout (*Oncorhynchus mykiss*).	Trout	PCB-105, -118, -114, -118, -156, -167	Multiple exposure Yes	Fish fed feed spiked with Aroclor mixtures, but congener specific analysis of the feed.
Coristine et al. (1996). Elimination rates of selected di-ortho, mono-ortho, and non-ortho substituted polychlorinated biphenyls in rainbow trout (*Oncorhynchus mykiss*).	Tainbow trout	PCB-77, -81, -126, -169, -105, -118, -156	Single exposure Yes	Influence of chlorine substitution pattern on elimination rate constants. *i.p.* injection. Corn oil spiked with PCB mixture.
Isosaari et al. (2002). Feeding trial on rainbow trout: comparison of dry fish feed and Baltic herring as a	Rainbow trout	Mixtures of PCDD/Fs + DL-PCBs	Multiple exposure	Dietary exposure. TEQs provided.

Reference	Species	Compounds	Exposure Elimination period	Comments
source of PCDD/Fs and PCBs.			No	
Drew et al. (2007). Dietary influence of replacing fish meal and oil with canola protein concentrate and vegetable oils on growth performance, fatty acid composition and organochlorine residues in rainbow trout (*Oncorhynchus mykiss*).	Rainbow trout	Mixtures of PCDD/Fs + DL-PCBs	Multiple exposure No	TEQs

Table 53. Studies retrieved in the literature search and selection for relevance to inform the toxicokinetics and transfer in **other fish species**

Reference	Compounds	Species	Exposure Elimination period	Comments
Nilsson et al. (2006). Selective supercritical fluid extraction to identify aged sediment-bound PCBs available for uptake by eel.	PCB-105, PCB-118	Eel	Unclear Unclear	Sediment to fish transfer.
De Boer and Pieters (1991). Dietary accumulation of polychlorinated biphenyls chlorinated pesticides and mercury by cultivated eels *anguilla-anguilla* L.	PCB-118	Eel	Multiple exposure No	Dietary exposure, but feed not spiked. Analyses in fed and fish muscle.
Ruus et al. (2012). Accumulation of polychlorinated biphenyls from contaminated sediment by Atlantic cod (*Gadus morhua*): Direct accumulation from resuspended sediment and dietary accumulation via the polychaete *Nereis virens*.	PCB-118	Cod	Unclear Unclear	(i) Fish exposed to sediments naturally contam with PCBs. (ii) Fish fed plychaetes worms previously exposed to sediment. Congener specific analysis of 7 indicator PCBs in sediments and fish.
Ingebrigtsen et al. (1990). Species-specific accumulation of the polychlorinated biphenyl (PCB) 2,3,3',4,4'-pentachlorobiphenyl in fish brain - a comparison between cod *(Gadus-morhua*) and rainbow-trout (*oncorhynchus-mykiss*).	PCB-105	Cod	No	Radiography, not analysed tissue concentrations of PCB-105
Zhang et al. (2011). Bioaccumulation and trophic transfer of dioxins in marine copepods and fish.	unclear	Black seabream	Multiple exposure No	Waterborne exposure. Uptake of dioxin in the black seabreams. Unclear what is referred by 'dioxins'.
Ábalos et al. (2011). Decontamination trends in the aquacultured fish gilthead seabream (*Sparus aurata*) after feeding long-term a PCDD/F spiked feed.	Mixtures PCDD/Fs	Gilthead seabream	Multiple exposure Yes	
Kobayashi et al. (2011). Dietary uptake kinetics of polychlorinated biphenyls from sediment-contaminated sandworms in a marine benthic fish (*Pseudopleuronectes yokohamae*).	PCB-77, -105, -114, -118, -123, -156, -157, -167	Marbled sole	Multiple exposure Yes	Sole fed PCB-contaminated sandworms and then uncontaminated sandworms. No report of congener specific concentrations in sandworms.

Reference	Compounds	Species	Exposure Elimination period	Comments
Antunes et al. (2008). Organ-specific accumulation and elimination patterns of PCBs in adult seabass (*Dicentrarchus labrax*).	PCB-105, -118	Seabass	Multiple exposure Yes	Exposure via food added to the water
Nacher-Mestre et al. (2009). Effects of fish oil replacement and re-feeding on the bioaccumulation of organochlorine compounds in gilthead sea bream (*Sparus aurata* L.) of market size.	PCB-105, -118, -126	Seabream	Multiple exposure No	
Hellou et al. (1999). Levels, persistence and bioavailability of organic contaminants present in marine harbor sediments impacted by raw sewage.	PCB-118, OCDD, TCDF	Winter flounder	Multiple exposure No	Transfer sediment to fish. Doubts about identification of dioxins/furans.
Blanco et al. (2007). Dietary uptake of dioxins (PCDD/PCDFs) and dioxin-like PCBs in Spanish aquacultured turbot (*Psetta maxima*).	Mixtures PCDD/Fs, DL-PCBs	Turbot	Multiple exposure No	Dietary exposure, but feed was not spiked. Analysis of feed and fish muscle.
Steward et al. (1996). Disposition and metabolism of 2,3,7,8-tetrachlorodibenzofuran by channel catfish (*Ictalurus punctatus)*.	TCDF	Channel catfish	Single exposure Unclear	Blood, bile, liver, kidney, stomach, stomach contents, intestines, intestinal contents, abdominal fat, muscle fillets, and carcass analysed.
Burreau et al. (1997). Dietary uptake in pike (*Esox lucius*) of some polychlorinated biphenyls, polychlorinated naphthalenes and polybrominated diphenyl ethers administered in natural diet.	PCB-77, -118	Pike	Single exposure No	Dietary exposure. Pike fed trout spiked with compounds. Congener specific analysis.
Hajslovia et al. (1997). Elimination of PCBs from heavily contaminated carp (*Cyprinus carpio* L) in clean water-depuration study.	PCB-118	Carp	Multiple exposure Yes	Elimination of PCBs, including PCB-118
Kuehl et al. (1987a). Bioavailability of polychlorinated dibenzo-*p*-dioxins and dibenzofurans from contaminated wisconsin river sediment to carp.	TCDD	Carp	Multiple exposure Yes	Exposure of fish to TCDD contaminated sediments.
Kuehl et al. (1985). Bioavailability of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin from municipal incinerator fly-ash to fresh-water fish.	TCDD	Carp	Multiple exposure Unclear	Exposure of fish to fly ash. Aquatic exposure.
Liu et al. (2010). The influence of diet on the assimilation efficiency of 47 polychlorinated biphenyl congeners in Japanese koi (*Cyprinus carpio*).	PCB-105, -118	Japanese koi	Multiple exposure Unclear	Feed contaminated with an Aroclor mixture. Info on congener specific concentration in diets in supplemental information.
Paterson et al. (2010). Contribution of Fecal Egestion to the Whole Body Elimination of Polychlorinated Biphenyls by Japanese Koi (*Cyprinus carpio*).	PCB-105, -118, -156	Japanese koi	Single exposure Yes	Fish *i.p* injected with Aroclor mixtures, but then congener specific analysis.
Loonen et al. (1994). Bioconcentration of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans in guppies after	Mixtures PCDD/Fs	Cuppies	Multiple exposure Unclear	Water-fish transfer. Water 'spiked' with fly ash. Uptake and elimination constants.

Reference	Compounds	Species	Exposure Elimination period	Comments
aqueous exposure to a complex pcdd pcdf mixture - relationship with molecular-structure.				
Madenjian et al. (2008). Net trophic transfer efficiencies of polychlorinated biphenyl congeners to lake whitefish (*Coregonus clupeaformis*) from their food.	PCB-105, PCB-118, PCB-156	lake whitefish	Multiple exposure Unclear	Whitefish fed trout. Concentrations determined in both at the start and end of feeding experiment. Transfer efficiency.
Madenjian et al. (2014). Laboratory estimation of net trophic transfer efficiencies of PCB Congeners to lake trout (*Salvelinus namaycush*) from its prey.	Individual target PCDD/Fs or DL-PCBs	Fish		*Video Journal*
Bernhoft et al. (1994). Distribution and effects on hepatic xenobiotic-metabolizing enzymes of 2,3,3',4,4'-pentachlorobiphenyl (PCB-105) in cod (*Gadus-morhua*) and rainbow-trout (*Oncorhynchus-mykiss*).	PCB-105	Cod, trout	Multiple exposure No	
Sijm et al. (1995). Allometry in the uptake of hydrophobic chemicals determined in-vivo and in isolated-perfused gills.	OCDD	Rainbow trout, guppies	No	Aquatic exposure and perfused gills
Fisk et al. (1997). Accumulation, depuration and hepatic mixed-function oxidase enzyme induction in juvenile rainbow trout and lake whitefish exposed to dietary 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.	TCDD	Rainbow trout, Lake whitefish	Multiple exposure Yes	Dietary exposure.
Wang and Lee (2010). Polychlorinated dibenzo-*p*-dioxin, polychlorinated dibenzofurans and polychlorinated biphenyls in farmed fish, water, sediment, and feed.	Mixtures PCDD/Fs, DL-PCBs	Orange spotted grouper	Multiple exposure No	TEQs. Not a feeding trial, but data for feed and fish of different ages fed commercial feed.
O'Keefe et al. (1986). Nonaccumulation of chlorinated dioxins and furans by goldfish exposed to contaminated sediment and fly-ash.	TCDD	Goldfish	Multiple exposure No	Transfer from fly ash to fish. Aquatic exposure
Doi et al. (2006). Intestinal bioavailability and biotransformation of 3,3 ',4,4 '-tetrachlorobiphenyl (CB 77) in in situ preparations of channel catfish following dietary induction of CYP1A.	PCB-77	Channel catfish	Multiple exposure No	
Hektoen et al. (1992). Interspecies differences in tissue distribution of 2,3,7,8-tetrachlorodibenzo-para-dioxin between cod (*Gadus-morhua*) and rainbow-trout (*Oncorhynchus-mykiss*).	TCDD	Rainbow trout, Cod	Single exposure No	Intragastrical administration. Autoradiography of radiolabelled TCDD. Not chemical analysis.

Table 54. Other studies retrieved in the literature search and selection for relevance to inform the toxicokinetics and transfer in **fish**

Reference	Compounds	Species	Comments
Vives et al. (2005). Age dependence of the accumulation of organochlorine pollutants in brown trout (*Salmo trutta*) from a remote high mountain lake (Redo, Pyrenees).	PCB-118	trout	Field exposure. Determination of PCB-118 in muscle fish and water.
Madenjian et al. (2012). Net trophic transfer efficiencies of polychlorinated biphenyl congeners to lake trout (*Salvelinus namaycush*) from its prey.	PCB-105, 118, -156	lake trout	Transfer from bloater to trout (prey-predator)
Helm et al. (2008). Occurrence and biomagnification of polychlorinated naphthalenes and non- and mono-ortho PCBs in Lake Ontario sediment and biota.	Individual DL-PCBs	lake trout	Transfer from prey to predator. TEQs.
Catalan et al. (2004). The roles of food and water in the bioaccumulation of organochlorine compounds in high mountain lake fish.	PCB-118	trout	PCB-118 as part of the 7 indicator PCBs. Stomach of trout analysed for PCB-118
Endicott et al. (1994). Modeling the partitioning and bioaccumulation of tcdd and other hydrophobic organic-chemicals in lake-Ontario.	Mixtures of PCDD/Fs	lake trout	Transfer sediment-fish.
Burkhard et al. (2004). Biota-sediment accumulation factors for polychlorinated biphenyls, dibenzo-*p*-dioxins, and dibenzofurans in southern Lake Michigan lake trout (*Salvelinus namaycush*).	Mixtures of PCDD/Fs + DL-PCBs	lake trout	Sediment-trout accumulation factors. No spiking. Bioaccumulation factors.
Niimi and Oliver (1983). Biological half-lives of polychlorinated biphenyl (PCB) congeners in whole fish and muscle of rainbow-trout (*Salmo-gairdneri*).	PCB-77	lake trout	Compounds administered via gelatine capsule directly into stomach.
Metcalfe and Metcalfe (1997). The trophodynamics of PCBs, including mono- and non-ortho congeners, in the food web of North-Central Lake Ontario.	PCB-77, -81, -126, -169, 105, -118, -156	trout, white sucker and sculpin	Prey-trout transfer. No spiking. TEQs
Bhavsar et al. (2010). Estimating Sediment Quality Thresholds To Prevent Restrictions on Fish Consumption: Application to Polychlorinated Biphenyls and Dioxins-Furans in the Canadian Great Lakes.	Mixtures of PCDD/Fs	lake trout, lake whitefish, rainbow trout, and channel catfish	Transfer sediment-fish. TEQs.
Frakes et al. (1993). Bioaccumulation of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) by fish downstream of pulp and paper-mills in maine.	TCDD	smallmouth bass, brown trout, white sucker, white perch	Bioaccumulation factors from water to fish.
Giesy et al. (1999). Polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs) in muscle and eggs of salmonid fishes from the Great Lakes.	Individual PCDD/Fs	coho salmon, lake trout, and chinook salmon	ADME, field study
Berge et al. (2011). Accumulation of Polychlorinated Dibenzo-*p*-Dioxins and Furans in Atlantic Cod (*Gadus morhua).* Cage Experiments in a Norwegian Fjord.	Mixtures of PCDD/Fs	Atlantic cod	Exposure via water. Accumulation of PCDD/Fs in fish.
Vuorinen et al. (2012).	Mixtures of	salmon	Field experiment (no spiking / no

Reference	Compounds	Species	Comments
Biomagnification of organohalogens in Atlantic salmon (*Salmo salar*) from its main prey species in three areas of the Baltic Sea.	PCDD/Fs + DL-PCBs		contam feed). Analysis of the salmon and what they eat (Baltic sprat and herrings). Biomagnification factors.
Kelly et al. (2008). Persistent organic pollutants in aquafeed and Pacific salmon smolts from fish hatcheries in British Columbia, Canada.	Mixtures of PCDD/Fs + DL-PCBs	Pacific salmon	TEQs. Monitoring data on feed and salmon, not a feeding trial.
Madenjian et al. (1999). Variation in net trophic transfer efficiencies among 21 PCB congeners.	PCB-105	salmon	Net trophic transfer efficiency
Kelly et al. (2007). Lipid reserve dynamics and magnification of persistent organic pollutants in spawning sockeye salmon (*Oncorhynchus nerka*) from the Fraser River, British Columbia.	Mixtures of PCDD/Fs	Pacific sockeye salmon	Occurrence
Debruyn et al. (2004). Magnification and toxicity of PCBs, PCDDs, and PCDFs in upriver-migrating Pacific salmon.	Mixtures of PCDD/Fs + DL-PCBs	sockeye salmon	Occurrence.
Kelly et al. (2011). Tissue residue concentrations of organohalogens and trace elements in adult Pacific salmon returning to the Fraser River, British Columbia, Canada.	Mixtures of PCDD/Fs + DL-PCBs	Pacific sockeye, chinook salmon	TEQs. Maternal transfer (muscle-eggs ratios)
Verweij et al. (2004). Assessment of bioavailable PAH, PCB and OCP concentrations in water, using semipermeable membrane devices (SPMDs), sediments and caged carp.	PCB-118	Carp	Field exposure. Analysis of muscle fish (caged), water and sediments.
Wu et al. (2008). Bioaccumulation of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in wild aquatic species from an electronic waste (e-waste) recycling site in South China.	PCB-118	Carp	Field exposure. Analysis of fish and water
Wu et al. (2001a). Accumulation and partition of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/F) in the muscle and liver of fish.	Mixtures of PCDD/Fs	Common carp	Field study (exposure via water and sediments). Analysis levels in fish muscle, liver and sediments. TEQs provided.
Zhu et al. (2015). Bioconcentration and trophic transfer of polychlorinated biphenyls and polychlorinated dibenzo-*p*-dioxins and dibenzofurans in aquatic animals from an e-waste dismantling area in East China.	Mixtures of PCDD/Fs + DL-PCBs	carp, eel	TEQs (PCDD/Fs plus some DL-PCBs) BCF ratios between conc in water and in biota.
Wu et al. (2001b). Bioaccumulation of polychlorinated dibenzo-*p*-dioxins and dibenzofurans in the foodweb of Ya-Er Lake area, China.	Mixtures of PCDD/Fs	Common carp and bighead	Transfer/bioaccumulation in foodweb, different aquatic animals, aquatic plants, duck eggs, fish-eating bird eggs and breast tissue. Sediment and water samples collected from the sites also analyzed. TEQs.
Moermond et al. (**2004).** Uptake of sediment-bound bioavailable polychlorobiphenyls by benthivorous carp (*Cyprinus carpio*).	PCB-105, -118	Carp	Sediment-fish transfer
Kuehl et al. (1987b). Isomer dependent bioavailability of polychlorinated dibenzo-*p*-dioxins and dibenzofurans from municipal	Individual PCDD/Fs	Carp	Transfer fly ash-fish

Reference	Compounds	Species	Comments
incinerator fly-ash to carp.			
Koslowski et al. (1994). The distribution of 42 PCBs, including 3 coplanar congeners, in the food-web of the western basin of lake Erie.	PCB-77, -126, -169, -118, -105	Carp and gizzard shad	Transfer - follow-up of an incident (field study)
Colombo et al. (2007). Bioaccumulation of anthropogenic contaminants by detritivorous fish in the Rio de la Plata estuary: 2-Polychlorinated biphenyls.	PCB-105, -118, -156	Sabalo	Biota sediment accumulation factors
Cappelletti et al. (2015). Bioaccumulation of dioxin-like PCBs and PBDEs by detritus-feeding fish in the Rio de la Plata estuary, Argentina.	PCB-77, -126, -169, -105, -118, -123, -156, -167, -189	Sabalo, Prochilodus linneatus	Measurements in settling particles and in a detritivorous fish
Sakurai et al. (2009). Non-food-chain transfer of sediment-associated persistent organic pollutants to a marine benthic fish.	PCB-118	Sole	Exposure via sediment/water. Non-food exposure.
Serrano et al. (2003). Biomagnification study on organochlorine compounds in marine aquaculture: the sea bass (Dicentrarchus labrax) as a model.	PCB-118	Seabass	Field experiment. Fish fed feed and the contents of PCBs analysed in both the feed and the fish. Not spiked. Levels in muscle, liver and visceral fat.
Loizeau et al. (2001). A steady-state model of PCB bioaccumulation in the sea bass (*Dicentrarchus labrax*) food web from the Seine estuary, France.	PCB-105, -118	Seabass	Transfer - follow-up of an incident (field study)
vanderOost et al. (1996). Biomonitoring aquatic pollution with feral eel (*Anguilla anguilla*) .1. Bioaccumulation: Biota-sediment ratios of PCBs, OCPs, PCDDs and PCDFs.	Individual PCDD/Fs or DL-PCBs	Eel	Sediment-fish transfer. No spiking. Some DL-PCBs and some PCDD/Fs. TEQs provided. Bioaccumulation factors.
Jahnke et al. (2014). Silicone passive equilibrium samplers as 'chemometers' in eels and sediments of a Swedish lake.	PCB-118	Eel	PCB-118 as part of the 7 indicator PCBs. Sediment-silicone surface-eel.
Hendriks et al. (1998). Accumulation of metals, polycyclic (halogenated) aromatic hydrocarbons, and biocides in zebra mussel and eel from the Rhine and Meuse rivers.	PCB-77, -126, -169, -114, -157, -167	Eel	Transfer - follow-up of an incident (field study)
Stapanian et al. (2013). Sexual difference in PCB congener distributions of burbot (*Lota Iota*) from Lake Erie.	Individual DL-PCBs	Burbot	Differences in concentration according to age. Field study, 86 PCB congeners, two DL-PCB congeners.
Chang et al. (2010). Polychlorinated dibenzo-*p*-dioxins and dibenzofuran contents in fish and sediment near a pentachlorophenol contaminated site.	Mixtures of PCDD/Fs	Milk fish and tilapia	I-TEQs
Antunes et al. (2007). Depuration of PCBs and DDTs in mullet under captivity clean conditions.	PCB-105, -118	Mullet	Fish taken from contaminated area and allowed to depurate in clean water and clean feed. Elimination of PCBs (two DL-PCBs). Field exposure.
Hoekstra et al. (2003). Trophic transfer of persistent organochlorine contaminants (OCs) within an Arctic marine food web from the southern Beaufort-Chukchi Seas.	PCB-105, -118	Cod and other	Food web magnification. Data on sum PCBs from field study.

Reference	Compounds	Species	Comments
Peltonen et al. (2007). Predicting effects of exploitation rate on weight-at-age, population dynamics, and bioaccumulation of PCDD/Fs and PCBs in herring (*Clupea harengus* L.) in the Northern Baltic Sea.	Mixtures of PCDD/Fs + DL-PCBs	Herring	TEQs.
Nguyen Van et al. (2015). Transport and bioaccumulation of polychlorinated dibenzo-*p*-dioxins and dibenzofurans at the Bien Hoa Agent Orange hotspot in Vietnam.	Mixtures of PCDD/Fs	Tilapia	Transfer - follow-up of an incident (field study)
McLeod et al. (2014). Effect of Season and Habitat on PCB Bioaccumulation by Caged Bluegill Sunfish Deployed in a Great Lakes Area of Concern.	PCB-118	Bluegill Sunfish	Exposure via water and sediments. Accumulation.
Johnson et al. (1996). Dispersal and persistence of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in a contaminated aquatic ecosystem, Bayou Meto, Arkansas.	TCDD	bluegill, big- and smallnouth buffalo, crappies	No BCF calculated or similar.
Porte and Albaiges (1994). Bioaccumulation patterns of hydrocarbons and polychlorinated-biphenyls in bivalves, crustaceans, and fishes.	PCB-118	red mullet and tuna	ADME. Transfer - follow-up of an incident (field study)
Wu et al. (2009). Biomagnification of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls in a highly contaminated freshwater food web from South China.	PCB-105, -118, -157	Fish	Transfer - follow-up of an incident (field study).
Fisk et al. (2001). Influence of chemical and biological factors on trophic transfer of persistent organic pollutants in the northwater polynya marine food web.	PCB-105, -118, -156	Fish	Field study, trophic transfer, includes DL-PCB-118 and -156
Fatemi et al. (2009). Prediction of biomagnification factors for some organochlorine compounds using linear free energy relationship parameters and artificial neural networks.	PCB-77, -105, 118, -126, -169	Fish	No original data, prediction of biomagnification factors for PCBs (includes 3 DL-PCBs)
Kobayashi et al. (2015). Trophic magnification of polychlorinated biphenyls and polybrominated diphenyl ethers in an estuarine food web of the Ariake Sea, Japan.	PCB-118	Fish	Transfer - follow-up of an incident (field study)
Kim et al. (2016). Evaluating the roles of biotransformation, spatial concentration differences, organism home range, and field sampling design on trophic magnification factors.	PCB-118	Fish	Modelling. Transfer - follow-up of an incident (field study)
Buckman et al. (2006). Biotransformation of polychlorinated biphenyls (PCBs) and bioformation of hydroxylated PCBs in fish.	PCB-105, -114, -118, -156, -167	trout	Food spiked with Aroclors but the congener specific analysis of PCB-105, -114, -118, -156, -167.
Gewurtz et al. (2009). Factors influencing trends of polychlorinated naphthalenes and other dioxin-like compounds in lake trout (*Salvelinus namaycush*) from Lake Ontario, North America (1979-2004).	Mixtures of PCDD/Fs + DL-PCBs	lake trout	Field trial

Reference	Compounds	Species	Comments
Allan et al. (2013). *In vivo* passive sampling of nonpolar contaminants in brown trout (*Salmo trutta*).	PCB-118	trout	Field study
Wang et al. (2009). Modelling the depuration rates of polychlorinated biphenyls in Oncorhynchus mykiss with quantum chemical descriptors.	PCB-77, -81, -123, -126, -105, -114, -118, -169, -156, -157, -189	trout	Depuration rates: PCB-77, -81, -123, -126, -105, -114, -118, -169, -156, -157, -189. Modelling, no original exposure data
McLeod et al. (2015). PCB Food Web Dynamics Quantify Nutrient and Energy Flow in Aquatic Ecosystems.	PCB-118	trout	PCB-118 among other NDL-PCBs. Congener specific analysis and results.
Niimi and Oliver (1986). Biological half-lives of chlorinated dibenzo-para-dioxins and dibenzofurans in rainbow-trout (salmo-gairdneri).	Individual PCDD/Fs	rainbow trout	Half-life DL-PCBs.
Hektoen et al. (1994). Response of hepatic xenobiotic-metabolizing enzymes in rainbow-trout (*oncorhynchus-mykiss*) and cod (*gadus-morhua*) to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD).	TCDD	trout, cod	Distribution/metabolism. Whole body autoradiography of TCDD distribution and dynamics (enzyme induction)
Gewurtz et al. (2006). A comparison of contaminant dynamics in arctic and temperate fish: A modeling approach.	Individual DL-PCBs	lake trout and arctic char	Modelling of PCBs. Includes only PCB-118
Daley et al 2012). Bioamplification and the selective depletion of persistent organic pollutants in Chinook salmon larvae.	PCB-118	salmon	ADME
Daley et al. (2013). The effect of food provisioning on persistent organic pollutant bioamplification in Chinook salmon larvae.	PCB-118	salmon	ADME. Data only given for PCB-180, only DL-PCB included was PCB-118
Paterson et al. (2007). Gordon,Drouillard, Kenneth G.,Haffner, G. Douglas. PCB elimination by yellow perch (*Perca flavescens*) during an annual temperature cycle.	PCB-118	yellow pearch	Modelling. Elimination
Phua et al. (2007). A new risk framework for predicting chemical residue(s) - Preliminary research for PCBs and PCDD/Fs in farmed Australian Southern Bluefin Tuna (*Thunnus maccoyii*).	Mixtures of PCDD/Fs + DL-PCBs	Southern bluefish tuna	Modelling
Kobayashi et al. (2013). Respiratory uptake kinetics of neutral hydrophobic organic chemicals in a marine benthic fish, Pseudopleuronectes yokohamae.	PCB-105, -114, -118, -156, -167	Flounder	Fish exposed to water spiked with PCBs. Respiratory uptake of Arochlor.
Barber et al. (1991). Modeling bioaccumulation of organic pollutants in fish with an application to PCBs in lake-Ontario salmonids.	PCB-77	Alewife, coho salmon, rainbow trout, brown trout, lake trout	PCB-77 (and non DL-PCB-153 and -155)
Mehrtens and Laturnus (1999). Mixed function oxidase dependent biotransformation of polychlorinated biphenyls by different species of fish from the North Sea.	PCB-77	dab, plaice, cod	Metabolism
Bytingsvik et al. (2015). Current status, between-year comparisons and maternal transfer of organohalogenated	PCB-105, -118	Arctic char	Muscle/ovary partition.

Reference	Compounds	Species	Comments
compounds (OHCs) in Arctic char (*Salvelinus alpinus*) from Bjornoya, Svalbard (Norway).			
Di Paolo et al. (2010). Black Carbon Inclusive Multichemical Modeling of PBDE and PCB Biomagnification and -Transformation in Estuarine Food Webs.	PCB-118	Fish	Modelling
Burkhard et al. (2006). A hybrid empirical-mechanistic modeling approach for extrapolating biota-sediment accumulation factors and bioaccumulation factors across species, time, and/or ecosystems.	PCB-118	Fish	Modelling of PCBs (only DL PCB is PCB-118)
Fatemi and Chahi (2012). QSPR-based estimation of the half-lives for polychlorinated biphenyl congeners.	PCB-105, 114, -118, 156, -189	Fish	QSPR modelling of elimination of PCBs (includes 4 DL-PCBs)
Laender et al. (2010). Seasonal PCB bioaccumulation in an arctic marine ecosystem: a model analysis incorporating lipid dynamics, food-web productivity and migration.	PCB-118	Fish	Modelling of field data of ICES7
Xiao et al. (2015). Towards an improved understanding of processes controlling absorption efficiency and biomagnification of organic chemicals by fish.	Individual target PCDD/Fs or DL-PCBs	Fish	Modelling of uptake of dioxins and other organic Chemicals in rainbow trout
Abbott et al. (1995). Pilot-scale validation of the river-fish bioaccumulation modelling program for nonpolar hydrophobic organic-compounds using the model compounds 2,3,7,8-TCDD and 2,3,7,8-TCDF.	TCDD, TCDF	Fish	Model for field exposure to pollutants

ANNEX A.5. STUDIES IN RODENTS WITH EXPOSURE VALIDATED AND AT OR BELOW THE BENCHMARK CUT-OFF, PERFORMED WITH CONGENERS OR MIXTURES OTHER THAN TCDD

The CONTAM Panel was asked to take into account not only studies with TCDD, but also other PCDD/Fs and DL-PCBs with assigned TEF-values. Therefore, initially studies on all these compounds showing effects on relevant end-points were selected, focussing on those with TEQ-based dose levels that could result in lower body burdens than those in the two critical studies with TCDD used by SCF (2001). However, at a later stage it was judged that such animal studies on other individual PCDD/Fs, DL-PCBs or mixtures would be less suitable than studies with TCDD. The issue is that TEFs are weighted factors based on a range of relative potencies and set to distinct values on a log scale to express an order of magnitude difference with the potency of TCDD rather than a very precise value. At best such a lower TEQ based reference point could be an argument to re-evaluate the TEFs. Nevertheless, the initially selected studies are described below as an example of studies which show effects at rather low TEQ-based levels.

Mated female Sprague Dawley rats (n = 8/group) were dosed daily by gavage from GD13–19 with 0, 2.5, 25 or 250 ng PCB-126/kg bw (Wakui et al., 2010). At necropsy of the F1-males (n = 10/group) after 7, 10, 13 or 17 weeks, no effect on body weight, relative testis and epididymes weights, serum testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) were observed. After 7, 10 and 13 weeks, the F1-males of the high-dose group showed increased rates of seminiferous tubules with step 19 spermatid retention. No other histopathological changes of the testis and number of Sertoli cells per seminiferous tubular were observed. Cauda epidydimal sperm numbers were decreased in the high-dose group after 7, 10 and 13 weeks. After 17 weeks, cauda epidydimal sperm numbers and testicular morphology were similar between the groups. This may point to a delay in development of the male animals of the high-dose group. The LOAEL of the study was 250 ng PCB-126/kg bw per day and the NOAEL was 25 ng PCB-126/kg bw per day. The LOAEL was based on inhibition of mature spermatid release and epidydimal sperm counts, which were decreased at 7, 10 and 13 weeks. The CONTAM Panel noted that the study had some limitations. Reproductive data were not presented and therefore the CONTAM Panel could not judge the selection/randomisation of pups used for the F1-observations. Furthermore, body weights of F1-males during lactation until 7 weeks of age were not shown. The maternal NOAEL GD19 body burden was estimated to be 27 ng TEQ/kg bw, based on a WHO_{2005}-TEF of 0.1.

Mated female Sprague Dawley rats (n = 5/group) were dosed daily by gavage from GD13–19 with 0, 0.025, 2.5 or 250 ng PCB-126/kg bw per day or 7.5 µg PCB-126/kg bw per day. F1-females (n = 10/group) were analysed on PNDs 30 and 50 (Muto et al., 2003). No differences were seen between the groups in fecundity, pup mortality and pup weight apart from a 18% decrease in body weight in the female offspring of the high-dose group at PND30. Vaginal opening was delayed in the two highest dose groups and starting of oestrus cyclicity was delayed in all groups except the low-dose group as compared to the control. On PND50, serum 17β-oestradiol and progesterone levels were decreased in female rats of the ≥2.5 ng/kg bw/day groups. No malformations of the external genitalia were observed in any of the PCB-126-treated groups. No change in ovary weights was observed at PND30. On PND50, ovary weights of F1-females of the 7.5 µg/kg bw per day group were decreased. Histopathology of endometrium and vagina was normal, while fewer antral follicles in the 2.5, 250 ng and 7.5 µg PCB-126/kg bw per day groups were noted on PND30 and 50. Higher numbers of atretic follicles were observed in F1-females of the ≥2.5 ng/kg bw per day groups, relative to controls. The LOAEL of the study was 2.5 ng PCB-126/kg bw based on the delayed starting day of normal cyclicity, decreased number of antral follicles and increased number of atretic follicle number in the ovaria, and decreased estradiol and progesterone concentrations. The NOAEL of the study was 0.025 ng PCB-126/kg bw per day. The CONTAM Panel noted that the study had some limitations such as low number of pregnant females and F1-offspring used for observations. Reproductive data were not presented and therefore the CONTAM Panel could not judge the selection/randomisation of pups used for the F1-observations. Furthermore, there was no information on pup and body weight of F1-females during lactation but only on PND30. Several parameters

should be corrected for body weight. Due to these limitations this study was not further considered for body burden calculations.

Male and female Sprague Dawley rats were administered PCB-105 in the diet at 0.05, 0.5, 5 or 50 mg/kg diet (Chu et al., 1998). PCB-105 was synthesized according to the method of Bergman et al. (1990), and eluted through a charcoal/celite column as an additional purification step to remove possible impurities of coplanar PCB congeners. The purity reported was greater than 99.9%. The authors stated that the congener was free of chlorinated dibenzo-*p*-dioxins at detection levels below 1 µ/g by GC/MS analysis. Urine analysis was performed at 12 weeks and clinical chemistry at termination of the study at 13 weeks. Most statistically significant changes in organ weight and clinical chemistry were observed at the highest dose of 50 mg/kg diet including increased relative liver weight and decreased thymus weight. Significant changes in hepatocellular histopathology were observed at the higher doses but considered adaptive and although measured, no data were reported for liver function other than significant elevation of hepatic porphyrin levels, serum albumin and cholesterol, and increased urinary excretion of ascorbic acid at 50 mg/kg diet. This exposure was estimated by the authors as an average 4,327 and 3,960 µg PCB-105 ingested/kg bw per day for males and females, respectively. At these dose levels, changes (not dose-related) in brain biogenic amines were detected in both sexes. A NOEL for PCB-105 of 0.05 mg/kg diet was concluded, equal to 3.9 and 4.2 µg/kg bw per day, for males and females, respectively. However, based on thymus involution weight in both sexes and reduced cortical volume in females, a NOAEL of 0.5 mg PCB-105/kg diet was estimated. At the end of the exposure period the NOAEL body burden was estimated to be 40 ng TEQ/kg bw, based on the WHO_{2005}-TEF of 0.00003.

Pregnant Long-Evans (n = 15/group) were exposed to a mixture 0, 0.05, 0.2, 0.8 or 1.0 µg TEQ/kg bw by gavage on GD15. The TEQ mixture was composed as follows: TCDD + PeCDD + TCDF + 1,2,3,7,8-PeCDF + 2,3,4,7,8-PeCDF + OCDF + PCB-77 + PCB-126 + PCB-169 (Hamm et al. (2003). An additional study (n = 15/group) was performed with 0 and 2.0 µg TEQ/kg bw. Pup mortality was observed in the 2.0 µg TEQ/kg bw group. The three highest dose groups showed a delay in vaginal opening and preputial separation. However, the differences were small and the relation to body weights was not described. Weight of the seminal vesicles and prostate was decreased from 0.2 µg TEQ/kg bw and higher (data presented for only 5–7 males) on PND 32 and PND 49, respectively. This effect was only observed on PND 49 and PND 63 in the 2.0 µg/kg bw group for the seminal vesicles and on PND 63 in the 2.0 µg/kg bw for the seminal vesicles (absolute and relative). On PND 63, a decrease in sperm counts was observed in all treated groups. Observations were made in 8–10 animals selected from different litters. A NOAEL for this effect was not detected. Permanent vaginal threads (n = 10+) were observed in the 0.2 µg TEQ/kg bw group and higher and cleft phallus in the 2.0 µg TEQ/kg bw group (n = 10+). The CONTAM Panel considered 0.05 µg TEQ/kg bw as the LOAEL based on the decreased sperm counts. The CONTAM Panel noted that the randomisation/selection of the F0- and F1-animals was not described. A LOAEL GD15 body burden of 78 ng TEQ/kg bw was calculated.

Sprague Dawley rats (20/sex/group) were initially dosed by gavage with 4 daily loading doses followed by 6 biweekly maintenance doses of five different mixtures consisting of TCDD, PeCDD, 1,2,3,4,7,8-HxCDD and HpCDD (TEQ value for males 0.22, 2.59, 15.6, 46.7 or 70 µg TEQ/kg bw and for females 0.14, 1.73, 10.4, 31.1 or 46.7 µg TEQ/kg bw for groups 2, 3, 4, 5 or 6, respectively) (Viluksela et al., 1998a,b). Group 1 was the vehicle control group and group 7 was dosed with PeCDD (males 70 and females 46.7 µg TEQ/kg bw) and group 8 was dosed with HxCDD (males 70 and females 46.7 µg TEQ/kg bw). Half of the rats were necropsied after the 13-week dosing period and the other half after an additional period of 13-week off-dose. Body weights were decreased in group 5-8 in both sexes. In addition, mortality due to wasting, haemorrhage and anaemia was increased in groups 5-8 (Viluksela et al., 1998a). The biochemical markers were described in Viluksela et al. (1998b). EROD activity was dose-relatedly increased with a maximum in group 4. Serum glucose concentrations were increased in groups 5–8 in males and in groups 4-8 in females. Serum T3 levels were significantly affected. Serum T4 levels were affected in the three highest dose levels of the mixture (groups 4, 5 and 6) and in the PeCDD and HxCDD groups (groups 7 and 8). The NOAEL of this study for males was 15.6 µg TEQ/kg bw and for females 10.4 µg TEQ/kg bw (group 3). The dosing schedule was chosen such that during the entire exposure period a near 'steady-state' was achieved for all of the mixture components. At the end of the exposure period this near 'steady-state'

was revealed by measuring each of the mixture component's hepatic concentration. For the lowest dose tested this resulted in a body burden of 484 ng TEQ/kg bw in male, and 428 ng TEQ/kg bw in female animals.

Crofton et al. (2005) exposed rats for 4 days to a mixture of 18 different polyhalogenated aromatic hydrocarbons (2 PCDDs, 4 PCDFs and 12 PCBs, including DL- and NDL-PCBs). On the day following the last dose, (total) serum T4 was measured. Tested doses were 1.2, 4.2, 12, 42, 83 and 125 ng TEQ/kg/day. The study does not provide a BMD(L). However, the dose-response suggests a $BMD(L)_5$ to lie between 4.2 and 12 ng TEQ/kg bw/day. Given the 4-day exposure duration of this study the corresponding body burden at the end of the exposure period is expected to lie between 4 × 0.5 x 4.2 = 8.4 ng TEQ/kg bw, respectively 4 × 0.5 × 12 = 24 ng TEQ/kg bw. These body burdens are lower than the one used by SCF for calculating its HBGV, i.e. a LOAEL body burden of 40 ng/kg bw, a NOAEL body burden of 20 ng/kg bw.

ANNEX A.6. STUDIES IN EXPERIMENTAL ANIMALS (RODENTS AND PRIMATES)

A.6.1. Studies in rodents

Table 55. Overview of the rat studies retrieved in the literature search in which exposure was validated

Studies with exposure levels at or below the intake cut-off [a]	
Bell et al. (2007a). Toxicity of 2 TCDD in the developing male Wistar(Han) rat. I: No decrease in epididymal sperm count after a single acute dose	TCDD
Bell et al. (2007b). Toxicity of TCDD in the developing male Wistar(Han) rat. II: Chronic dosing causes developmental delay	TCDD
Harrill et al. (2016). AHR knockout rats are insensitive to the pathological effects of repeated oral exposure to TCDD	TCDD
Jämsä et al. (2001). Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on bone in two rat strains with different aryl hydrocarbon receptor structures	TCDD
Nohara et al. (2000). The effects of perinatal exposure to low doses of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on immune organs in rats	TCDD
Rebourcet et al. (2010). The effects of an in utero exposure to 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin on male reproductive function: identification of Ccl5 as a potential marker	TCDD
Rowlands et al. (2006). Sex ratio of the offspring of Sprague-Dawley rats exposed to TCDD in utero and lactationally in a three-generation study	TCDD *No effect. No NOAEL identified*
Viluksela et al. (2000). Liver tumor-promoting activity of TCDD in TCDD-sensitive and TCDD-resistant rat strains	TCDD
Phadnis-Moghe et al. (2016). Immunological characterization of the aryl hydrocarbon receptor (AHR) knockout rat in the presence and absence of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)	TCDD
Wakui et al. (2010). Testicular spermiation failure in rats exposed prenatally to 3,3 ',4,4 ',5-pentachlorobiphenyl	PCB-126
Muto et al. (2003). Estrous cyclicity and ovarian follicles in female rats after prenatal exposure to 3,3 ',4,4 ',5-pentachlorobiphenyl	PCB-126
Wu et al. (2016). 3,3 ',4,4 ',5-Pentachlorobiphenyl (PCB 126) Decreases Hepatic and Systemic Ratios of Epoxide to Diol Metabolites of Unsaturated Fatty Acids in Male Rats	PCB-126
Chu et al. (1998). Subchronic toxicity of PCB 105 (2,3,3',4,4'-pentachlorobiphenyl) in rats	PCB-105
Hamm et al. (2003). A mixture of dioxins, furans, and non-ortho PCBs based upon consensus toxic equivalency factors produces dioxin-like reproductive effects	TEQ mixture
Viluksela et al. (1998a). Subchronic/chronic toxicity of a mixture of four chlorinated dibenzo-*p*-dioxins in rats - I. Design, general observations, hematology, and liver concentrations	TEQ mixture
Viluksela et al. (1998b). Subchronic/chronic toxicity of a mixture of four chlorinated dibenzo-*p*-dioxins in rats - II. Biochemical effects	TEQ mixture
Crofton et al. (2005). Thyroid-hormone-disrupting chemicals: Evidence for dose-dependent additivity or synergism	TCDD, PeCDD, other individual, mixture
Brix et al. (2004). Characterization of bronchiolar metaplasia of the alveolar epithelium in female Sprague-Dawley rats exposed to 3,3 ',4,4 ',5-pentachlorobiphenyl (PCB126)	*Based on NTP study* PCB-126
Nyska et al. (2004). Exocrine pancreatic pathology in female harlan Sprague-Dawley rats after chronic treatment with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and dioxin-like compounds	*Based on NTP study* TCDD, PCB-126, PeCDF, TEQ mixture
Nyska et al. (2005). Olfactory epithelial metaplasia and hyperplasia in female Harlan Sprague-Dawley rats following chronic treatment with polychlorinated biphenyls	*Based on NTP study* TCDD, PCB-126, PeCDF, TEQ mixture
Walker et al. (2005). Dose-additive carcinogenicity of a defined mixture of "dioxin-like compounds"	*Based on NTP study* TCDD, PCB-126, PeCDF, TEQ mixture
Yoshizawa et al. (2005). Gingival carcinogenicity in female Harlan Sprague-Dawley	*Based on NTP study*

Studies with exposure levels at or below the intake cut-off [(a)]	
rats following two-year oral treatment with TCDD and dioxin-like compounds	TCDD, PCB-126, PeCDF, TEQ mixture
Walker et al. (2006). Comparison of chronic toxicity and carcinogenicity of TCDD in 2-year bioassays in female Sprague-Dawley rats	*Based on NTP study* TCDD
Walker et al. (2007). Pulmonary lesions in female Harlan Sprague-Dawley rats following two-year oral treatment with dioxin-like compounds	*Based on NTP study* TCDD, PCB-126, PeCDF, TEQ mixture
Yoshizawa et al. (2009). Reproductive Lesions in Female Harlan Sprague-Dawley Rats Following Two-Year Oral Treatment with Dioxin and Dioxin-like Compounds	*Based on NTP study* TCDD, PCB-126, PeCDF, PCB-118, TEQ mixture
Yoshizawa et al. (2010). Thyroid Follicular Lesions Induced by Oral Treatment for 2 Years with TCDD and Dioxin-like Compounds in Female Harlan Sprague-Dawley Rats	*Based on NTP study* TCDD, PCB-126, PeCDF, PCB-118, TEQ mixture
Hassoun et al. (2001). Production of superoxide anion, lipid peroxidation and DNA damage in the hepatic and brain tissues of rats after subchronic exposure to mixtures of TCDD and its congeners	*Based on NTP study* TEQ mixture
Studies with exposure levels above the intake cut-off	
Kransler et al. (2007a). Comparative developmental toxicity of TCDD in the hamster, rat and guinea pig	TCDD
Kransler et al. (2007b). Gestational exposure to TCDD alters retinoid homeostasis in maternal and perinatal tissues of the Holtzman rat	TCDD
Kransler et al. (2008). Effects of Helicobacter infection on developmental toxicity of TCDD in Holtzman rats	TCDD
Kransler et al. (2009). Lung Development in the Holtzman Rat is Adversely Affected by Gestational Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin	TCDD
Tuomisto et al. (2000). Changes in food intake and food selection in rats after TCDD exposure	TCDD
Nishimura et al. (2001). Induction of metallothionein in the livers of female Sprague-Dawley rats treated with TCDD	TCDD
Nishimura et al. (2002). Immunohistochemical localization of thyroid stimulating hormone induced by a low oral dose of TCDD in female Sprague-Dawley rats	TCDD
Nishimura et al. (2003). Rat thyroid hyperplasia induced by gestational and lactational exposure to TCDD	TCDD
Ishimura et al. (2002). Increased glycogen content and glucose transporter 3 mRNA level in the placenta of Holtzman rats after exposure to TCDD	TCDD
Shirota et al. (2007). Internal dose-effects of TCDD in gonadotropin-primed weanling rat model	TCDD
Kakeyama et al. (2003). Perinatal exposure to 2 TCDD alters activity-dependent expression of BDNF mRNA in the neocortex and male rat sexual behavior in adulthood	TCDD
Fletcher et al. (2001). Hepatic vitamin A depletion is a sensitive marker of TCDD exposure in four rodent species	TCDD
Fattore et al. (2000). Relative potency values derived from hepatic vitamin A reduction in male and female Sprague-Dawley rats following subchronic dietary exposure to individual polychlorinated dibenzo-*p*-dioxin and dibenzofuran congeners and a mixture thereof	TCDD, 2,3,4,7,8-PeCDF
Faqi et al. (1998a). Reproductive toxicity and tissue concentrations of PCB 77 in male adult rats	PCB-77
Rice (1999). Effect of exposure to PCB 126 throughout gestation and lactation on development and spatial delayed alternation performance in rats	PCB-126
Rice and Hayward (1998). Lack of effect of PCB 126 throughout gestation and lactation on multiple fixed interval fixed ratio and DRL performance in rats	PCB-126
Rice and Hayward (1999). Effects of exposure to PCB 126 throughout gestation and lactation on behavior (concurrent random interval-random interval and progressive ratio performance) in rats	PCB-126
Shimada et al. (2015). Absorption of PCB126 by upper airways impairs G protein-coupled receptor-mediated immune response	PCB-126
Fisher et al. (2006). Effect of PCB 126 on hepatic metabolism of thyroxine and perturbations in the hypothalamic-pituitary-thyroid axis in the rat	PCB-126
Studies used in the previous SCF (2000, 2001) assessment	

Studies with exposure levels at or below the intake cut-off [(a)]	
Faqi et al. (1998b). reproductive toxicity and tissue concentrations of low doses of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in male offspring rats exposed throughout pregnancy and lactation	TCDD
Ohsako et al. (2001). Maternal exposure to a low dose of 2378-tetrachlorodibenzo-*p*-dioxin (TCDD) suppressed the development of reproductive organs of male rats: dose-dependent increase of mRNA levels of 5a-reductase type 2 in contrast to decrease of androgen receptor in the pubertal ventral prostate	TCDD
Studies not considered in the risk assessment for the reason indicated	
Boverhof et al. (2006). Comparative toxicogenomic analysis of the hepatotoxic effects of TCDD in Sprague Dawley rats and C57BL/6 mice	TCDD *Ovariectomized animals*
Herlin et al. (2010). Quantitative characterization of changes in bone geometry, mineral density and biomechanical properties in two rat strains with different Ah-receptor structures after long-term exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin	TCDD *Hepatectomised animals*
Bell et al. (2007c). Relationships between tissue levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), mRNAs, and toxicity in the developing male wistar(han) rat	TCDD *Only levels. No toxicity study*
Hurst et al. (2000). Acute administration of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in pregnant Long Evans rats: Association of measured tissue concentrations with developmental effects	TCDD *Reassessment of previous studies*
Kawakami et al. (2006). Differential susceptibilities of Holtzman and Sprague-Dawley rats to fetal death and placental dysfunction induced by TCDD despite the identical primary structure of the AHR	TCDD *Not eligible endpoint*
Hailey et al. (2005). Classification of proliferative hepatocellular lesions in Harlan Sprague-Dawley rats chronically exposed to dioxin-like compounds	TCDD *No endpoint (kinetic study)*
Dean et al. (2002). Nonadditive hepatic tumor promoting effects by a mixture of two structurally different polychlorinated biphenyls in female rat livers	PCB-126 *Not eligible endpoint*
van der Plas et al. (1999). Induction of altered hepatic foci by a mixture of dioxin-like compounds with and without 2,2 ',4,4 ',5,5 '-hexachlorobiphenyl in female Sprague-Dawley rats	TEQ mixture *Explanatory study not fit as a basis for risk assessment. The study aimed at exploring the TEQ concept*
Desaulniers et al. (2003). Effects of postnatal exposure to mixtures of non-ortho-PCBs, PCDDs, and PCDFs in prepubertal female rats	TEQ Mixture
Croutch et al 2005. TCDD and 1,2,3,4,7,8-HxCDD alter body weight by decreasing insulin-like growth factor I (IGF-I) signalling	TCDD, HxCDD *Loading plus maintenance dosing not clearly described.*

(a): The CONTAM Panel decided to select from the retrieved literature only studies with effects considered relevant and occuring at body burdens at or below those estimated for the NOAEL in the study by Ohsako et al. (2001) of 20 ng/kg bw, or for the LOAEL in the study by Faqi et al. (1998) of 40 ng/kg bw. To select such studies, it was decided to apply a (screening) 'body burden cut-off' of 100 ng/kg bw. So all retrieved studies in which either a single dose, or repeated doses could lead to a body burden at or below 100 ng/kg bw were selected. In rodents a body burden of 100 ng/kg bw is expected after chronic gavage dosing of 10 ng/kg bw per day, therefore selected as the chronic intake cut-off value. In a similar way, intake cut-off values for less than subacute, subacute and subchronic exposure duration were developed and used for screening such studies. For more details see Section 3.1.2.1).

Table 56. Toxicity studies performed in rats administered TCDD retrieved by the literature search, in which exposure was validated and the external dose was at or below the intake cut-off. Details about the risk of bias appraisal can be found in Annex A.7

Reference	Species Compound(s) Dose regime Study type Route admin	Parameters measured and measures of effects	NOAEL and/or LOAEL Risk of bias tier
Viluksela et al. (2000). Liver tumor-promoting activity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in TCDD-sensitive and TCDD-resistant rat strains	Han/Wistar, Long-Evans TCDD Cumulative doses of 0.17, 1.7, 17, 170 µg/kg via loading doses of 0.035, 0.35, 3.5 and 35 ng/kg bw/day, followed by weekly maintenance doses of 0.007, 0.07, 0.7 and 7 ng/kg bw/day, respectively. Rats received loading dose in week 1, and maintenance doses for the remaining 19 weeks. Calculated daily doses: 1, 10, 100, 1,000 ng/kg bw/day, respectively. A satellite H/W group received a cumulative dose of 1,700 µg/kg as a single *s.c.* injection or via a loading dose of 350 µg/kg, following by weekly loading doses of 70 µg/kg. Chronic (20 weeks) Subcutaneous (*s.c.*)	**Body weight and mortality**. Body weight gain dose dependently decreased in LE rats and H/W rats at ≥1.7 and ≥17 µg/kg, respectively. **Organ weights**. Body weight related liver weights dose-dependently increased in both strains, and statistically significant at 1.7 and 17 µg/kg for LE and H/W rats, respectively. Dose-dependently decreased bw-related thymus weights in both rat strains, and for both H/W and L-E rats statistically significant at 17 µg/kg. **Quantitative stereology of GST-P-positive hepatic foci**. No foci detected in untreated -/- control rats of H/W and LE rats. Dose-dependently increase in the number of GST-P-positive foci in both rats H/W and LE strains. **Liver histopathology**. Altered hepatic foci in LE rats at 1.7 and 17 µg/kg and in comparably treated H/W rats at 170 and 1,700 µg/kg. Changes characteristic of TCDD-induced liver toxicity at 17 µg/kg in L-E rats and at ≥ 17 µg/kg in H/W rats. These changes induced inflammatory and/or necrotic foci, fibrosis, multinucleated hepatocytes, cytoplasmic vacuolisation, bile duct dilation, bile duct hyperplasia and extramedullary hematopoiesis. **Plasma enzyme activities**. ALAT and ASAT activities elevated in exposed rats. L-E were more sensitive than H/W rats, exhibiting increased plasma enzyme activities at 1.7 and 17 µg/kg, whereas H/W rats typically responded at 170 µg/kg. **Micronucleated erythrocytes in bone marrow and peripheral blood**. Tendency for MNPCE and MNRET to increase (only significant in H/W at 170 µg/kg).	Long-Evans (*Turku/AB*) rats: **NOAEL= 1 ng/kg bw/day** Based on increased liver weight and AST and increased incidence of histopathological findings in the liver. Han Wistar rats: **NOAEL=100 ng/kg bw/day** Based on decreased body weight gain, increase relative liver weight and decrease in thymus weight, and histopathological findings in the liver. Risk of bias tier: 2
Jämsä et al. (2001). Effects	Han/Wistar and Long-Evans	**Body weight and Mortality.** No deaths during the study. Significant	**NOAEL= 1 ng/kg bw/day**

Reference	Species Compound(s) Dose regime Study type Route admin	Parameters measured and measures of effects	NOAEL and/or LOAEL Risk of bias tier
of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on bone in two rat strains with different aryl hydrocarbon receptor structures	(*Turku/AB*) TCDD Cumulative doses of 0.17, 1.7, 17, 170 µg TCDD/kg via loading doses of 0.035, 0.35, 3.5 and 35 µg/kg bw/day, followed by weekly maintenance doses of 0.007, 0.07, 0.7, 7 µg/kg bw/day. Animals received the loading dose in week 1, and maintenance doses for the remaining 19 weeks. Calculated daily doses: 1, 10, 100, 1000 ng TCDD/kg bw/day. Chronic (20 weeks) Subcutaneous (*s.c.*)	impairment of body weight at the highest dose in each strain ($P<0.001$). LE rats more sensitive than H/W rats: at 17 µg TCDD/kg, body weight gain of LE rats was 63.3% of controls, while for H/W rats it was 82.6%, which was not statistically significant. At 170 µg/kg, H/W rats body weight gain significantly reduced (49.9%). LE rats considered to be 10-fold more sensitive to impaired body weight development than H/W rats. **Tibial length, geometry and density.** Decreased tibial length in LE rats at ≥17 µg/kg. Effects only seen in H/W rats at the high dose. Dose-dependent decrease in bone cross-sectional size, which was present in LE rats from 1.7 µg/kg. Reduction in bone size accompanied by a reduction in ash weight. **Mechanical properties.** The three-point bending breaking force of the tiba reduced in H/W rats at 170 µg TCDD/kg ($p<0.05$) and at 17 µg TCDD/kg in LE rats. Reduction in breaking force accompanied by a dose-dependent decrease in bending stiffness ($p<0.01$). **Histology.** No significant changes in TBV in H/W rats. Significant reduction in TBV in LE rats at 17 µg/kg) ($p<0.05$). **Biochemical analysis (ALP activity).** Plasma ALP activities dose-dependently and significantly increased in LE rats at 1.7 or 17 µg/kg, and in H/W rats at 17 or 170 µg/kg.	Based on decreased tibia length, tibia geometry parameters, tibia ash weight, and increased plasma ALP activity (calculated dose based on loading dose + maintenance scheme) Risk of bias tier: 2
Harrill et al. (2016). Aryl hydrocarbon receptor knockout rats are insensitive to the pathological effects of repeated oral exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin	Sprague-Dawley TCDD Wildtype AhR rats administered with 0, 3, 22, 100, 300, 1,000 ng/kw bw per day 4-5 days per week, for 4-weeks from PND56 ± 4 (total of 19 doses). Sub-acute (28 days) Oral: Gavage	**Body weights.** At 1,000 ng/kg bw/day inhibited body weight gain. **Tissues weights.** Dose-dependent increase in the liver-to-body weight % and a dose-dependent decrease in the thymus-to-body weight percentage. Doses ranging from 22 to 1,000 ng/kg bw/day increased liver-to body weight % compared with the control. Doses ranging from 300 to 1,000 ng/kg bw/day decreased thymus-to-body weight %. Significant decrease in spleen-to-body weight % observed at 1,000 ng TCDD/kg bw/day as compared to controls. **Serum chemistry.** Dose-dependent increase in serum ALP, AST, TBIL, TBA, TP, GLOB and CHOL. Dose-dependent decrease in TRIG and GLUC. **Hematology.** Dose-dependent increase in RBC count, HB, HCT and a dose-dependent decrease in MCV, MCH and PLT. **Histopathology.** Dose-related in severity and observed in groups	**NOAEL = 100 ng/kg bw/day** Based on bile duct hyperplasia and thymus atrophy Risk of bias tier: 1

Reference	Species Compound(s) Dose regime Study type Route admin	Parameters measured and measures of effects	NOAEL and/or LOAEL Risk of bias tier
		treated with 22 ng/kg bw/day and higher in the liver and groups treated with 300 ng/kg bw/day and higher in the thymus. In the liver, dose-related increased severity of hepatocellular vacuolation consistent with fatty change and inflammatory cell foci. Hepatocellular hypertrophy of moderate degree at 1,000 ng/kg bw/day and of mild degree from 22-300 ng/kg bw/day. Histopathology changes indicative of thymic atrophy observed at 300 and 1,000 ng/kg bw/day. Changes included a loss of cellularity in the cortex of the thymus.	
Phadnis-Moghe et al. (2016). Immunological characterization of the aryl hydrocarbon receptor (AHR) knockout rat in the presence and absence of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)	Sprague Dawley TCDD Oral gavage 0, 3, 22, 100, 300, 1,000 ng/kg/day, 4 weeks (5days per week)	In wild type animals, lymphocyte subpopulations were influenced, suppression of the percentage of LPS-induced IgM+ cells, yet an increment of (ex vivo LPS-induced) proliferation, indicating in a dysregulation of the humoral immune response with an effect level in the wild type animals of 100 ng/kg. Also the NK percentage decreased at this dose.	**NOAEL = 22 ng/kg bw/day** Based on distribution of lymphocytes and NK cells Risk of bias tier: 2
NTP (2006)	Sprague Dawley TCDD Female rats N= 81/82 per group) 8 weeks old administered 0,3,10,22,46,100 ng/kg bw per day for 5 days a week for up to 105 weeks. Oral; Gavage Interim culls (10 per group) at 14, 31 and 53 weeks. As stop exposure group was administered TCDD 100 ng/kg bw per day for 30 weeks then	**Body weights.** Survival of rats was similar to controls but decreasing body weight. For 100 ng/kg bw per day occurred from week 13. **Thyroid hormone.** T4 levels significantly decreased by 14 weeks at 22 ng/kg bw per day. **Histopathology**. Besides hypertrophy, broad range of dose related toxic hepatic lesions by 101 weeks first observed as multinucleated liver cells at 31 weeks at 46 ng/kg bw per day but more encompassing hepatopathy at the 100 ng/kg bw per day dose. At 53 weeks 46 ng/kg bw per day and at 105 weeks 10 ng/kg bw per day. After 105 weeks at highest dose there was a significant increase in hepatocellular adenomas and cholangiocarcinomas Small incidences of neoplastic changes in oral mucosa, lung, uterus, pancreas. Many non-neoplastic effects recorded including thymic atrophy, adrenal cortex atrophy and hyperplasia, cardiopathy, mesenteric artery inflammation, nephropathy, squamous hyperplasia of forestomach and thyroid gland follicular cell hypertrophy.	**NOAEL = 3 ng/kg bw/day** Based on hepatopathy at 105 weeks Risk of bias tier: 1

Reference	Species Compound(s) Dose regime Study type Route admin	Parameters measured and measures of effects	NOAEL and/or LOAEL Risk of bias tier
	returned stopped for remainder of 105 weeks		
Nohara et al. (2000). The effects of perinatal exposure to low doses of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on immune organs in rats	Holtzman TCDD Dams were dosed with 0, 12.5, 50, 200 or 800 ng/kg bw on GD15 Develop - GD15 Oral: Gavage	**CYP1A1 mRNA**. Dose-dependent CYP1A1 mRNA induction in the thyme on PND5, whereas CYP1A1 mRNA induction in the spleen very weak. CYP1A1 mRNA induction in the thymus decreased gradually from PND 5–21 and 49. On PND 49, the induction of CYP1A1 mRNA hardly detected in the spleen maternally exposed to 800 ng TCDD/kg. **Cytokine mRNA**. No change was detected in the mRNA levels examined, including those for IL- 1b, IL-1a, IL-6, TGF- b and GM-CSF. **Cell numbers**. Thymus cell numbers not affected on PND21, 49, or 120. Spleen cellularity decreased in a dose-dependent manner, with a significant reduction at 800 ng/kg on PND49. No reproducible change seen in spleen T or B cell proportion at this age. No change detected by TCDD exposure in spleen cellularity on PND21 and 120. **Body and organ weights**. No changes in the body weight, thymus or spleen weight of M offspring on PND5, 21, 49 or 120 for any dose as compared to controls.	**NOAEL = 200 ng/kg bw** Based on decreased spleen cellularity at puberty Risk of bias tier: 1
Bell et al. (2007a). Toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the developing male Wistar(Han) rat. I: No decrease in epididymal sperm count after a single acute dose	Wistar TCDD Female rats (n=55-70/group) were administered with 0, 50, 200, 1000 ng/kg bw on GD15. Acute, develop - single dose Oral: Gavage	**Littering and offspring.** Four animals had total litter loss. The litter size in the high-dose group significantly lower than control during lactation, at PND21 the number of offspring per litter 12 % lower in the high dose group compared to control. For the measurements on PND70, 25 males per group were selected (1 pup/ litter). The remaining F1 males 58, 61, 60 and 23 were necropsied on PND120. **F1 body weight gain and balano-preputial separation (BPS).** Pups in the high-dose group showed reduced body weight up to PND21, and pups in the mid-dose group showed slightly reduced body weight up to PND7. BPS significantly delayed in the high-dose group male offspring compared to control ($p<0.01$) (incidence rate 67% slower than in control). **F1 males**: No dose-response relationship in learning and motor activity. No significant effects when the offspring were subjected to a functional observational battery. **Reproductive capacity of F1 males**. No significant effects observed. Statistically significant elevation of sperm counts (~30%) in the two highest dose groups at PND120, compared to control. However, this	**LOAEL= 200 ng/kg bw** **NOAEL= 50 ng/kg bw** Based on decreased pup weight from PND1 to PND7 Risk of bias tier: 1

Reference	Species Compound(s) Dose regime Study type Route admin	Parameters measured and measures of effects	NOAEL and/or LOAEL Risk of bias tier
		effect within the normal range of sperm counts for this strain of rat, was not reflected in testicular spermatid counts nor PND70 data, and is therefore postulated to have no biological significance. Increase in the proportion of abnormal sperm at PND70, but seminology parameters otherwise unremarkable. **Body weight and pathology**. Testis weights in the high-dose group slightly decreased at PND70 and 120. At PND120, brain weight lower in the high-dose group (2.2%), liver to body weight ratios were increased for all three dose groups 3-3.5% (not dose-related).	
Bell et al. (2007b). Toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the developing male Wistar(Han) rat. II: Chronic dosing causes developmental delay	CRL:WI(Han) TCDD Female rats, 5 to 6 weeks old were provided with diet containing 0, 28, 93, 530 ng TCDD/kg diet *ad libitum* for 12 weeks premating, during mating and gestation. Average dose is 0, 2.4,8 or 46 ng TCDD/kg bw/day. Sub-chronic (15 weeks) Oral: Feed	**Parental health.** No significant difference in weight gain of F between groups over the premating, gestation and lactation periods. Food intake of the high dose group higher during premating period, but no differences during the lactation. **Littering and Offspring.** No differences in the precoital time, mating, fertility, and fecundity indices between groups. The number of implantations not significantly decreased in the treated groups. Significant decrease in the number of pups alive on day 1 in the high-dose group, and the number of pups surviving between days 1 and 4 (as a ratio of number of pups alive day 1) also statistically significantly reduced in the high-dose group. For the measurements on PND70, 25 males per group were selected (1 pup/ litter. The remaining F1 males 74, 73, 67 or 42 were necropsied on PND120. **F1 body weight, weight gain and BPS.** High and mid dose offsprings showed decreased weights at various ages. BPS significantly delayed in all three dose groups compared to control (by 1.8, 1.9, and 4.4 days for low, mid and high dose, respectively). **F1 males learning and Motor Activity.** No adverse effects on learning and memory in the swimming maze or in the performance in the functional observational battery observed, except the offsprings of animals from the high-dose group in a motor activity test. **F1 males reproductive capacity**. No significant effects on the fertility of the M rats or on the F1 or F2 sex ratio. No significant effect in sperm parameters of F1 M rats at PND70 and 120, except for an increase in the proportion of abnormal sperm in the high dose group at	**LOAEL= 2.4 ng/kg bw/day** Based on delayed balano-preputial separation (diet: 12 week premating, mating and gestation period) Risk of bias tier: 1

Reference	Species Compound(s) Dose regime Study type Route admin	Parameters measured and measures of effects	NOAEL and/or LOAEL Risk of bias tier
		PND70 associated with the developmental delay in puberty in this dose group. **F1 males body weight and pathology**. Terminal body weight at PND70 not significantly different between the groups, but significant decrease at PND120 in the high-dose group (6.9%) compared to control. No remarkable findings on organ weights, except that testis weights reduced by ~10% at PND70 (but not PND120). Ventral prostate weight not reduced. No significant effects upon histopathological comparison of high-dose and control group organs.	
Rebourcet et al. (2010). The effects of an in utero exposure to 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin on male reproductive function: identification of Ccl5 as a potential marker	Sprague-Dawley TCDD Time pregnant female rats administered 0, 10, 100, 200 ng/kg bw on GD15. F1 males necropsied on PND 28, 40, 67 or 145 Acute, develop - single dose Oral: Gavage	**Effect on F1 Males.** No treatment-related differences regarding litter size, sex ratio or body weight of pups if data expressed per litter. Intra-testicular levels of testosterone and 4-androstenedione in the normal range in 28-, 40-, 67- and 145-day old rats at 200 ng/kg bw. Testicular and epididymal weights within the normal range in rats of the differently dosed groups compared with controls. Gross histology of the testes normal throughout development. **Sperm counts and DSP in F1 Males.** No statistically significant effects in sperm counts at 10 and 100 ng TCDD/kg bw. TCDD at 200 ng/kg bw induced significant decreases in sperm reserves in the F1 males at PND67, but not at PND145. **Reproductive performance of F1 M and the F2 generation** (no control group used; data were compared to the control group of the F0-generation and their offspring). No statistically significant differences in pregnancy outcome, litter size and sex ratio. No difference in male pup weight between groups, hepatic Cyp1a1 gene expression levels remained at nadir in both groups and Ccl5/Rantes mRNA testicular levels measured in 67- and 145-day-old rats were in the same range in both groups. Sperm counts and DSP in the normal range in rats of the F2 generation, in both groups. **Gene expression**. Three genes were up- and five genes were down-regulated by ±1.4 fold in the testis of the F1-males from the high-dose group. In the F1-males of the high-dose group Ccl5/Rantes gene expression was inhibited throughout the study and at PND67 and 145 in the 100 ng TCDD group (other time points not studied).	**LOAEL= 200 ng/kg bw** **NOAEL= 100 ng/kg bw** Based on decreased pup weights and decreased sperm reserves Risk of bias tier: 2

Table 57. Overview of the mice studies retrieved in the literature search in which exposure was validated

Studies with exposure levels at or below the intake cut-off [(a)]	
Li et al. (2006). The early embryo loss caused by TCDD may be related to the accumulation of this compound in the uterus	TCDD
Fader et al. (2015). TCDD Alters Lipid Metabolism and Depletes Immune Cell Populations in the Jejunum of C57BL/6 Mice	TCDD *NOAEL/LOAEL above intake cut-off*
Nault et al. (2016). Dose-dependent metabolic reprogramming and differential gene expression in TCDD-elicited hepatic fibrosis	TCDD *NOAEL/LOAEL above intake cut-off*
van Esterik et al. (2015). Compound- and sex-specific effects on programming of energy and immune homeostasis in adult C57BL/6JxWB mice after perinatal TCDD and PCB 153	TCDD *Intermediate endpoint*
Studies with exposure levels above the intake cut-off	
Patterson et al. (2003). Induction of apoptosis by TCDD following endotoxin exposure	TCDD
Aragon et al. (2008). In utero and lactational TCDD exposure: Effects on fetal and adult cardiac gene expression and adult cardiac and renal morphology	TCDD
Morris et al. (1998). Characterization of the effects of TCDD in B6C3F1 and DBA/2 mice following single and repeated exposures	TCDD
DeKrey et al. (2013). 2,3,7,8- TCDD Slows the Progression of Experimental Cutaneous Leishmaniasis in Susceptible BALB/c and SCID Mice	TCDD
Kimura et al. (2015). Developmental origin of abnormal dendritic growth in the mouse brain induced by in utero disruption of aryl hydrocarbon receptor signalling	TCDD
Fletcher et al. (2001). Hepatic vitamin A depletion is a sensitive marker of TCDD exposure in four rodent species	TCDD
Huang et al. (1998). Pre- and postnatal exposure to PCB-77: I. Effects on breeding ability and sperm fertilizing ability in male mice	PCB-77
Huang et al. (1998). Pre- and postnatal exposure to PCB-77: II. Effects on the reproductive capacity and fertilizing ability of eggs in female mice	PCB-77
Studies not considered for the reason highlighted	
Kopec et al. (2008). Comparative toxicogenomic examination of the hepatic effects of PCB126 and TCDD in immature, ovariectomized C57BL/6 mice	TCDD, PCB-126 *Ovariectomized animals*
Kopec et al. (2010). Automated Dose-Response Analysis and Comparative Toxicogenomic Evaluation of the Hepatic Effects Elicited by TCDD, TCDF, and PCB126 in C57BL/6 Mice	TCDD, PCB-126, TCDF *Ovariectomized animals*
Kopec et al 2011. Non-additive hepatic gene expression elicited by TCDD and PCB153 co-treatment in C57BL/6 mice	TCDD *Ovariectomized animals*
Boverhof et al 2005. Temporal and dose-dependent hepatic gene expression patterns in mice provide new insights into TCDD-mediated hepatotoxicity	TCDD *Ovariectomized animals*
Boverhof et al 2006. Comparative toxicogenomic analysis of the hepatotoxic effects of TCDD in Sprague Dawley rats and C57BL/6 mice	TCDD *Ovariectomized animals*
Slezak et al. (2000). Oxidative stress in female B6C3F1 mice following acute and subchronic exposure to TCDD	TCDD *Intermediate endpoint*
Thomae et al. (2004). A maternal Ahr null genotype sensitizes embryos to chemical teratogenesis	TCDD *Intermediate endpoint*

(a): The CONTAM Panel decided to select from the retrieved literature only studies with effects considered relevant and occuring at body burdens at or below those estimated for the NOAEL in the study by Ohsako et al. (2001) of 20 ng/kg bw, or for the LOAEL in the study by Faqi et al. (1998) of 40 ng/kg bw. To select such studies, it was decided to apply a (screening) 'body burden cut-off' of 100 ng/kg bw. So all retrieved studies in which either a single dose, or repeated doses could lead to a body burden at or below 100 ng/kg bw were selected. In rodents a body burden of 100 ng/kg bw is expected after chronic gavage dosing of 10 ng/kg bw per day, therefore selected as the chronic intake cut-off value. In a similar way, intake cut-off values for less than subacute, subacute and subchronic exposure duration were developed and used for screening such studies For more details see Section 3.1.2.1).

Table 58. Toxicity studies performed in mice administered TCDD retrieved by the literature search, in which exposure was validated and the external dose was at or below the intake cut-off. Details about the risk of bias appraisal can be found in Annex A.7

Reference	Species Compounds Dose regime Study type Route admin	Parameters measured and measures of effects	NOAEL (and/or LOAEL)
Li et al. (2006). The early embryo loss caused by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin may be related to the accumulation of this compound in the uterus	NIH mice TCDD Pregnant and pseudo-pregnant mice were daily administered with 0, 2, 50, 100 ng/kg bw during GD1-8, preimplantation stages (days 1-3) and peri-implantation to early post-implantation stages (days 4-8). Sub-acute (GD1-GD8) Oral: Unspecified	Number of implanted embryos significantly reduced on GD9 in the dams dosed with 50 and 100 ngTCDD/kg. The number of implantation sites was lower in animals exposed to TCDD on days 1-3 when compared to the animals exposed on days 4-8. No effects on the estradiol levels but progesterone was significantly lower on day 9 in all treatment groups when compared to control.	**NOAEL = 2 ng/kg bw** Based on embryonic loss Risk of bias tier: 1

Table 59. Overview of the guinea pig studies retrieved in the literature search in which exposure was validated

Studies with exposure levels at or below the intake cut-off [(a)]	
Fletcher et al. (2001). Hepatic vitamin A depletion is a sensitive marker of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) exposure in four rodent species	TCDD
Studies with exposure levels above the intake cut-off	
Kransler et al. (2007a). Comparative developmental toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the hamster, rat and guinea pig	TCDD

(a): The CONTAM Panel decided to select from the retrieved literature only studies with effects considered relevant and occuring at body burdens at or below those estimated for the NOAEL in the study by Ohsako et al. (2001) of 20 ng/kg bw, or for the LOAEL in the study by Faqi et al. (1998) of 40 ng/kg bw. To select such studies, it was decided to apply a (screening) 'body burden cut-off' of 100 ng/kg bw. So all retrieved studies in which either a single dose, or repeated doses could lead to a body burden at or below 100 ng/kg bw were selected. In rodents a body burden of 100 ng/kg bw is expected after chronic gavage dosing of 10 ng/kg bw per day, therefore selected as the chronic intake cut-off value. In a similar way, intake cut-off values for less than subacute, subacute and subchronic exposure duration were developed and used for screening such studies For more details see Section 3.1.2.1).

Table 60. Overview of the studies in hamsters retrieved in the literature search in which exposure was validated

Studies with exposure levels at or below the intake cut-off [(a)]	
Fletcher et al. (2001). Hepatic vitamin A depletion is a sensitive marker of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) exposure in four rodent species	TCDD
Studies with exposure levels above the intake cut-off	
Kransler et al. (2007a). Comparative developmental toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the hamster, rat and guinea pig	TCDD

(a): The CONTAM Panel decided to select from the retrieved literature only studies with effects considered relevant and occuring at body burdens at or below those estimated for the NOAEL in the study by Ohsako et al. (2001) of 20 ng/kg bw, or for the LOAEL in the study by Faqi et al. (1998) of 40 ng/kg bw. To select such studies, it was decided to apply a (screening) 'body burden cut-off' of 100 ng/kg bw. So all retrieved studies in which either a single dose, or repeated doses could lead to a body burden at or below 100 ng/kg bw were selected. In rodents a body burden of 100 ng/kg bw is expected after chronic gavage dosing of 10 ng/kg bw per day, therefore selected as the chronic intake cut-off value. In a similar way, intake cut-off values for less than subacute, subacute and subchronic exposure duration were developed and used for screening such studies For more details see Section 3.1.2.1).

A.6.2. Studies in primates

Summary of the consideration of studies in primates in previous risk assessments

In 2000, SCF considered the studies by Schantz and Bowman (1989) and Rier et al. (1993) for the determination of the tolerable daily intake (TDI) for TCDD. In these studies TCDD was administered to groups of female rhesus monkeys of one colony providing a LOAEL of 0.15 ng/kg bw per day after prolonged dietary administration. SCF was however not able to determine the clinical significance for humans of the findings by Schantz and Bowman (1989). These included a subtle, non-persistent, neurobehavioural change in the offspring of the TCDD treated monkeys. In the study by Rier et al. (1993), the development of endometriosis in the animals some 10 years after the dietary TCDD treatment had been discontinued was noted. Problems in the reporting and results were identified (e.g. it was not clear whether identical surgical procedures had been carried out on control and treated monkeys, that body weights had not been reported and that the colony had a very high incidence of endometriosis) (SCF, 2000). In its re-evaluation in 2002, SCF considered two additional studies of these monkeys by Rier et al. (2001a,b) and supplemental unpublished data. These new data addressed some of the concerns SCF had identified in the study on endometriosis by Rier et al. (1993), e.g. similar surgical procedures had been carried out on animals of both the earlier treated and control groups. However, due to the uncertainties raised by the new studies, SCF had less confidence in the quantitative relationship between exposure to TCDD and the incidence of endometriosis in monkeys. Therefore, SCF decided not to include Rier et al. (1993) as a pivotal study in its 2002 assessment, although it recognized that effects were reported at body burdens similar to those calculated for other (rat) studies. Regarding the behavioural effects reported in Schantz and Bowman (1989) and the concerns about its clinical significance for humans, the two new studies did

not provide new information. Therefore, the SCF decided not to include this study as a pivotal study in its 2002 assessment.

The study by Rier et al. (2001b) studied the effects of TCDD exposure on the immune system of rhesus monkeys (i.e. the phenotype and function of peripheral blood mononuclear cells). SCF noted that clinical studies have indicated a relationship between endometriosis and deficiencies in humoral and cell-mediated immunity. However, SCF considered that it was not possible to establish causality of immune system changes in rhesus monkeys receiving TCDD in the diet and therefore did not include this study as a pivotal study in the updated 2002 assessment. Due to the issues above, SCF decided to base its 2002 assessment on the rodent studies rather than on the rodent and monkey studies.

US-EPA (2012) selected the studies by Bowman et al. (1989a,b), Schantz and Bowman (1989), Schantz et al. (1986) and Yang et al. (2000) for noncancer dose-response modeling, and estimated a candidate reference dose (RfD) of 0.027 pg/kg bw per day based on neurobehavioral effects from the studies by Schantz and Bowman mentioned above, based on a LOAEL of 8.2 pg/kg bw per day and using an overall uncertainty factor of 300. It was noted that there are no published toxicokinetic models to estimate TCDD disposition in monkey studies, so first-order body burden models were applied.

Table 61. Studies on the effects of PCDD/Fs and DL-PCBs in primates considered in the risk assessment. Details about the risk of bias appraisal can be found in Annex A.7

Reference	Strain Sex Age Study type	Compounds Route admin Dose regime Duration	Dose groups Animals/group	Parameters measured and measures of effect Tier of reliability
Yasuda et al. (2005). In utero and lactational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) affects tooth development in rhesus monkeys	Rhesus macaque (*Macaca mulatta*) F 3-10 years Chronic, Developmental study	TCDD *s.c.* 0, 30, 300 ng/kg on GD20. Dams received additional injection of 5% of the initial dose every 30 days until day 90 after delivery. Total dose administered to the higher dose group: 405 ng/kg (300+15×7 for dams with gestation length less than 170 days) or 420 ng/kg (300+15×8 for dams with gestation length 170 days or more) and that to the lower-dose group was 40.5 or 42 ng/kg. Approx. 240 days	3 dose groups Pregnant females Control: n=23 Low-dose: n=20, High-dose: n=20 Additional high-dose: n=9 Dental findings in offspring, Control: n=13, Low-dose: n=13, High-dose: n=8 +3	**Pregnancy outcomes.** No statistically significant effect on maternal health. Abortions, stillbirths and early postnatal deaths occurred in higher frequency in high dose TCDD groups (not statistically significant). Prenatal and early postnatal mortality rate of the offspring was higher in the 300 ng/kg group (41%) than in the control group (26%). No statistically significant differences in the length of gestation or birth weight. **Dental findings.** Dental examination of the dead offspring showed tooth abnormalities in the 300 ng/kg group only. Three out of 5 animals had tooth abnormalities (e.g. precocious eruption, dysplasia, incomplete calcification, and missing teeth). The incidence of tooth abnormalities in the 300 ng/kg group was high (60%), but it did not differ significantly from the control incidence (0%; $P > 0.1$). The incidence of tooth abnormalities in surviving offspring was significantly higher in the 300 ng/kg bw group ($p < 0.01$). The CONTAM Panel agrees with the author's conclusion that prenatal and lactational exposure to TCDD with an initial dose of 300 ng/kg and a maintenance dose of 15 ng/kg affected tooth development in rhesus monkeys. Risk of bias tier: 2
Negishi et al. (2006). Gestational and lactational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin affects social behaviors between developing rhesus monkeys (Macaca mulatta)	Rhesus macaque (*Macaca mulatta*) F 3-10 years Chronic, Developme	TCDD *s.c.* 0, 30, 300 ng/kg on GD20, followed by additional injections at 5% of the initial dose (1.5 or 15 ng/kg) every 30 days during pregnancy and lactation until PND90. The total dose administered to the	3 dose groups Pregnant F: Control: 23 Low-dose: 20 High-dose: 20 Aditional high-dose: 9 Offspring tested: Finger maze test: Control: 4 males	**General observations (survival of offspring, gestational length, bw at birth).** No significant effect on the sex ratio or on the gestation length. TCDD exposure did not affect body weight at birth. No effects on anogenital distances were seen in M of F neonates. No external abnormalities were observed. **Behavioural observations - Finger maze-learning test.** No effects observed in finger maze-learning test, but the offspring of the 300 ng/kg group appeared to learn more quickly than the control. **Behavioural observations - Encounter tests.** Exposure to TCDD

Reference	Strain Sex Age Study type	Compounds Route admin Dose regime Duration	Dose groups Animals/group	Parameters measured and measures of effect Tier of reliability
	ntal study	higher dose group was 405 ng/kg (300 + 15 × 7 for dams with gestation length less than 170 days) or 420 ng/kg (300 + 15 × 8 for dams with gestation length 170 days or more) and that to the lower-dose group was 40.5 or 42 ng/kg.. Approx 240 days	Low-dose: 4 males High-dose: 3 males Encounter test: 2 males and 2 females /group Eye contact test: 28 offspring, groups not described	significantly affected behavioural responses in the encounter tests. In the first encounter test, more visual exploration and mutual proximity but less stereotypy behaviour was observed in monkeys exposed to TCDD when compared to controls. These differences were not noticed in the second test repeated 12 months later. **Behavioural observations - Eye-contact test.** No significant effect of TCDD exposure. Risk of bias tier: 2
Korenaga et al. (2007). Long-term effects of subcutaneously injected 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on the liver of rhesus monkeys	Rhesus macaque (*Macaca mulatta*) F 4-10 years (author confirmed in email this is the Yasuda study) Chronic, 4 years after initial administration	TCDD *s.c.* 0, 30, 300 ng/kg on GD20. As a maintaining dose, the dams received 5% of the initial dose (i.e., 1.5 or 15 ng/kg) every 30 days during pregnancy and lactation until PND 90. The total dose administered to the higher dose group was 405 ng/kg (300 + 15 × 7 for dams with gestation length less than 170 days) or 420 ng/kg (300 + 15 × 8 for dams with gestation length 170 days or more) and that to the lower-dose group was 40.5 or 42 ng/kg.	3 dose groups Pregnant females Control: n=23 Low-dose: n=20 High-dose: n=20 Additional high-dose: n=9 Liver effects: 3 (control), 4 (low-dose) 3 high-dose	**General effects**. No effects on external appearance, behaviour or body weight. No significant difference in the liver weight among three dose groups. Significant pathological abnormalities observed in the liver tissue. **Effects of pregnancy and offspring.** No significant changes in the length of gestation, pregnancy outcomes, and offspring birth weight among the three dose groups **Histopathological findings in the liver tissues**. Focal fatty changes localized at the periphery and infarction with hemorrhage found in the liver at 30 and 300 ng/kg. Focal fatty change represented nodular or tumor formation. Coagulation necrosis or cytolytic change and haemorrhage indicated in the infarction and infarctoid lesions of the liver. Parenchymal hemorrhage, sinusoidal ectasia and intrasinusoidal microthrombiformation observed in TCDD-exposed monkeys. Small cell hypercellularity of hepatocytes in hepatic lobules evident in 5/7 monkeys injected with TCDD. Bile duct epithelial hyperplasia found. No dose-relationship in the abnormalities. In most treated monkeys an intrasinusoidal alpha-SMA-positive cell hyperplasia was noticed which indicated satellite cell hyperplasia or transformation into the myofibroblasts. Densely arranged small hepatocytes within hepatic lobules showed no labelling with MIB-1 antibody but high MIB-1 labeling indices were shown in the hyperplastic epithelium of bile ducts. Sinusoidal endothelical cell injury and swelling with degeneration and

Reference	Strain Sex Age Study type	Compounds Route admin Dose regime Duration	Dose groups Animals/group	Parameters measured and measures of effect Tier of reliability
				sinusoidal luminal stenosis in the liver of TCDD treated monkeys were revealed by electron microscopic examination. Dose-dependent decrease in AhR and VE cadherin protein levels (significantly in the high-dose group) observed in liver tissue of the TCDD treated animals. The increase in CYP1A1 protein level was significantly higher in the liver tissues of the monkeys at 300 ng/kg. AhR and VE cadherin protein levels decreased in a dose-dependent manner in the liver of the TCDD- treated monkeys. CYP1A1 and TGF-beta protein levels increased in a dose-dependent manner in the liver tissues of the TCDD-treated monkeys. CYP1A1 protein level significantly higher in the liver tissues at 300 ng/kg. VE cadherin protein expression significantly decreased in liver tissues at the high-dose compared to controls. Risk of bias tier: 2
Hermsen et al. (2008). *In utero* and lactational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) affects bone tissue in rhesus monkeys	Rhesus macaque (*Macaca mulatta*) F 4-10 years Chronic, Developmental study	TCDD *s.c.* 0, 30, 300 ng/kg on GD20. As a maintaining dose, the dams received 5% of the initial dose (i.e., 1.5 or 15 ng/kg) every 30 days during pregnancy and lactation until PND 90. The total dose administered to the higher dose group was 405 ng/kg (300 + 15 × 7 for dams with gestation length less than 170 days) or 420 ng/kg (300 + 15 × 8 for dams with gestation length 170 days or more) and that to the lower-dose group was 40.5 or 42 ng/kg.	3 dose groups Pregnant females Control: n=23 Low-dose: n=20 High-dose: n=20 Additional high-dose: n=9 Dental findings in offspring control: n=13, Low-dose: n=13 High-dose: n=8 +3 Number of offspring: 10 in control group (4 males and 6 females), 9 in low-dose group (6 males and 3 females) and 5 in high-dose group (3 M and 2 F)	**Bone composition and geometry (pQCT scan).** Significant increases in trabecular bone mineral content (BMC;+84.6%,$p < 0.05$,F-value(F)=5.9) in the metaphyseal part of the femur bones in F offspring in the low dose treatment group compared with controls. Analysis of the mid-diaphyseal part revealed increases in total BMC (+21.3%, $p < 0.05$, F=5.2) and cortical cross-sectional area (CSA; +16.4%, $p < 0.01$, F=7.4) in the female offspring from the low dose group when compared with the controls. **Biomechanical testing.** In males, changes in biomechanical properties indicating more fragile bone. Displacement at failure significantly increased in the males low dose group compared to controls (+38.0%, $p < 0.05$, F=11). The high TCDD dose did not induce any significant changes in bone morphology. **Serum analysis of bone biomarkers.** No significant changes in none of the bone biomarkers ALP, CTX-1 and 25-OH vitamin D. **Immunohistochemistry.**No differences in vWF, ICAM-1, osteocalcin and AhR expression found between treatment levels.

Reference	Strain Sex Age Study type	Compounds Route admin Dose regime Duration	Dose groups Animals/group	Parameters measured and measures of effect Tier of reliability
				Risk of bias tier: 2
Arima et al. (2009). In utero and lactational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) induces a reduction in epididymal and ejaculated sperm number in rhesus monkeys	Rhesus macaque (*Macaca mulatta*) F 4-10 years Chronic , developmental study	TCDD *s.c.* 0, 30, 300 ng/kg *s.c.* on GD20 and then 5 % of initial dose (1.5 or 15 ng/kg) every 30 days during the gestation and lactation periods until PND90. The total dose administered to the higher dose group was 405 ng/kg (300 + 15 × 7 for dams with gestation length less than 170 days) or 420 ng/kg (300 + 15 × 8 for dams with gestation length 170 days or more) and that to the lower-dose group was 40.5 or 42 ng/kg.	3 dose groups Pregnant females Control: n=23 Low-dose: n=20 High-dose: n=20 Additional high-dose: n=9 Offspring tested: Anogenital distance on PND 1/820 measured in: n=5/5 (control), n=8/7 (low-dose), n=8/5 (high-dose); Reproductive organ weight and histology in: n=3 (control), n=5 (low-dose), n=3 (high-dose) Semen quality: n=4 (control), n=6 (low-dose), n=5 (high-dose)	**Maternal and reproductive outcome data.** No effects on maternal general condition, bw, food consumption or gestational length. Relatively high frequencies of abortions, stillbirth and postnatal death observed in all groups and control. Survival rate at 7 years was comparable, if the deaths within 1 month after birth were excluded. No differences in sex ratio at birth or pre-and postnatal loss ratio. **Developmental landmarks.** The body weight of offspring from the 300 ng/kg group was supressed by 10% from the age of 3 years compared controls. No differences in AGD between groups. A paired absolute testes weight was reduced by approx. 70% in the TCDD groups compared to the control. **Semen quality and hormone levels.** Reduction in total sperm number (by 1/3 when compared to control) and in sperm concentration observed in male offspring from the high dose group. Slight decrease in sperm viability and activity and increase of semen volume and coagulum weight in both treatment groups. No obvious differences in mean circulatory testosterone, mean intra-testicular testosterone and DHT level. **Histopathology of the testis.** Reduction in paired testis weight, diameter of the seminiferous tubules and number of spermatids in seminiferous tubules (around 70, 89 and 77%, respectively) in the high dose group compared to controls. Very slight decrease in the number of spermatogonia and spermatocytes at 300 ng/kg, but no differences in the ratio of spermatogonia per Sertoli cell compared to controls. **Histopathology of the epididymis.** No differences in epidydimal weight, but clearly smaller ductus epididymis in both treatment groups. The area of the ductus epididymis and cavity of the ductus epididymis at 30 and 300 ng/kg and the reserved sperm in the ductus epididymis in both treatment groups were reduced. Risk of bias tier: 2
Arima et al. (2010). *In utero* and	Rhesus macaque	TCDD	3 dose groups	**Histopathology of prostate.** No significant differences in the absolute or relative prostate weight of offspring exposed *in utero* and via lactation

Reference	Strain Sex Age Study type	Compounds Route admin Dose regime Duration	Dose groups Animals/group	Parameters measured and measures of effect Tier of reliability
lactational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) induces disruption of glands of the prostate and fibrosis in rhesus monkeys	(*Macaca mulatta*) F 4–10 years Chronic , Developmental study	*s.c.* 0, 30, 300 ng/kg *s.c.* on GD20 and then 5 % of initial dose every 30 days during the gestation and lactation periods until PND90. The total dose administered to the higher dose group was 405 ng/kg (300 + 15 × 7 for dams with gestation length less than 170 days) or 420 ng/kg (300 + 15 × 8 for dams with gestation length 170 days or more) and that to the lower-dose group was 40.5 or 42 ng/kg.	Pregnant females Control: n=23 Low-dose: n=20 High-dose: n=20 Additional high-dose: n=9 Observations in 3 offspring/group	at 0, 30 and 300 ng/kg. Dose-dependent decrease in the number of glands of the prostate and a dose-dependent increase in interstitial tissue at 30 and 300 ng/kg (not significant). Epithelial height of glands significantly decreased in both treatment groups (significant, however the effect was comparable in both groups). Inflammatory cell infiltration in the glandular lumens, disruption of the glandular epithelium and a large number of fibroblasts at 300 ng/kg. **Global gene expression analysis in prostate in offspring.** Differential mRNA expression associated with fibrosis, inflammatory response and disruption of cell components. **mRNA expression levels of selected genes.** Up-regulation of TGM4, TGFB1, COL1A1 and MMP2 genes confirmed by quantitatively by real-time PCR analysis. All four genes had increased levels of expression in the 300 ng/kg group when compared with the control. Risk of bias tier: 2

M: male; F: female.
(a): No tissues analysed but final concentration of the administered TCDD was confirmed by GC (data not presented).

ANNEX A.7. RISK OF BIAS APPRAISAL OF STUDIES IN EXPERIMENTAL ANIMALS (RODENTS AND PRIMATES)

A.7.1. Studies in rodents

Table 62. Risk of bias appraisal of studies in rats (score of one individual appraisal, unless indicated) Note: appraisal of individual studies focused only on risk of bias; additional quality aspects were considered when evaluating the overall confidence in the body of evidence (see Section 2.2.1.2 of the opinion).

Viluksela et al. (2000) [(a)]		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	+	No information on randomisation. Authors mentioned in their follow-up study (Jämsä et al., 2001) that animals in the current study are randomised.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	++	TCDD was analysed in the liver at termination and the targeted dosing was confirmed. Concentration data are presented in a figure, while tabulated TCDD-concentration data is provided in the follow-up study by Jämsä et al. (2001). Details on tissue extraction and analytical methods are given.
Detection	**KQ-C** - Can we be confident in the outcome assessment?	+	Outcome data, including body and organ weight data, liver endpoints and related serum biochemistry, are well described and reported and so are the methods used for assessing the end-points. The complete data set is not tabulated but sometimes reported in figures or summarized in text.
Confounding	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	++	TCDD purity >99% assessed by GC-MS; bought from Ufa oil institute. Confirmed no background contamination in animal room. No information on stability check of dosing solution.
Performance	Were experimental conditions identical across study groups?	++	Control and exposed animals had the same conditions including diet, dosing, vehicle, housing etc according to description.
Performance	Were the outcome assessors blinded to study group or exposure level?	-	Insufficient information on blinding.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Number of animals are given in methods, tables and sometimes also in figures. 1 animal in 1 strain died/was killed.
Selective reporting	Were all measured outcomes reported?	+	All data reported; sometimes in figures only.
Other bias	Were statistical methods appropriate?	++	Statistical analyses by appropriate standard methods
Jämsä et al. (2001)		**Risk of bias Tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	+	Some information on randomisation is given. The bones used are from the animals of the study by Viluksela et al. (2000).
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	++	TCDD was analysed in the liver at termination for all animals individually in the study and the targeted dosing was confirmed. Concentration data are

			tabulated. More details on tissue extraction and analytical methods are given in the mother study by Viluksela et al. (2000), who also provide TCDD tissue concentration data in figure-format
Detection	**KQ-C** - Can we be confident in the outcome assessment?	++	Outcome data, including bone geometry, density, histology and biomechanical results, are well described and reported. The methods used for assessing the effects were well described.
Confounding	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	++	TCDD purity >99% assessed by GC-MS; bought from Ufa oil institute. Confirmed no background contamination in animal room. No information on stability check of dosing solution
Performance	Were experimental conditions identical across study groups?	++	Control and exposed animals had the same conditions in diet dosing, vehicle, housing, etc according to description.
Performance	Were the outcome assessors blinded to study group or exposure level?	-	Not mentioned/Insufficient information on blinding.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Number of animals are given in methods, tables and sometimes also in figures)
Selective reporting	Were all measured outcomes reported?	+	All data reported. Sometimes figures only
Other bias	Were statistical methods appropriate?	++	Statistical analyses by appropriate standard methods
Harrill et al. (2016) [(a)]		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	+	Stated that animals were randomized, however exact method not specified.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	++	TCDD concentrations were analysed and reported for liver and adipose tissue.
Detection	**KQ-C** - Can we be confident in the outcome assessment?	++	Endpoints determined as in regulatory toxicology studies, including body and tissue weights, histopathology, hematology and serum chemistry.
Confounding	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	++	99.1% pure TCDD purchased. Careful check of dosing solutions over course of the study (each lot within 20% of target concentration).
Performance	Were experimental conditions identical across study groups?	++	Control and exposed animals had the same conditions, including dosing, vehicle and other experimental conditions.
Performance	Were the outcome assessors blinded to study group or exposure level?	+	Insufficient information on blinding, however study was performed by different independent contractors.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	N is given for all groups in tables/text.
Selective reporting	Were all measured outcomes reported?	+	Tissues from some organs stored for possible future evaluation. Urinary tract histology was not shown.
Other bias	Were statistical methods appropriate?	+	Statistical analyses by common methods appropriate for the study.

Phadnis and Moghe et al. (2016)		Risk of bias tier: 1	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	+	Authors confirm this was conducted on the same animals as described by Harrill et al. (2016). Animals were randomized but method not specified.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	++	Described in Harrill et al. (2016)
Detection	**KQ-C** - Can we be confident in the outcome assessment?	++	The methods used for assessing the effects were well described and according generally accepted protocols.
Confounding	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	++	99.1% pure TCDD purchased. Careful check of dosing solutions over course of the study (each lot within 20% of target concentration) as in Harrill et al. (2016).
Performance	Were experimental conditions identical across study groups?	+	Animals were exposed to different concentrations of TCDD in corn oil. There is no specific mention of identical other treatment of the different groups, but it can be assumed that they are.
Performance	Were the outcome assessors blinded to study group or exposure level?	-	There is no indication of blinding of personnel carrying out the analysis. Bias may have occurred therefor we with respect to thymus and spleen weight. It is not envisioned that bias could have influenced the cell culture activation, proliferation, and flow cytometry. However, flow cytometry was repeated once. The scores of the separate experiments were not given, but the two analyses were combined. It is unclear why this was. Whereas Facs analyses may give some variation, it cannot be excluded that this was done in order to see some results that were not there in the first round.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	The number of animals per group was 5. Facs analysis was repeated once, and again the N was 5, these results were combined. No numbers were indicated in any of the figures. There was no mention of missing animals or data.
Selective reporting	Were all measured outcomes reported?	-	There is no mention of missing information. However, never in the figures the real numbers were indicated.
Other bias	Were statistical methods appropriate?	++	Appropriate.
NTP (2006)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	+	Rats described as being randomized but no details. Concurrent control group with identical treatment and weight distribution. Male rats included, but not treated, to ensure normal oestrus cycling of all females
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	++	Purity >98% and fully characterised chemically. impurities identified. Stability of TCDD determined on batches at least every 3 months.
Detection	**KQ-C** - Can we be confident in the outcome assessment?	+	Critical histopathological examinations and categorisations were performed independently by laboratory and quality assessment pathologists. Inconsistencies were referred to a NTP pathology Working Group who reviewed slides independent of knowledge of dose or previous assessment. Members were experienced in other NTP studies to ensure consistency of diagnoses.
Confounding	Did the study design or analyses account for	++	Diets identical and periodically analysed for feed composition and contaminants. Cages were changed

	important confounding and modifying variables (including unintended co-exposures) in experimental studies?		and rotated to different racks every 2 weeks to ensure consistent environmental conditions
Performance	Were experimental conditions identical across study groups?	++	Identical vehicle used for test and controls (99:1 corn oil; acetone). TCDD compositions of dose batches and stabilities analysed at least every 3 months in 2 year study.
Performance	Were the outcome assessors blinded to study group or exposure level?	++	Analyses of various laboratories parameters undertaken by different contract labs. Critical histopathological examinations and categorisations were performed independently by laboratory and quality assessment pathologists. Inconsistencies were referred to a NTP pathology Working Group who reviewed slides independent of knowledge of dose or previous assessment. Members were experienced in other NTP studies to ensure consistency of diagnoses.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	Very high survival rate and each fully reported.
Selective reporting	Were all measured outcomes reported?	++	Fully reported. The study was conducted in compliance with FDA regulations. Records were submitted to NTP Archives and audited by an independent quality assurance contractor.
Faqi et al. (1998b)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	+	Randomization of animals to exposure groups, but methods of randomization were not given.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	++	Purity was 97%, in addition, liver and fat tissue TCDD content was measured after exposure.
Detection	**KQ-C** - Can we be confident in the outcome assessment?	+	Sperm analysis was performed manually (Haemacytometer).
Confounding	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	+	Purity of the chemical 97%.
Performance	Were experimental conditions identical across study groups?	++	Groups were treated identically.
Performance	Were the outcome assessors blinded to study group or exposure level?	-	Blinding was not described in the manuscript.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	All animals remained in the groups throughout the study.
Selective reporting	Were all measured outcomes reported?	++	Values for all parameters indicated were provided
Other bias	Were statistical methods appropriate?	+	Statistical evaluation seems adequate, although correction for multiple testing was not provided. It seems that correction would not have influenced the results.
Nohara et al. (2003)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**

Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	+	Author mention that offspring were randomly reduced to 8 pups.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	+	GC-MS method for analyses of TCDD tissue concentrations is well described and data are presented in Table 3.
Detection	**KQ-C** - Can we be confident in the outcome assessment?	+	Several novel end-points, which still are lacking status as "gold standard".
Confounding	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	+	No reason to believe there was significant co-exposure, yet more details could have been given including also type of diet, etc.
Performance	Were experimental conditions identical across study groups?	++	Control and exposed animals had the same conditions including vehicle according to description.
Performance	Were the outcome assessors blinded to study group or exposure level?	-	Insufficient information on blinding.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	There is reporting about the number of pups in the individual F1-groups in foot notes.
Selective reporting	Were all measured outcomes reported?	+	All data reported.
Other bias	Were statistical methods appropriate?	+	Statistical analyses by appropriate methods. Could have included more detailed dose-response analyses.
Bell et al. (2007a)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	+	F0 animals randomised. Use/randomisation of F1-pups not totally clear.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	+	Purity not mentioned in this publication. However mentioned in Bell et al. (2007) to be 99%. Purity verified by HRMS.
Detection	**KQ-C** - Can we be confident in the outcome assessment?	++	
Confounding	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	+	Chemicals highest quality available Standard lab diet.
Performance	Were experimental conditions identical across study groups?	++	
Performance	Were the outcome assessors blinded to study group or exposure level?	+	Not mentioned (maybe described in SOP).
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	GLP.
Other bias	Were statistical methods	++	

	appropriate?		
Bell et al. (2007b)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	+	F0 females randomised. Use/randomisation of F1-pups not totally clear.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	+	Purity not mentioned in this publication. However mentioned in Bell et al. (2007c) to be 99%. Purity verified by HRMS.
Detection	**KQ-C** - Can we be confident in the outcome assessment?	++	
Confounding	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	+	Chemicals highest quality available Standard lab diet.
Performance	Were experimental conditions identical across study groups?	++	
Performance	Were the outcome assessors blinded to study group or exposure level?	+	Not mentioned (maybe described in SOP).
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	GLP.
Other bias	Were statistical methods appropriate?	++	Accounted for litter effects.
Rebourcet et al. (2010)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	+	Data on F1 not presented therefore it cannot be confirmed that all F1 animals were mated or used in the study.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	+	
Detection	**KQ-C** - Can we be confident in the outcome assessment?	+	
Confounding	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	-	The number of animals in the low and mid dose group to low.
Performance	Were experimental conditions identical across study groups?	+	
Performance	Were the outcome assessors blinded to study group or exposure level?	-	Blinding not mentioned
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from	-	Not clear what happened to 4 out of 9 litters in the control and TCDD 200 groups; may be all used for measurement of relative expression by Cyp1a1 by Q-

	analysis?		PCR. Reproductive data not presented.
Selective reporting	Were all measured outcomes reported?	-	See Attrition/exclusion bias.
Other bias	Were statistical methods appropriate?	+	

(a): Combined score of two independent appraisals.

Table 63. Risk of bias appraisal of studies in mice (combined score of two independent appraisals) Note: appraisal of individual studies focused only on risk of bias; additional quality aspects were considered when evaluating the overall confidence in the body of evidence (see Section 2.2.1.2 of the opinion).

Li et al. (2006)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	+	Number of animals assigned to each group not mentioned. Tables mention 10 pregnant animals/group.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	+	AhR reporter assay was used. Several tissues were analysed. Purity of test substance given.
Detection	**KQ-C** - Can we be confident in the outcome assessment?	+	Several novel end-points, which still are lacking status as "gold standard". Making reference to methodology text book and publications.
Confounding	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	+	TCDD from Accustandard given by gavage in sesame oil, yet more details could have been given including also type of diet, feeding regimen, drinking water etc.
Performance	Were experimental conditions identical across study groups?	++	Control and exposed animals had the same conditions including vehicle according to description.
Performance	Were the outcome assessors blinded to study group or exposure level?	-	Insufficient/no information on blinding.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Number of animals at start study not described. There is reporting about the number of dams in most figures. Could have been better described across the paper.
Selective reporting	Were all measured outcomes reported?	+	Assumed all data reported. Animals at start study not known.
Other bias	Were statistical methods appropriate?	+	Statistical analyses by common methods. Use of SEM should be replaced by SD. Could have included more detailed dose-response analyses.

A.7.2. Studies in primates

Table 64. Risk of bias appraisal of studies in monkeys (score of one individual appraisal). Note: appraisal of individual studies focused only on risk of bias; additional quality aspects were considered when evaluating the overall confidence in the body of evidence (see **Section 2.2.1.2** of the opinion).

Yasuda et al. (2005)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or	-	Only mentioned animals were divided into 3

	exposure level adequately randomised? (including selection of groups during the study)?		groups. Additional high-dose group added.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	+	
Detection	**KQ-C** - Can we be confident in the outcome assessment?	+	
Confounding	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	+	Diet from official supplier Harlan Teklan, Sprague Dawley Inc, USA. Diet analyses not described. Contamination between groups also not described.
Performance	Were experimental conditions identical across study groups?	+	It was not described how animals divided over the different rooms.
Performance	Were the outcome assessors blinded to study group or exposure level?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	In the text it is described that there are two survivors among the offspring of the additional group. However, in Table 4 there are three.
Selective reporting	Were all measured outcomes reported?	+	
Other bias	Were statistical methods appropriate?	+	
Korenaga et al. (2007)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	-	Only mentioned animals were divided into 3 groups. Additional high-dose group added. Selection of 3 control, 4 low-dose, and 3 high-dose adult females liver effects not described.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	+	
Detection	**KQ-C** - Can we be confident in the outcome assessment?	-	The number of effects observed in the control group is not explained. Most obviously no blinding is used.
Confounding	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	+	Diet from official supplier Harlan Teklan, Sprague Dawley Inc, USA. Diet analyses not described. Contamination between groups also not described.
Performance	Were experimental conditions identical across study groups?	+	It was not described how animals divided over the different rooms.
Performance	Were the outcome assessors blinded to study group or exposure level?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Other bias	Were statistical methods appropriate?	+	
Hermsen et al. (2008)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	-	Only mentioned animals were divided into 3 groups. Additional high-dose group added.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	+	
Detection	**KQ-C** - Can we be confident in the outcome assessment?	++	

Confounding	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	+	Diet from official supplier Harlan Teklan, Sprague Dawley Inc, USA. Diet analyses not described. Contamination between groups also not described.
Performance	Were experimental conditions identical across study groups?	+	It was not described how animals divided over the different rooms.
Performance	Were the outcome assessors blinded to study group or exposure level?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	The selection of offspring fort his parameter is not clear (in Table 4 of Yasuda 2009) a higher number of survivors is described.
Selective reporting	Were all measured outcomes reported?	++	
Other bias	Were statistical methods appropriate?	++	
Negishi et al. (2006)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	-	Only mentioned animals were divided into 3 groups. Selection of offspring is not clear and also the number of offspring tested in the eye contact test.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	+	
Detection	**KQ-C** - Can we be confident in the outcome assessment?	-	Not clear especially as in the behaviour encounter test the number of animals/groups were not described. Sex can be important in this kind of testing.
Confounding	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	+	Diet from official supplier Harlan Teklan, Sprague Dawley Inc, USA. Diet analyses not described. Contamination between groups also not described.
Performance	Were experimental conditions identical across study groups?	+	It was not described how animals divided over the different rooms; also not of the infants as this is important for behavioural testing.
Performance	Were the outcome assessors blinded to study group or exposure level?	-	Not described
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	Not clear especially as in the behaviour encounter test the number of animals /group were not described.
Selective reporting	Were all measured outcomes reported?	+	
Other bias	Were statistical methods appropriate?	+	
Arima et al. (2010)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	-	Only mentioned animals were divided into 3 groups. Additional high-dose group which was mentioned in Yoshida et al. not described. Prostate glands of 3 offspring were evaluated. Not presented how these animals were chosen.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	+	
Detection	**KQ-C** - Can we be confident in the outcome assessment?	+	
Confounding	Did the study design or analyses account for important confounding and modifying variables (including	+	Diet from official supplier Harlan Teklan, Sprague Dawley Inc, USA. Diet analyses not described. Contamination between groups also

	unintended co-exposures) in experimental studies?		not described.
Performance	Were experimental conditions identical across study groups?	+	It was not described how animals divided over the different rooms.
Performance	Were the outcome assessors blinded to study group or exposure level?	-	Not described
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	No reason presented for the different number of offspring tested for different parameters.
Selective reporting	Were all measured outcomes reported?	-	Only 3 animals chosen selection not described.
Other bias	Were statistical methods appropriate?	+	
Arima et al. (2009)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Selection	**KQ-A** - Was administered dose or exposure level adequately randomised? (including selection of groups during the study)?	-	Only mentioned animals were divided into 3 groups. Additional high-dose group which was mentioned in Yoshida et al. not described. No reason presented for the different number of offspring tested for different parameters.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	+	
Detection	**KQ-C** - Can we be confident in the outcome assessment?	-	Anogenital distance and sperm analyses.
Confounding	Did the study design or analyses account for important confounding and modifying variables (including unintended co-exposures) in experimental studies?	+	Diet from official supplier Harlan Teklan, Sprague Dawley Inc, USA. Diet analyses not described. Contamination between groups also not described.
Performance	Were experimental conditions identical across study groups?	+	It was not described how animals divided over the different rooms.
Performance	Were the outcome assessors blinded to study group or exposure level?	-	Anogenital distance and sperm analysis not blinded.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	No reason presented for the different number of offspring tested for different parameters.
Selective reporting	Were all measured outcomes reported?	-	Different number of animals.
Other bias	Were statistical methods appropriate?	+	

ANNEX A.8. EPIDEMIOLOGICAL STUDIES

A.8.1. Studies on male reproductive effects

Table 65. Epidemiological studies on the association between exposure to PCDD/Fs and DL-PCBs and **male reproductive effects.** Details about the risk of bias appraisal can be found in Annex A.9.1.

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of Exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
SPERM QUALITY					
Dhooge et al. (2006). Serum dioxin-like activity is associated with reproductive parameters in young men from the general Flemish population. Flemish Environment and Health Study FLEHS (Belgium, Antwerp and Peer)	Cross-sectional n/a	100 Mean (SD) age at outcome assessment: 32.6 (5.8) 1999	CALUX determined BEQ levels Blood Lipid adjusted	BEQs (pg/L serum) (n=100) Median: 62.3 Mean: 90.0 BEQs (pg/g fat): Median: 11.9 Mean: 14.6	**Sperm characteristics** (concentration, volume, motility, total count) Pronounced drop in semen volume of 16% (p=0.03); sperm concentration rose by 25.2% (p=0.07). No relationship with total sperm count or sperm morphology. Inhibin B, FSH, LH, testosterone, free fraction of testosterone, oestradiol, SHBG**:** 2-fold increase in BEQ >16 pg/L associated with 7.1% and 6.7% decrease in total and free testosterone (p=0.04), respectively. Risk of bias tier: 1
Toft et al. (2007). Semen quality in relation to xenohormone and dioxin-like serum activity among Inuits and three European populations.	Cross-sectional n/a	319 (Poland 83, Greenland 54, Ukraine 86, Sweden 96) Mean (P5-P95) age at outcome assessment: Warsaw: 30 (26–38)	CALUX determined BEQ levels Blood serum Lipid adjusted	Median (P5–P95) (n = 319) (pg BEQ/g fat) Warsaw: 320 (130–360)	**Semen parameters** (concentration, motility and morphology) No significant association between BEQs and sperm motility or sperm morphology Significant geographic differences for

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of Exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Warsaw, Poland Greenland Kharkiv, Ukraine Sweden (fishermen)		Greenland: 30 (20–40) Kharkiv:28 (20–38) Sweden:46 (32–62) 2002–2004		Greenland: 190 (100–600) Kharkiv: 330 (180–630) Sweden: 460 (220–920)	associations between BEQ and sperm concentration (positive association to sperm concentration in Warsaw), combined analysis was therefore not conducted for this outcome. Risk of bias tier: 2
Cok et al. (2008). Concentrations of polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like PCBs in adipose tissue of infertile men. n/a (Turkey, Ankara)	Case control n/a	45 (fertile men 23, infertile men 22) Mean (SD) age at outcome assessment: Fertile men: 35.1 (6.5) Infertile men:33.8 (6.5) 2003–2005	17 PCDD/Fs, 4 DL-PCBs (PCB-77, -81, -126, -169) Adipose tissue Lipid adjusted	Mean (SD) (pg/g fat) Fertile men (n = 23): PCDD/Fs WHO_{2005}-TEQ: 7.2 (3.9) Total WHO_{2005}-TEQ: 12.5 (6.6) Infertile men (n = 22): PCDD/Fs WHO_{2005}-TEQ: 7.0 (3.1) Total WHO_{2005}-TEQ: 9.4 (4.0)	**Semen parameters** (concentration, motility and morphology) No statistical significant difference for individual congeners except TCDD (fertile=0.6±0.5 pg/g fat; infertile=1.4±1.1 pg/g fat; p=0.0029) and OCDD (fertile=2.1±1.3 pg/g fat; infertile=4.3±3.6 pg/g fat; p=0.01). Statistically significant, but in opposite direction, for non-*ortho* and mono-*ortho* PCBs. Risk of bias tier: 2
Mocarelli et al. (2008). Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. Seveso Cohort (Italy, Seveso)	Cohort 22 years	135 exposed, 184 comparison Mean (SD) age at outcome assessment: Exposed Group 22–31 years (n=71): 28.1 (2.5) (1–9 years old at	TCDD Blood Lipid adjusted	Median (pg/g fat) per age group Exposed (n = 135) 22–31 32–39 Comparison (n = 184) 22–31 32–39 At explosion in 1976: 210 164 ≤15 ≤15	**Sperm concentration** The associations depend on age at explosion: (Exposed vs Controls) Childhood (1–9 years old at explosion): Negative associations - Sperm concentration: 53.6 vs 72.5 million/mL - Progressive motility: 33.2 vs 40.8%

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of Exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		explosion) Group 32–39 years (n = 44): 35.0 (2.2) (10–17 years old at explosion) Group 40–47 years (n = 20): 43.3 (2.2) (18–26 years old at explosion) Comparison Group 22–31 years (n = 82): 27.3 (2.9) Group 32–39 years (n = 71): 35.5 (2.3) Group 40–47 years (n = 31): 43.1 (2.3) 1976–1977, 1997–1998		In 1998: 3.04 4.67 <6.0 <6.0 Age group 40–47 Exposed (n = 20): 123	- Motile sperm count: 44.2 vs 77.5 x 10^6 Puberty (10–17 years old at explosion): Positive associations. - Total sperm count: 272 vs 191.9 x 10^6 - Motile sperm count: 105 vs 64.9 x 10^6 Adults (18–26 years old at explosion): No associations. **Testosterone, Inhibin B, FSH, estradiol:** Childhood (1–9 years old at explosion): - Increase in FSH (3.58 vs 2.98 IU/L; p=0.055) - Reduced estradiol (76.2 vs 95.9 pmol/L; p=0.001) Puberty (10–17 years old at explosion): - Increased FSH (4.1 vs 3.2 UI/L; p=0.038) - Reduced estradiol (74.4 vs 92.9 pmol/L; p < 0.001) Adults (18–26 years old at explosion): No effects observed Risk of bias tier: 1
Mocarelli et al. (2011). Perinatal exposure to low doses of dioxin can permanently impair human semen quality.	Cohort 18–26 years	39 exposed group (21 breast-fed, 18 formula fed), 58 comparison group (36 breast-fed, 22 formula fed)	TCDD Maternal blood Lipid adjusted	Median (pg/g fat) *At exposure (1976):* Mothers who breast-fed (n = 20): 46.8	**Sperm morphology** Breast-fed sons whose exposed mothers had median serum TCDD concentration ≥19 pg/g fat at conception had lower sperm concentration (36.3 vs. 86.3 million/mL;

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of Exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Seveso Cohort (Italy, Seveso)		Mean (SD) age at outcome assessment: Exposed: 22.5 (2.2) Comparison: 24.6 (2.0) Mean (SD) age of mothers at conception: Exposed: 28.2 (5.4) Comparison: 28.1 (4.8) 1976–1977		Mothers who formula-fed (n = 17): 55.7 Comparison: 10 (assumed) *At conception calculated for 20–42 years of age using a TCDD half-life of 4 years:* Mothers who breast-fed (n = 20): 19 Mothers who formula-fed (n = 17): 27.9 *At the time of the study:* Exposed group Breast fed group (n = 21): 2.4 Formula fed group (n = 18): 1.1 Comparison group Breast fed group (n = 36): 1.8 Formula fed group (n = 22): 1.0	p=0.002), total count (116.9 vs. 231.1; p=0.02), progressive motility (35.8 vs. 44.2%; p=0.03), and total motile count (38.7 vs. 98 million; p=0.01) than did the 36 breast-fed comparisons. Formula-fed exposed and formula-fed/breast-fed comparisons (maternal dioxin background 10 pg/g fat at conception) had no sperm-related differences. **FSH, Inhibin B:** FSH higher in breast-fed exposed group than in breast-fed comparisons (4.1 vs. 2.63 IU/L; p = 0.03) or formula-fed exposed (4.1 vs. 2.6 IU/L; p = 0.04). Inhibin B lower (breast-fed exposed group, 70.2; breast-fed comparisons, 101.8 pg/mL, p = 0.01; formula-fed exposed, 99.9 pg/mL, p = 0.02). Risk of bias tier: 2
Den Hond et al. (2015). Human exposure to endocrine disrupting chemicals and fertility: a case–control study in male subfertility patients. n/a (Belgium)	Cross-sectional case control n/a	120 (40 cases, 80 controls) Age (P25; P75) at outcome assessment: Controls: 34.1 (30.0; 38.5) Cases:	CALUX determined BEQ levels (PCDD/Fs-BEQs and DL-PCBs BEQs) Said to be lipid adjusted, but	Geometric mean (P25; P75) (pg BEQ/g) Controls (n = 40): DL-PCB-BEQs: 0.069 (0.050; 0.080) PCDD/F-BEQs: 0.19 (0.16; 0.21)	**Semen parameters** (concentration, motility and morphology) No statistically significant differences in BEQs between cases and controls neither before nor after adjusting for confounders. Risk of bias tier: 2

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of Exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		31.6 (29.0; 35.0) Time of tissue sampling: not reported	reported as pg BEQ/g	Cases (n = 80): DL-PCB-BEQs: 0.063 (0.050; 0.070) PCDD/F-BEQs: 0.23 (0.16; 0.31)	
Mínguez-Alarcón et al. (2017). A Longitudinal Study of Peripubertal Serum Organochlorine Concentrations and Semen Parameters in Young Men: The Russian Children's Study. Russian Children's Study (Russia, Chapaevsk)	Cohort 2003–2005	133 Enrolled at age 8–9 years Age at outcome assessment (in 2015): 18–19 2003–2005	17 PCDD/Fs, 10 DL-PCBs (-77, -81, -126, -169, -105, -118, -156, -157, -167, -189) Blood (serum) Lipid adjusted	Median (Min, Max) (n = 133) (pg WHO_{2005}-TEQ/g fat): Total TEQ: 21.9 (1.88, 107) TCDD: 2.9 (0.35–12.1) PCDD-TEQ: 8.7 (0.95–36.0) PCDF-TEQ: 4.8 (0.55–50.6) DL-PCB-TEQ (sum of PCB-77, -81, -126, -169): 6.9 (0.52–67.2)	**Sperm motility and sperm concentration** Higher serum TCDD and PCDD-TEQs associated with significantly lower semen parameters 10 years later. In adjusted models, on average, men in the highest quartile of serum TCDD had 40% lower sperm concentration (p, trend=0.005), 29% lower total sperm count (p, trend=0.05) and 30% lower total motile sperm count (p, trend=0.05), compared to those in the lowest quartile. Men in the highest quartile of serum PCDD TEQs had a decrease of 39% in sperm concentration (p, trend=0.02), 36% in total sperm count (p, trend=0.04), and 40% in total motile sperm count (p, trend=0.05), compared with the lowest quartile of PCDD TEQs. No significant associations between semen parameters and summed concentrations of PCDDs, PCDFs, co-PCBs or with PCDF-TEQs, DL-PCB-TEQs or total TEQs.

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of Exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					* Additional information was obtained from the authors. See documentation submitted to EFSA and **Section 3.1.4.3.1** of the opinion. Risk of bias tier: 1
CHRYPTORCHIDISM					
Virtanen et al. (2012). Associations between congenital cryptorchidism in newborn boys and levels of dioxins and PCBs in placenta. Danish-Finnish Joint Prospective Cohort Study (Denmark, Finland)	Case control n/a	280 (95 cases (56+39), 185 controls (56+129)) Age at outcome assessment: at birth and at 3 months. 1997–2001	17 PCDD/Fs, 12 DL-PCBs Placenta Lipid adjusted	Median (range) (pg WHO_{1998}-TEQ/g fat) Finland: Cases (n = 56): 11.66 (4.78–25.73) Controls (n = 56): 10.58 (3.54–37.04) Adjusted p=0.64 Denmark: Cases (n = 39): 13.94 (8.89–31.01) Controls (n = 129): 13.00 (4.93–35.61) Adjusted p=0.60	**Congenital cryptorchidism** No association found between exposure to current background levels of PCDD/Fs and DL-PCBs (evaluated as placenta levels) and congenital cryptorchidism. FSH, LH, SHBG**:** No statistically significant associations between PCDD/Fs and DL-PCB levels and reproductive hormones levels, except for DL-PCB-TEQ levels associated positively with infant LH levels (b=0.47, p=0.01) in the Finnish samples. Risk of bias tier: 1
Koskenniemi et al. (2015). Association between levels of persistent organic pollutants in adipose tissue and cryptorchidism in early childhood: a case-control study. n/a (Finland (Turku), Denmark (Copenhagen))	Cross sectional n/a	82 (44 cases, 38 controls) Mean (SD) age at operation: Cases: 2.3 (1.0) Controls: 2.9 (2.2) Controls not matched to cases in any way	17 PCDD/Fs, 12 DL-PCBs Adipose tissue Not lipid adjusted	Median (range) (total pg WHO_{1998}-TEQ/g) Finland: Cases (n = 30): 7.44 (3.24–40.7) Control (n = 29): 5.43 (2.65–64.1) p 0.85 Denmark:	**Congenital cryptorchidism** Sum of PCDD/F-TEQs: Unadjusted OR = 1.41, 95% CI 0.79–2.61 Adjusted OR = 3.69, 95% CI, 1.45–10.9 Total-WHO_{1998}-TEQ: Unadjusted OR = 1.17, 95% CI, 0.71–1.93 Adjusted OR = 3.21. 95% CI, 1.29–9.09 Risk of bias tier: 1

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of Exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		2002–2006		Cases (n = 14): 18.5 (3.41–56.0) Control (n = 9): 13.0 (2.64–42.0) p 0.73 Finland and Denmark: Cases (n = 44): 9.78 (3.24–56.0) Control (n = 38): 7.50 (2.64–64.1) p 0.55	
PUBERTAL DEVELOPMENT					
Den Hond et al. (2002). Sexual maturation in relation to polychlorinated aromatic hydrocarbons: Sharpe and Skakkebaek's hypothesis revisited. Environment and Health Study (Belgium)	Cross-sectional n/a	80 boys Mean (SD) age at outcome assessment: 17.3 (0.8) 1999	CALUX-determined BEQ levels Blood serum Fat was determined	Geometric mean (95% CI) (ng BEQ/L) Peer (rural) (n = 40): 0.15 (0.12–0.20) Wilrijk (urban) (n = 21): 0.15 (0.10–0.22) Hoboken (urban) (n= 19): 0.20 (0.13–0.29) *p*-value: 0.51	**Staged sexual maturation, testicular volume** No change in genital development or pubic hair growth with increase in serum BEQs was observed. Testicular volume did not correlate with serum BEQs. Serum concentrations of testosterone, estradiol, SHBG, Inhibin B, LH, FSH: No correlation of BEQs and serum hormones levels Risk of bias tier: 2
Leijs et al. (2008). Delayed initiation of breast development in girls with higher prenatal dioxin	Cohort 14–19 years	14 boys Median age at outcome assessment: 14.3	17 PCDD/Fs, 3 DL-PCBs (-77, -126, -169)	Median (n = 14) Human milk PCDD/F-TEQs: 28.6 pg I-TEQ/g fat	**Genital development, testicular volume, age at first ejaculation, growth axillar hair stage**

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of Exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
exposure; a longitudinal cohort study Amsterdam/Zaandam Cohort (The Netherlands)		1987–1991	Human milk (perinatal exposure), blood (serum) (current) Lipid adjusted	Current PCDD/F-TEQs: 2.3 pg WHO_{2005}-TEQ/g fat Current DL-PCB-TEQs: 1.5 pg WHO_{2005}-TEQ/g fat	Negative trend with age at first ejaculation (n = 6 for total TEQ). For pubic hair, axillary hair, genital stage, testicular volume: no significant relation. Risk of bias tier: 2 *Comments*: Too low n.
Korrick et al. (2011). Dioxin Exposure and Age of Pubertal Onset among Russian Boys. Russian Children's Study (Russia, Chapaevsk)	Cohort 3 years study duration	489 boys Age (range) at outcome assessment: 8–12 2003–2005	17 PCDD/Fs, 10 DL-PCBs (-77, -81, -126, -169, -105, -118, -156, -157, -167, -189) Blood serum Lipid adjusted	Mean (SD) (pg WHO_{2005}-TEQ/g fat) Total TEQ (n = 473): 27.7 (22.0) Q1 (< 14) Q2 (14 to < 20) Q3 (20 to < 30) Q4 (30 to 175) TCDD (n = 473): 3.1 (3.1) Q1 (< 1.3) Q2 (1.3–2.7) Q3 (2.8–3.9) Q4 (4.0–45)	**Pubertal onset (growth and pubertal assessments):** stage 2 or higher for genitalia (Tanner scale G2+) or testicular volume > 3 mL Higher TCDD and PCDD TEQs associated with later pubertal onset by testicular volume. For TCDD, the HR (95% CI) TV > 3 ml was: Q2: 0.97 (0.70-1.34) Q3 0.89 (0.63-1.24) Q4 0.69 (0.48-0.98), p for tend 0.04. For PCDD-TEQ the HRs were Q2 0.87 (0.62-1.21), Q3 0.61 (0.43-0.85) Q4 (0.68 (0.49-0.95) p for trend 0.006. Similar associations not observed for G2+. Risk of bias tier: 1 *Comments*: Co-exposure with other contaminants in the cohort not adjusted for.
Humblet et al. (2011). Dioxin and Polychlorinated	Cohort	444 boys	17 PCDD/Fs, 10 DL-PCBs (-77, -	Maternal Total TEQ (pg WHO_{2005}-TEQ/g fat):	**Pubertal onset:** genitalia stage 2 or higher, testicular volume >3 mL, pubic hair stage 2

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of Exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Biphenyl Concentrations in Mother's Serum and the Timing of Pubertal Onset in Sons. Russian Children's Study (Russia, Chapaevsk)	3 years	Mean age (SD) at outcome assessment: 8.4 (0.5) 2003–2005	81, -126, -169, -105, -118, -156, -157, -167, -189) and NDL-PCBs Blood serum Lipid adjusted	25 Detailed information has been published previously (Burns et al., 2009). min: 4.6 P10: 12 P25: 17 P50: 25 P75: 36 P90: 51 max: 173	or higher Primary analysis: Maternal serum Total TEQ concentrations were not associated with son's pubertal onset. Secondary analysis: Dose-related delay in pubertal onset (only for G2 or higher) seen among boys who were breast-fed for 6 months or more. Risk of bias tier: 1 *Comments*: Potential for exposure misclassification because of interval (8–9 years) between pregnancy and collection of blood samples for analysis. Could bias results towards null. Co-exposure with other contaminants in the cohort not adjusted for.
Su et al. (2012). The effect of *in utero* exposure to dioxins and polychlorinated biphenyls on reproductive development in eight year-old children. Part of a prospective study of dioxins/PCBs for the general population (Taiwan)	Cohort 2001–2009	23 boys Mean age at outcome assessment: 8 2000–2001	17 PCDD/Fs, 12 DL-PCBs Placenta Lipid adjusted	Median (range) (pg WHO_{1998}-TEQ/g fat) Maternal total (n = 56): 14.8 (6.8, 29.1) Maternal boys (n = 23): 15.2 (7, 29.1)	**Indicators of reproductive development (Tanner stage)** No sex characteristics of boys were affected by the level of exposure to PCDD/Fs and PCBs *in utero* (data not shown). Testosterone, estradiol, LH, FSH levels: generally unaffected by PCDD/Fs. Estradiol concentrations significantly lower in children exposed to higher levels than median of total-TEQ compared to children exposed to levels lesser than median (P=0.003).

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of Exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					Analyses stratified by sex not reported. Risk of bias tier: 2
Croes et al. (2014). Monitoring chlorinated persistent organic pollutants in adolescents in Flanders (Belgium): Concentrations, trends and dose-effect relationships (FLEHS II). Flemish Environment and Health Study FLEHS II (Belgium, Flanders, Hotspots: Genk-Zuid and Menen)	Cross-sectional n/a	324 Age at outcome assessment: 13.6–17.0 2008–2011	CALUX determined BEQ levels Blood serum Lipid adjusted	Geometric mean (95% CI) referents, both sexes (n = 210) (pg BEQ/g fat): PCDD/F-BEQs: 108 (101, 114) DL-PCB-BEQs: 32.1 (30.1, 34.2) Concentrations were significantly lower in hotspot areas	No significant association between genital or pubic hair development and BEQ levels. Testosterone, LH, SHBG, total 17β-estradiol: No significant relationship. Risk of bias tier: 2 *Comments*: Reported only significant associations, no details on male sexual development provided. Incomplete report on outcome assessment in boys.
Burns et al. (2016). Associations of Peripubertal Serum Dioxin and Polychlorinated Biphenyl Concentrations with Pubertal Timing among Russian Boys. Russian Children's Study (Russia, Chapaevsk)	Cohort study 9 years	473 Age at outcome assessment: 8–9 until 17–18 2003–2005	17 PCDD/Fs, 10 DL-PCBs (-77, -81, -126, -169, -105, -118, -156, -157, -167, -189) Blood (serum) Lipid adjusted	Levels at age 8–9 years (n = 473) (pg WHO_{2005}-TEQ/g fat) Q1: 4.0–14.5 Q2: 14.6–21.0 Q3: 21.1–33.2 Q4: 33.3–174.7	**Pubertal onset** (genitalia stage 2 or higher, testicular volume >3mL, pubic hair stage 2 or higher), **Sexual maturity** (genitalia stage 5 or higher, testicular volume >10mL, pubic hair stage 5 or higher) Pubertal onset (months, 95% CI) by testicular volume Q2 4.0 (-1.9-9.8), Q3 7.5 (0.6, 14.4), Q4 11.6 (3.8-19.4), p for trend 0.003. Pubertal onset by genitalia stage ≥ 2 Q2 8.1 (1.5-14.7), Q3 10.1 (2.3-17.9) Q4 (10.1 (1.4-18.8), p for trend 0.03. Sexual maturity by testicular volume Q2 6.0 (1.6-10.5), Q3 8.8 (3.7-14.0)

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of Exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					Q4 11.6 (5.7-17.6), p for trend <0.001. Sexual maturity by genitalia stage 5 Q2 4.4 (-0.5-9.3), Q3 7.5 (1.9-13.2) Q4 9.7 (3.1-16.2), p for trend 0.004. Pubic hair staging was not associated with serum total TEQ or NDL-PCBs. Risk of bias tier: 1 *Comments*: Co-exposure with other contaminants in the cohort not adjusted for.

FSH: follicle stimulating hormone; LH: luteinizing hormone; SHBG: sex hormone binding globulin; n/a: not applicable.

A.8.2. Studies on female reproductive effects

Table 66. Epidemiological studies on the association between exposure to PCDD/Fs and DL-PCBs and **female reproductive effects.** Details about the risk of bias appraisal can be found in **Annex A.9.2**.

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
ENDOMETRIOSIS					
Pauwels et al. (2001). The risk of endometriosis and exposure to dioxins and polychlorinated byphenyls: a case-control study of infertile women. n/a (Belgium)	Case-control	69 (42 cases, 27 controls) Median (range) age at outcome assessment: Cases: 31 (25–42) Controls: 32 (24–41) 1996–1998	CALUX determined BEQ levels Blood (serum) Lipid adjusted	Median (range) (pg BEQs/g fat) Cases (n=34 above LOD): 29 (0–160) Controls (n=24 above LOD): 27 (0–135)	**Endometriosis determined by laparoscopy in infertile women** No significant association between exposure and endometriosis. Risk of bias tier: 2
Eskenazi et al. (2002a). Serum dioxin concentrations and endometriosis: A cohort study in Seveso, Italy. Seveso Women's Health Study (SWHS) (Italy, Seveso)	Cohort 20 years	601 ≤30 years of age at exposure Age at outcome assessment: 20–29 years: 20% 30–39 years: 39% ≥40 years: 41% 1976–1977 (n=559) 1978–1981 (n=25) 1996 (n=17)	TCDD Blood (serum) Lipid adjusted	Median (range) (pg/g fat) (n = 601): 54.9 (2.5–17,300) Median by group: Cases: 77.3 Non-diseased: 61.0 Uncertain: 49.0	**Endometriosis** Relative risk ratios (RRRs) for women with serum TCDD levels of 20.1–100 pg/g fat and >100 pg/g fat were 1.2 (90% CI=0.3–4.5) and 2.1 (90% CI=0.5–8.0), respectively, relative to women with TCDD levels ≤20 pg/g fat. Tests for trend using the above exposure categories and continuous log TCDD were non-significant. Risk of bias tier: 2 *Comments*: Small number of women with

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					endometriosis. Inability to perform laparoscopy on entire cohort may have reduced power of study.
Fierens et al. (2003). Dioxin / polychlorinated biphenyl body burden, diabetes and endometriosis: findings in a population-based study in Belgium. n/a (Belgium; Cockerill (iron and steel plant), Mont-Saint-Guibert (waste dumping site), Pont-de-Loup (MWSI), Thumaide (MWSI), Rural areas in Southern Belgium)	Cross-sectional n/a	142 (10 cases, 132 controls) Mean age at outcome assessment: Cases: 49.0 Controls: 51.2 2000–2001	17 PCDD/Fs, 4 DL-PCBs (-77, -81, -126, -169) Blood Lipid adjusted	Mean levels (pg WHO_{1998}-TEQ/g fat) (n = 10 cases, n = 132 controls) Sum of PCDD/F-TEQs: Cases: 26.2 (18.2–37.7) Controls: 25.6 (24.3–28.9) Sum of DL-PCB-TEQs: Cases: 7.97 (5.05–12.6) Controls: 7.45 (6.69–8.30) Total TEQs: Cases: 34.6 (23.7–50.4) Controls: 34.5 (31.7–37.6)	**Endometriosis** No difference in exposure between endometriosis cases and controls. Risk of bias tier: 2 *Comments*: Small number of cases. Controls were not matched to cases before collection of data. Other potential confounders than age, BMI, serum lipids, e.g. smoking, not considered in analysis.
De Felip et al. (2004). Dioxin-like compounds and endometriosis: a study on Italian and Belgian women of reproductive age. n/a (Italy (Rome), Belgium (Brussels))	Case control n/a	40 (23 cases, 17 controls) Age at outcome assessment: 18–40 2000–2001	17 PCDD/Fs, 12 DL-PCBs Blood Lipid adjusted	Range (pooled concentrations per country) (pg WHO_{1998}-TEQ/g fat) Italy (n = 10 controls and 12 cases): 17.7–18.5 Belgium (n = 7 controls and 11 cases): 34.4–48.6	**Endometriosis** No difference case/control. Higher concentrations in Belgium than in Italy. Risk of bias tier: 2 *Comments*: Small study size (pilot study). Pooled samples (in total 6 pools).
Heilier et al. (2005). Increased dioxin-like compounds in the serum of women with peritoneal endometriosis and deep	Case control n/a	71 (25 PEND, 25 DEN, 21 controls) Mean (SD) age at outcome assessment:	17 PCDD/Fs, 12 DL-PCB Blood (serum)	Non-standardised mean (pg WHO_{1998}-TEQ/g fat) PCDD/F-TEQs Controls (n = 21):	**Endometriosis (peritoneal endometriosis, PEND) and deep endometriotic (Deep endometriotic nodules, DEN)**

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
endometriotic (adenomyotic) nodules. n/a (Belgium)		Controls: 31.1 (6.0) Peritoneal endometriosis (PEND): 31.8 (6.5) Deep endometriosis (DEN): 30.8 (7.0) 2001–2003	Lipid adjusted	15.5 (13.1–18.4) PEND (n = 25): 20.9 (18.1–24.0) DEN (n = 25): 26.0 (21.9–30.8) DL-PCB-TEQs Controls (n = 21): 8.5 (6.9–10.5) PEND (n = 25): 11.0 (9.1–13.3) DEN (n = 25): 12.4 (10.3–14.9)	After adjustment for age/BMI mean TEQ levels were 24.21 (controls), 30.62 (PEND), and 37.60 (DEN) pg TEQ/g fat. Logistic regression analysis indicated a significantly increased risk of DEN (OR=3.3, 95% CI 1.4–7.6) for an increment of 10 pg in Total TEQ levels/g fat. A marginal significant increased risk also found for PEND (OR=1.9, 95% CI 0.9–3.8) for total TEQ levels and for PCDD/Fs alone (OR=3.2, 95% CI 1.0–9.9). Risk of bias tier: 1 *Comments*: Small study size. Residual confounding possible due to factors not considered. Controls may have endometriosis.
Tsukino et al. (2005). Associations between serum levels of selected organochlorine compounds and endometriosis in infertile Japanese women. n/a (Japan)	Case-control study n/a	139 (58 cases, 81 controls) Mean age at outcome assessment: Controls: 32.9 Cases: 32.4 1999-2000	17 PCDD/Fs, 10 DL-PCBs (-77, -81, -126, -169, -105, -118, -156, -157, -167, -189) Blood (serum) Lipid adjusted	Median (25th, 75th) (pg WHO_{1998}-TEQ/g fat) Cases (Stage 0-I) (n = 58): 22.76 (19.73, 29.14) Controls (Stage II-IV) (n = 81): 25.07 (20.27, 31.84)	**Endometriosis determined by laparoscopy in infertile women.** Stage 0 and 1 was designated controls and stage II-IV identified as cases. Serum total PCDDs TEQ was higher in controls than in cases (P=0.02). Total TEQ was not significantly different between cases and controls. Adjusted OR for endometriosis showed a non-significant (P for trend=0.06) decreasing trend with increasing serum total TEQ. Risk of bias tier: 1

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Niskar et al. (2009). Serum dioxins, polychlorinated biphenyls, and endometriosis: A case-control study in Atlanta. n/a (USA, Atlanta)	Case control study n/a	124 (60 cases, 64 controls) Mean age at outcome assessment: not reported 1998–1999	17 PCDD/Fs, 12 DL-PCBs Blood Lipid adjusted	Concentrations were low in cases and controls Examples (pg/g fat): Cases (n = 53) Controls (n = 51) PCB-126: 22.0 19.5 PCB-118: 10,100 9,300 TCDD: 1.84 2.02 1,2,3,7,8-PeCDD: 2.33 2.58 1,2,3,6,7,8-HxCDD: 29.3 24.6	**Endometriosis** Regression models of continuous and dichotomised exposure variables and endometriosis stage adjusted for different sets of modifying variables indicated no difference between cases and controls. Analyses including only histology confirmed controls (50% of controls) showed the same result. Risk of bias tier: 2 *Comments*: Small study size. Participants were seeking reproductive assistance, not representative for the general population. Low detection rate, e.g. TCDD detected in 7 out of 124 samples.
Porpora et al. (2009). Endometriosis and organochlorinated environmental pollutants: a case-control study on Italian women of reproductive age n/a (Rome , Italy)	Case-control study n/a	158 (80 cases, 78 controls) Mean (SD) age at outcome assessment: Cases: 31.6 (6.0) Controls: 29.5 (6.1) 2002–2005	CALUX determined BEQ levels Blood (serum) Lipid adjusted	pg BEQs/g fat Cases (n = 80): 18.6 (14.5–23.9) Controls (n = 78): 20.9 (17.3–25.2) p value 0.47	**Endometriosis determined by laparoscopy and histology.** No increased risk of endometriosis associated with serum concentrations of BEQs (covariate adjusted). No difference in stratified analyses based on endometriosis type and localisation. However, increased OR of endometriosis found for increasing serum levels of NDL-PCBs. Risk of bias tier: 1
Simsa et al. (2010).	Case	201 (96 cases, 105	CALUX determined	Median (range)	**Stage of endometriosis**

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Increased exposure to dioxin-like compounds is associated with endometriosis in a case-control study in women. n/a (Belgium, Leuven)	control study n/a	controls) Mean age at outcome assessment (years): 31.5 (similar in cases and controls) 2001–2005	BEQ levels Blood plasma collected before laparoscopic operation Lipid adjusted	(pg BEQs g/fat) Controls (n = 105): 19.4 (5.4–61.2) Endometriosis (all stages) (n = 96): 21.2 (7.7–54.9) Total (n = 200): 20.3 (5.4–61.2)	Patients with low concentrations (<25th centile) and group with high concentrations (>75th centile) of DL-compounds, age-adjusted OR to have endometriosis was 2.44 (95% CI=1.04–5.70; p=0.04) OR was 3.0 (95% CI=1.1–8.6; p=0.03) when only cases with moderate and severe endometriosis were considered. Risk of bias tier: 2 *Comments*: Did not consider important confounders including BMI, smoking history, age at menarche, reproductive history, disease duration, infertility duration, infertility diagnosis. Participants were seeking reproductive assistance, not representative for the general population.
Cai et al. (2011). Dioxins in ascites and serum of women with endometriosis: a pilot study. n/a (Japan, Tokai)	Case control n/a	17 (10 cases, 7 controls) Age at outcome assessment: Endometriosis group: 33.5 (3.6) Control group: 36.4 (5.9) 2004–2007	17 PCDD/Fs, 12 DL-PCBs Blood (serum), peritoneal fluid (ascites) Lipid adjusted	(pg WHO_{1998}-TEQ/g fat) Mean (SD) in blood Cases (n=10) Controls (n=7) PCDD/Fs: 16.1 (5.6) 14.3 (3.1) DL-PCBs: 7.2 (1.8) 7.5 (3.9) Mean (SD) in peritoneal fluid (ascites):	**Endometriosis** Higher concentrations of PCDFs and DL-PCBs observed in peritoneal fluid than in serum, whereas the reverse was shown for PCDDs. Higher levels of PCDD/F-TEQs in peritoneal fluid significantly associated with increased risk of endometriosis (OR=2.5; 95% CI 1.17–5.34; p=0.035). No association with blood PCDD/Fs.

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
				Cases Controls PCDD/Fs: 12.2 (10.5) 10.8 (12.3) DL-PCBs: 18.7 (5.3) 19.3 (9.7)	Risk of bias tier: 2 *Comments*: Small sample size; authors state study had too low power to detect any association.
Martínez-Zamora et al. (2015). Increased levels of dioxin-like substances in adipose tissue in patients with deep infiltrating endometriosis n/a (Spain, Catalonia)	Case control n/a	60 (30 DIE, 30 controls) Age at outcome assessment: DIE cases group: 32.5 (3.8) Control group: 31.1 (4.9) Time of tissue sampling: not reported	17 PCDD/Fs, 12 DL-PCBs Adipose tissue (collected during the surgical procedure) Lipid adjusted	Median (IQR) WHO_{2005}-TEQ for each individual congeners analysed, but Total TEQ not reported TCDD, Median (IQR) (pg/g fat) Cases (n = 30): 0.70 (0.53, 0.76) Controls (n = 30): 0.40 (0.32, 0.64)	**Deep infiltrating endometriosis (DIE)** OR (95% CI) TCDD: 1.41 (1.12-2.10) 1,2,3,7,8-PeCDD: 1.82 (1.36-7.14) For TCDD, 1,2,3,7,8-PeCDD, 2,3,4,7,8-PeCDF, PCB-126, PCB-114, PCB-156, PCB-189 significantly higher in patients with DIE compared to control group ($p<0.05$). Risk of bias tier: 1 *Comments*: Small study size, exploratory. Surgery-based sampling frame may induce selection bias.
Ploteau et al. (2017). Associations between internal exposure levels of persistent organic pollutants in adipose tissue and deep infiltrating endometriosis with or without concurrent ovarian endometrioma n/a (France)	Case control	99 (44 controls, 24 cases of DIE only, 25 cases of DIE+OvE) Age (range) at outcome assessment: 18–45. 2013–2015	17 PCDD/Fs, 12 DL-PCBs Adipose tissue Lipid adjusted	Median (P25, P75) total TEQ (pg WHO_{2005}-TEQ/g fat) Controls (n = 44): 9.88 (7.06, 12.82) Cases with DIE alone (n = 24): 8.94 (8.94, 14.24) Cases with DIE+OvE (n = 25):	**Deep infiltrating endometriosis (DIE), and DIE occurring alone or together with ovarian endometrioma (OvE)** Adjusted OR (95% CI) per 1 sd increase in Total TEQ: DIE vs controls (n=99, unclear from the study): 1.82 (1.02–3.45) DIE+OvE vs controls (n=69): 2.86 (1.29–7.38)

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
				14.36 (14.36, 19.23)	DIE only vs controls (n=68): 1.39 (0.72–2.82) DIE+OvE vs DIE only (n=49): 2.49 (1.03–7.24) The study investigated associations between exposure to multiple individual organochlorine compounds, and after adjustment for multiple comparison test the p was >0.05 and no more significant. Only the OR for OCDF for DIE vs controls and DIE+OvE vs controls remained significant after such adjustment. Risk of bias tier: 1
PUBERTAL DEVELOPMENT					
Warner et al. (2004). Serum dioxin concentrations and age at menarche. Seveso Women's Health Study (SWHS) (Italy, Seveso)	Cohort 20 years follow-up	282 Mean (SD) age at follow-up in 1996–98: 27.3 (3.8) 1976–1977 (n = 257) 1978–1981 (n = 23) 1996 (n = 2)	TCDD Blood (serum) Lipid adjusted	Median (n = 282) (pg/g fat) <11 years 183.5 11 years 109.7 12 years 122.0 13 years 207.5 14 years 135.0 >14 years 136.0 Total 140.3	**Age at menarche** No associations between TCDD (analysed as continuous as well as categorical variable) and age at menarche. Risk of bias tier: 1
Den Hond et al. (2002). Sexual maturation in relation to polychlorinated aromatic hydrocarbons: Sharpe and Skakkebaek's hypothesis revisited. Environment and Health Study (Belgium)	Cross-sectional n/a	120 girls Mean (SD) age at outcome assessment: 17.4 (0.8) 1999	CALUX determined BEQ levels Blood serum Fat was determined	Geometric mean (95% CI) (ng BEQ/L) Peer (rural) (n = 60): 0.11 (0.09–0.13) Wilrijk (urban) (n = 21): 0.17 (0.13–0.22)	**Female sexual development** A doubling of the serum dioxin concentrations increased the odds of not having reached the adult stage of breast development: OR=2.3 (p=0.02) Pubic hair growth: OR=1.0 (p=0.97) Serum concentrations of testosterone,

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
				Hoboken (urban) (n= 39): 0.21 (0.17–0.26) p-value <0.001	estradiol, SHBG, Inhibin B, LH, FSH: No correlation of CALUX-BEQs and serum hormones levels. Risk of bias tier: 2
Su et al. (2012). The effect of in utero exposure to dioxins and polychlorinated biphenyls on reproductive development in eight year-old children. Part of a prospective study of dioxins/PCBs for the general population (Taiwan)	Cohort 2001–2009	33 F Mean age at outcome assessment: 8 2000–2001	17 PCDD/Fs, 12 DL-PCBs Placenta Lipid adjusted	Median (range) (pg WHO_{1998}-TEQ/g fat) Maternal total (n = 56): 14.8 (6.8, 29.1) Maternal Girls (n = 33): 14.7 (6.8, 25.1)	**Indicators of reproductive development (Tanner stage)** Fundus and uterus lengths were not different in girls exposed to low vs. high maternal total TEQ. Hormone levels (testosterone, estradiol, LH, FSH): Hormone levels were generally unaffected by PCDD/Fs. Estradiol concentrations significantly lower in children exposed to higher levels than median of PCDD/F+PCB-TEQ compared to children exposed to levels lesser than median (P=0.003). Analyses stratified by sex not reported. Risk of bias tier: 2
Croes et al. (2014). Monitoring chlorinated persistent organic pollutants in adolescents in Flanders (Belgium): Concentrations, trends and dose-effect relationships (FLEHS II). Flemish Environment and	Cross-sectional n/a	282 girls Age at outcome assessment: 13.6–17.0 2008–2011	CALUX determined BEQ levels Blood serum Lipid adjusted	Geometric mean (pg BEQ/g fat) referents, both sexes: PCDD/F-BEQs: 108 (101, 114) DL-PCB-BEQs: 32.1 (30.1, 34.2)	**Female sexual development** DL-PCB-BEQs negatively correlated with breast development in girls (p=0.04, OR=0.56 after Ln transformation). Testosterone, LH, SHBG, total 17β-estradiol: No significant relationship.

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Health Study FLEHS II (Belgium, Hotspots: Genk-Zuid and Menen)				Concentrations were significantly lower in hotspot areas	Risk of bias tier: 2
OTHER EFFECTS IN FEMALE REPRODUCTION					
Den Hond et al. (2002). Sexual maturation in relation to polychlorinated aromatic hydrocarbons: Sharpe and Skakkebaek's hypothesis revisited. Environment and Health Study (Belgium)	Cross-sectional n/a	120 girls Mean (SD) age at outcome assessment: Girls: 17.4 (0.8) 1999	CALUX determined BEQ levels Blood serum Fat was determined	Geometric mean (95% CI) (ng BEQ/L) Peer (rural) (n = 60): 0.11 (0.09–0.13) Wilrijk (urban) (n = 21): 0.17 (0.13–0.22) Hoboken (urban) (n = 39): 0.21 (0.17–0.26) *p*-value <0.001	**Menstrual history** No associations were reported between exposure and menstrual cycle characteristics. Serum concentrations of testosterone, estradiol, SHBG, Inhibin B, LH, FSH: No correlation of CALUX-BEQs and serum hormones levels. Risk of bias tier: 2
Eskenazi et al. (2002b). Serum dioxin concentrations and menstrual cycle characteristics. Seveso Women's Health Study (SWHS) (Italy, Seveso)	Cohort 20–21 years	301 Mean (SD, range) age at outcome assessment: Women pre-menarcheal at the time of the explosion (n = 134): 27.1 (3.8, 20–37) Women post-menarcheal at the time of the explosion (n =	TCDD Blood (serum) Lipid adjusted	Median (IQR) (n = 301) (pg/g fat) 67.5 (30–194)	**Menstrual cycle characteristics (mean length of menstrual cycle, irregular menstrual cycles, mean number of days of menstrual flow, heaviness of menstrual flow)** Among women who were premenarcheal at the time of the explosion, a 10-fold increase in serum TCDD level was associated with a lengthening of the menstrual cycle by 0.93 days (95% CI 0.01–1.86) and a reduction in the odds of scanty menstrual flow (adjusted OR=0.33, 95% CI 0.10–1.06). Among women who were postmenarcheal at

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		167): 38.3 (3.9, 31–44) 1976–1985			the time of the explosion, TCDD was not associated with menstrual cycle length or scantiness of flow. In both menarche groups, TCDD levels associated with decreased odds of having irregular cycles (adjusted OR=0.46, 95% CI 0.23–0.95) but not related to days of flow. Risk of bias tier: 1
Chao et al. (2007). Placental transfer of polychlorinated dibenzo-*p*-dioxins, dibenzofurans, and biphenyls in Taiwanese mothers in relation to menstrual cycle characteristics. n/a (Taiwan, Central Taiwan, Taichung)	Cross-sectional n/a	119 (13 cases, 106 controls) Mean (SD) age at outcome assessment: 29.4 (4.5) 2000–2001	17 PCDD/Fs, 12 DL-PCBs Placenta Lipid adjusted	Median, Mean (SD) (pg WHO-TEQ/g fat) (n = 119) PCDD/F-TEQs: 10.2, 10.7 (4.11) DL-PCB-TEQs: 2.67, 2.92 (1.60) Total TEQs: 12.8, 13.6 (5.07) * WHO-TEF scheme not reported	**Menstrual cycle** Placental PCDD/F-TEQ level washigher in women (age ≥ 19 years) with irregular menstrual cycle than in those (age < 18 years) with regular menstrual cycle (p = 0.032). Placental DL-PCB-TEQ level was higher in women with menstrual cycles longer than 33 days versus less than 33 days (p = 0.006). No associations between Total TEQ and duration of menstrual cycle length or duration of menstrual bleeding per cycle. Risk of bias tier: 2
Warner et al. (2007). Serum dioxin concentrations and quality of ovarian function in women of Seveso. Seveso Women's Health Study	Cohort Recruitment 1996–1998 20 years	363 women who were 20–40 years of age and nonusers of oral contraceptives Menarche before	TCDD Blood (serum) Lipid adjusted	(pg/g fat) (n=163) Median (IQR) 77.3 (33–214)	**Ovarian function, progesterone and oestradiol levels** Serum TCDD was not associated with number or size of ovarian follicles.

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
(SWHS) (Italy, Seveso)	follow-up	explosion: Yes: 168 women No: 195 women 1976–1977 (n = 330) 1978–1982 (n = 25) 1996–1997 (n = 8)		Range: 2.8–17,300	Of women in luteal phase, 87 (67%) ovulated. Serum TCDD not associated with ovulation. Among those who had ovulated, serum TCDD not associated with serum progesterone or oestradiol. Risk of bias tier: 1
Eskenazi et al. (2010). Serum Dioxin Concentrations and Time to Pregnancy. Seveso Women's Health Study (SWHS) (Italy, Seveso)	Cohort >20 years	278 women who delivered a live birth that was not the result of contraceptive failure Mean (SD) maternal age at explosion: 17.2 (6.2) Mean (SD) maternal age at interview: 37.7 (6.2) 1976–1977 (n=431) 1978–1981 (n=13) 1996–1997 (n=19)	TCDD Blood (serum) Lipid adjusted	Median (IQR) (n = 463) (pg/g fat) At time of exposure: 50 (25–117) Extrapolated to time of conception: 13.4 (5.3–38.2)	**Time to pregnancy** For every 10-fold increase in serum TCDD a 25% increase in time to pregnancy (adjusted fecundability OR=0.75, 95% CI 0.60–0.95) and doubling in odds of infertility (OR=1.9, 95% CI 1.1–3.2) was observed. Risk of bias tier: 1
Eskenazi et al. (2007). Serum dioxin concentrations and risk of uterine leiomyoma in the Seveso Women's Health Study Seveso Women's Health Study	Cohort Around 20 years	956 Mean (SD) age at outcome assessment (at follow up): 40.4 (11.5)	TCDD Blood (serum) Lipid adjusted	TCDD categorised in 3 groups (pg/g fat): ≤20.0 (n = 151) 20.1–75.0 (n = 410) >75.0 (n = 395)	**Fibroids** HR (95% CI) for earlier onset of fibroids was associated with TCDD exposure. The estimated age-adjusted HR associated with a 10-fold increase in serum TCDD was 0.83 (95% CI 0.65-1.07)

Reference Trial or study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
(SWHS) (Italy, Seveso)		1976–1977 (n = 872) 1978–1981 (n = 56) 1996 (n = 28)			Compared with that for women with TCDD levels of ≤20 pg/g fat, the age-adjusted HR were 0.58 (95% CI 0.41-0.81) for women with levels of 20.1-75.0 pg/g fat and 0.62 (95% CI 0.44-0.89) for women with levels of >75.0 pg/g fat. Risk of bias tier: 1
Eskenazi et al. (2005). Serum dioxin concentrations and age at menopause Seveso Women's Health Study (SWHS) (Italy, Seveso)	Cohort 1–21 years for TCDD levels 20–22 years for health outcome assessment	616 Mean (SD) age at outcome assessment (interview): 47.8 (8.1) 1976–1977 (n = 564) 1978–1982 (n = 28) 1996–1997 (n = 24)	TCDD Blood (serum) Lipid adjusted	[Menopausal category N (%)], Median (IQR) (n = 616) (pg/g fat) Premenopause [260 (42.2%)], 43.6 (21–91) Natural menopause [169 (27.4%)], 45.8 (28-100) Surgical menopause [83 (13.5%)], 43.4 (28–98) Impending menopause [13 (2.1%)], 43.8 (24–105) Perimenopause [33 (5.4%)], 36.5 (22–85) Other [58 (9.4%)], 39.6 (17–85) Total [616 (100%)], 43.7 (24-95)	**Menopausal status** TCDD (pg/g fat) nmp/ntot (%) HR (95% CI) *Continuous* $\log_{10}$ TCDD 169/616 (27) 1.02 (0.8–1.3) *Quintiles* < 20.4 24/123 (20) 1.0 (reference) 20.4–34.2 35/123 (28) 1.1 (0.7–1.8) 34.3–54.1 41/123 (33) 1.4 (0.9–2.3) 54.2–118 37/124 (30) 1.6 (1.0–2.7) > 118 32/123 (26) 1.0 (0.6–1.8) Risk of bias tier: 2

PEND: peritoneal endometriosis; DEN: deep endometriotic nodules; DIE: deep infiltrating endometriosis; OvE: ovarian endometrioma; FSH: follicle stimulating hormone; LH: luteinizing hormone; SHBG: sex hormone binding globuline; n/a: not applicable.

A.8.3. Studies on birth outcomes

Table 67. Epidemiological studies on the association between exposure to PCDD/Fs and DL-PCBs and **birth outcomes.** Details about the risk of bias appraisal can be found in **Annex A.9.3**.

Reference **Trial or Study name (geography)**	**Study type** **Duration**	**Participants in the study** **Age at outcome assessment (years)** **Year of tissue sampling**	**Compounds** **Measurement of exposure**	**Levels of exposure**	**Parameters measured and Measures of effect** **Risk of bias tier**
SEX RATIO IN OFFSPRING					
Mocarelli et al. (2000). Paternal concentrations of dioxin and sex ratio of offspring Seveso study (Italy, Seveso)	Cohort n/a	535 parents, 674 births (346 girls, 328 boys) M, F (parents) Age of parents at exposure: 3–45. 1976–1977	TCDD Blood Lipid adjusted	Median (range) (pg/g fat) Fathers (n = 239) 96.5 (2.8–26,400) Mothers (n = 296) 62.75 (6.45–12,500)	Increased probability of female births (lower sex ratio) with increasing serum TCDD concentrations from fathers (*p* for trend=0.008). The sex ratio was lower in fathers that were younger than 19 years at exposure than those above. For exposed mothers, the sex ratio was not associated with exposure. A lower sex ratio in the Seveso region with highest exposure (zone A) was also observed in the period 1973–1976, i.e. starting before the accident. Risk of bias tier: 1
Schnorr et al. (2001). Spontaneous abortion, sex ratio, and paternal occupational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. NIOSH (USA)	Cross-sectional n/a	440 women (220 referents, 200 workers), 707 referents births, 300 births from workers before exposure, 332 births during or after exposure	TCDD Blood (serum) Levels at conception estimated based on levels in 1987 Lipid adjusted	Paternal median (range) at conception (pg/g fat) Referents (n = 79): 6 (2–19) Workers: - before exposure: 6 (all pre-exposure births assigned median referent	Sex ratio did not differ by TCDD exposure (0.53 and 0.54 among workers and referents, respectively), and did not change over quartiles of estimated TCDD in father at conception. Risk of bias tier: 2 *Comments*: Uncertainty associated with estimated levels at conception is unknown.

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		M Age of parents at exposure: Adults 1987–1988		value of 6) - estimated level at conception during and after exposure: 254 (3–16,340)	
Ryan et al. (2002). Sex ratios of children of Russian pesticide producers exposed to dioxin. Russia (Bashkortostan, Ufa)	Cohort n/a	198 parents, 227 births (150 boys, 48 girls) M, F Age of parents at exposure: Adults (no ages reported) 1992–2001	TCDD PeCDD Whole Blood Lipid adjusted	Mean values blood lipid sampled in 1997–2000 (n = 84) (pg/g fat) Bashkortostan subjects: TEQ: 27 TCDD: 4.8 Ufa subjects: TEQ: 47 TCDD: 17 * TEF scheme not reported.	Sex ratio (fraction male) of combined cohort of 227 children from 150 men and 48 women workers was 0.40, significantly lower (z-test=3.21; p<0.001) than those for city of Ufa (0.512). Analysis of sex ratio of children according to maternal or paternal exposure, resulted in decreased sex ratio for fathers (0.38, z-test=3.60; p<0.001) and normal sex ratio of 0.51 for the mothers. Risk of bias tier: 2 *Comments*: Blood samples collected many years after exposure in chemical manufacturing and only from a small subset. Individual exposures are not known.
't Mannetje et al. (2017). Sex ratio of the offspring of New Zealand phenoxy herbicide producers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.	Cohort	148 parents, 355 births (197 boys, 158 girls) M, F Age of parents at	TCDD in 2007–2008 (back-calculated to the time of their offspring's birth and to 1984 when production ceased)	Mean TCDD (pg/g fat) 9 (corresponding to 49 pg/g in 1984) Group of 60 workers	Overall sex ratio of as cohort of 355 children from 127 men and 21 women was 0.55 (197 boys, 158 girls). For current exposure < 4pg/g fat vs ≥ 4 pg/g fat in fathers: OR of male birth 0.46 (95% CI 0.29 to 0.73). With TCDD in quartiles < 2 to ≥ 8

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
n/a (New Zealand)		exposure: Adults 2007–2008	Blood (serum) Lipid adjusted	directly involved in herbicide production: 19 (corresponding to 109 pg/g in 1984)	pg/g fat (p for trend 0.01). For exposure back-calculated to child birth < 20 pg/g fat vs ≥2 0 pg/g fat in fathers: OR of male birth 0.49 (95% CI 0.30 to 0.79). With TCDD in quartiles <20 to ≥100 pg/g (p for trend 0.007). For the 21 exposed mothers, the sex ratio was not associated with exposure. Risk of bias tier: 2
BIRTH WEIGHT AND OTHER BIRTH OUTCOMES					
Tsukimori et al. (2013). Blood levels of PCDDs, PCDFs, and coplanar PCBs in Yusho mothers and their descendants: Association with fetal Yusho disease. 2002–2008 Yusho Cohort (Japan, Western Japan)	Cross sectional ~40 years follow-up	64 mothers, 117 births M, F Mean (range) age of the mothers at exposure: 15.8 (prenatal–29) Mean age (range) at blood sampling: 53.0 (32-70)	17 PCDD/Fs, 4 DL-PCBs (-77, -81, -126, -169) Blood (maternal) Lipid adjusted	Mean (SD), median (n = 64) (pg WHO_{2005}-TEQ/g fat) Black baby group PCDD-TEQs: 736.5 (526.5), 647.0 PCDF-TEQs: 1,923.9 (2,273.8), 1,313.1 DL-PCB-TEQs: 57.6 (30.4), 45.6 Non-black baby group PCDD-TEQs: 243.0 (275.9), 139.0 PCDF-TEQs: 460.7 (905.3), 141.6 DL-PCB-TEQs: 31.8 (29.7), 27.1	**Black baby, non-black baby (Foetal Yusho Disease, FYD)** Estimated PCDD-TEQ, PCDF-TEQ, DL-PCB-TEQ, and total TEQ in the maternal blood at delivery associated with significantly increased risk of FYD. OR (risk of FYD for a 10-fold increase in blood dioxin) largest for 1,2,3,6,7,8-HexaCDD (OR=28.6, 95% CI 1.67–489.9, p=0.02). Levels of 1,2,3,6,7,8-HexaCDD in both the Yusho mothers and their descendants with FYD were higher than the levels in those without FYD. Risk of bias tier: 2

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Tsukimori et al. (2012). Maternal exposure to high levels of dioxins in relation to birth weight in women affected by Yusho disease. Yusho Cohort (Japan, Western Japan)	Cohort 41 years	101 mothers, 190 births M, F Mean (range) age of the mothers at exposure: 16.8 (prenatal–35) At blood sampling: 54.2 (32–75) 2002–2008	17 PCDD/Fs, 4 DL-PCB (-77, -81, -126, -169) Blood Lipid adjusted	Mean maternal blood levels at sampling (n = 101) Total TEQ: 68.92 pg/g fat Estimated maternal blood levels at delivery Total PCDD/Fs and non-*ortho* PCB-TEQs: 1,077.1 pg/g fat	**Birth weight** Total PCDD-TEQ, total PCDF-TEQ and total non-*ortho* PCBs levels inversely associated with birth weight: Total PCDD-TEQ: adj β =−161.9 g; 95% CI=−265.3, −58.6 Total PCDF-TEQ: adj β =−105.9 g; 95% CI=−179.5, −32.2 Total non-*ortho* PCBs: adj β =−178.4 g; 95% CI=−318.3, −38.5 Significant inverse associations with birth weight for total PCDD-TEQ, total PCDF-TEQ, and total non-*ortho* PCB-TEQ levels among male infants, but not females. Significant inverse associations with birth weight found for 9 congeners among all infants; the adjusted β-coefficients largest for 1,2,3,6,7,8-HxCDD and smallest for 2,3,4,7,8-PeCDF. Risk of bias tier: 2
Konishi et al. (2009). Prenatal exposure to PCDDs/PCDFs and dioxin-like PCBs in relation to birth weight. Hokkaido Study on Environment and Children's	Cohort 3 years duration: Subjects recruited 2002-2005	398 mothers, 398 births (189 boys, 209 girls) M, F Maternal mean (SD) age:	17 PCDD/Fs, 12 DL-PCBs Blood Lipid adjusted	Mean (SD) maternal blood levels (n = 398) (pg WHO_{1998}-TEQ/g fat) PCDD-TEQ: 7.3 (3.3) PCDF-TEQ: 3.8 (1.6)	**Birth weight** Based on WHO_{2005}-TEQ Significant adverse effect observed for total PCDDs-TEQ (adj-β=-231.5g, 95% CI -417.4 to -45.6g) and total PCDFs-TEQ (adj-β=-258.8g, 95% CI -445.7 to -71.8g).

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Health (Japan, Hokkaido, Sapporo)		31.0 (4.7) 2002–2005		PCDD/F-TEQ: 11.1 (4.8) DL-PCB-TEQ: 6.4 (3.5) Total TEQ: 17.5 (7.7) (pg WHO_{2005}-TEQ/g fat) PCDD-TEQ: 7.4 (3.3) PCDF-TEQ: 2.6 (1.1) PCDD/F-TEQ: 10.0 (4.3) DL-PCB-TEQ: 4.9 (2.9) Total-TEQ: 14.9 (6.6)	For male infants, significant adverse associations with birth weight for total PCDDs-TEQ, total PCDD/Fs-TEQ, and total TEQ. Associations not observed among female infants. Significant negative association with 2,3,4,7,8-PeCDF (adj-β=-224.5g, 95% CI -387.4 to -61.5g). Risk of bias tier: 2
Halldorsson et al. (2009). Dioxin-like activity in plasma among Danish pregnant women: dietary predictors, birth weight and infant development. Danish National Birth Cohort (Denmark)	Cohort n/a	100 mother-child pairs M, F Maternal age (range): 25–35 1996–2002	CALUX determined BEQ levels Blood Lipid adjusted	Geometric mean (n = 100) (pg BEQ/g fat) 46.0 Percentiles: 5^{th}: 7.0 25^{th}: 19.6 50^{th}: 38.2 75^{th}: 56.6 95^{th}: 134.6	**Birth weight** Plasma dioxin-like activity not associated with birth weight. Risk of bias tier: 2
Papadopoulou et al. (2013). Maternal dietary intake of dioxins and polychlorinated biphenyls and birth size in the Norwegian Mother and Child Cohort Study (MoBa)	Cohort n/a	50,651 mother-child pairs M, F Maternal age (range): <25–≥35	17 PCDD/Fs, 12 DL-PCBs FFQ (as part of the MoBa study) Not lipid adjusted	Median (IQR) intake of PCDD/Fs and DL-PCBs (n = 50,651) (pg WHO_{2005}-TEQ/kg bw/day) 0.55 (0.37)	**Gestational age, birth weight, birth head circumference** Newborns of mothers in upper quartile of PCDD/Fs and DL-PCBs intake had 62 g lower birth weight (95% CI -73, -50), 0.26 cm shorter birth length (95% CI -0.31, -0.20) and 0.10 cm shorter head circumference (95% CI -0.14, -

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
MoBa Cohort (Norway)		Age at outcome assessment: newborns 2002–2008			0.06) than newborns of mothers in lowest quartile of intake. Negative association weaker as seafood intake was increasing. No association between dietary PCDD/Fs and DL-PCB intake and risk for small-for-gestational age neonate. Risk of bias tier: 2
Papadopoulou et al. (2014). Maternal diet, prenatal exposure to dioxin-like compounds and birth outcomes in a European prospective mother-child study (NewGeneris). European NewGeneris project (Greece, Spain, Norway, Denmark, UK)	Cohort n/a	604 mother-child pairs F Median maternal age: 31.3 Median gestational age: 273.8 days 2007–2010	CALUX determined BEQ levels Blood Lipid adjusted	Median (IQR) (n = 604) (pg BEQ/g fat) 39.3 (28.2)	**Gestational age, birth weight, parity** Upper tertile of BEQ-diet score associated with change in birth weight of -121g (95% CI -232, -10g) compared to lower tertile after adjustment. Non-significant reduction in gestational age observed (-1.4d, 95% CI-3.8, 1.0d) Risk of bias tier: 2
Lawson et al. (2004). Paternal occupational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and birth outcomes of offspring: birth weight, preterm delivery, and birth defects.	Cohort (birth outcomes)	393 mothers, 1,117 births M, F Maternal mean (SD) age: Referents:	TCDD Blood (serum) Lipid adjusted	Median (range) paternal TCDD at conception retrospective modelled (pg/g fat) Referents (n = 79): 6 (2–19) Workers:	**Length of gestation, birth weight, birth defects** (CNS, CVD, genitourinary, clubfoot, hip/lower limb, cleft lip/palate, Down's syndrome) Mean birth weight among full-term babies similar among referents, pre-exposed workers and workers exposed during pregnancy (3,420,

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
National Institute for Occupational Safety and Health (NIOSH) (USA)		26.1 (5.4) Workers before exposure: 23.4 (4.6) Workers during exposure: 27.4 (5.3) Mean age at outcome assessment: 9 months 1987–1988		- before exposure (n = 221): 6 (all pre-exposure births assigned median referent value of 6) - during exposure (n = 291): 254 (3–16,340) Current levels: measured	3,347, and 3,442 g, respectively). After adjustment, neither continuous nor categorical TCDD concentration had effect on birth weight. Risk of bias tier: 2
Wohlfahrt-Veje et al. (2014). Polychlorinated dibenzo-*p*-dioxins, furans, and biphenyls (PCDDs/PCDFs and PCBs) in breast milk and early childhood growth and IGF1. Copenhagen Mother Child Cohort of Growth and Reproduction (Denmark, Copenhagen)	Cohort n/a	417 mother-child pairs (218 boys, 199 girls) M, F Maternal age (range): <25–>35 Age at outcome assessment: 0, 3 (IGF1), 18 and 36 months 1997–2001	17 PCDD/Fs, 12 DL-PCBs Human milk Lipid adjusted	(pg WHO_{2005}-TEQ/g fat) (n = 417) Mean: 21.2 Median: 20.2 Range: 4.9–114.1	**Physical measurements at birth and early childhood growth until 3 years of age, serum IGF1** Total TEQ associated with lower % fat (-0.45, 95% CI-0.89,-0.04), non-significantly with lower weight and length at birth, accelerated height growth and early weight increase, and increased IGF1 serum levels at 3 months. Risk of bias tier: 1
Vartiainen et al. (1998). Birth Weight and Sex of Children and the Correlation	Cross-sectional n/a	167 mothers, 166 births	17 PCDD/Fs, 10 DL-PCBs, 2 mono-*ortho* PCBs	Mean (SD) (primiparae women) (n = 167) (pg/g fat)	**Birth weight** Mean weights of children were similar in the

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
to the Body Burden of PCDDs/PCDFs and PCBs of the Mother. n/a (Finland)		M, F Age (range) of the mothers: 19–41 1987	Human milk Lipid adjusted	Urban area: PCDD/Fs (I-TEQ): 26.3 (11.8) DL-PCBs (WHO-TEQ): 37.0 (24.8) Rural area: PCDD/Fs (I-TEQ): 20.1 (6.5) DL-PCBs (WHO-TEQs): 26.5 (9.90)	rural and urban areas among primiparae. Birth weight, especially of boys, was slightly decreased with increasing concentrations of PCDD/Fs, 2,3,4,7,8-PeCDF, 1,2,3,7,8-PeCDD, and TCDD. When the analysis was restricted to primiparae, no statistically significant correlation between birth weight and PCDD/Fs. No correlation found between the weight of the child and PCB-TEQs among all mothers or among boys or girls. Risk of bias tier: 1
Tajimi et al. (2005). Relationship of PCDD/F and Co-PCB concentration in breast milk with infant birthweights in Tokyo, Japan. n/a (Japan)	Cross-sectional n/a	240 mothers, 240 births M, F Age (range) of the mothers: 25–34 1999–2000	17 PCDD/Fs, 12 DL-PCBs Human milk Lipid adjusted	Mean (SD) (n = 240) (pg WHO_{1998}-TEQ/g fat) PCDD/Fs: 14.9 (6.0) DL-PCBs: 10.6 (5.1) Total: 25.6 (9.7)	**Birth weight** Statistically significant negative correlation between birth weight and most of the individual congeners. Significant negative correlations with DL-PCB-TEQ, and the sum of PCDD/F+DL-PCB-TEQ. Only OCDD significant in adjusted models. Risk of bias tier: 2
Govarts et al. (2016). Combined effects of prenatal exposures to environmental chemicals on birth weight Flemish Environment and Health Study FLEHS II	Cross-sectional n/a	248 mother-child pairs (128 boys, 120 girls) M, F Maternal age	CALUX determined BEQs Cord blood (plasma) Lipid adjusted	Mean (95% CI) P25, P75 (n = 248) (pg BEQ/g fat) 17.4 (16.3-18.6) 13.0, 24.00	**Birth weight** BEQs not associated with birth weight. Risk of bias tier: 2

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
(Belgium, Flanders)		(range): ≤25–>35 Age at outcome assessment: newborns 2008–2009			
Tsukimori et al. (2008). Long-term effects of polychlorinated biphenyls and dioxins on pregnancy outcomes in women affected by the Yusho incident. Yusho Cohort (Japan)	Cohort 36 years	214 mothers (512 pegnancies) F Maternal mean (SD) age at interview: 59.4 (12.2) 2001–2005	PeCDF, PCB-126 Blood (serum) Lipid adjusted	Geometric mean (min-max) (n = 97) (pg/g fat) <u>Year of delivery: 1968–1977</u> PeCDF: 2,899.3 (112.1–19942.7) PCB-126: 336.4 (89.5–1705.3) <u>Year of delivery: 1978–1987</u> PeCDF: 697.7 (52.4–2289.6) PCB-126: 159.0 (94.7–330.5) <u>Year of delivery: 1988–2003</u> PeCDF: 39.5 (4.0–951.8) PCB-126: 60.4 (16.9–118.8)	**Spontaneous abortion, preterm delivery, pregnancy loss** Within the first 10 years after exposure (pregnancy years 1968–1977), the proportion of preterm delivery (ORadj = 5.70; 95% CI 1.17–27.79; p=0.03) significantly increased compared with the proportion in pregnancy years 1958–1967 (10 years before the incident). Spontaneous abortion (ORadj=2.09; 95% CI 0.84–5.18), and pregnancy loss (ORadj=2.11; 95% CI 0.92-4.87) more frequent (OR=2.18; 95% CI 1.02-4.66). Not significant in pregnancy years 1968–1977. No significant increases in the proportions of adverse pregnancy outcomes in pregnancies occurring during 1978–1987 or 1988–2003 compared with those in pregnancies before 1968. Risk of bias tier: 2

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Eskenazi et al. (2003). Maternal serum dioxin levels and birth outcomes in Women of Seveso, Italy. Seveso Women's Health Study (SWHS) (Italy, Seveso)	Cohort 20 years	510 mothers, 888 pregnancies M, F Mean (SD) maternal age at explosion: 19.1 (7.9), at interview: 3.9.7 (8.0) Age at outcome assessment: newborns 1976–1977 (n=413) 1978–1981 (n=12) 1996 (n=19)	TCDD Blood (serum) Lipid adjusted	Median (IQR) maternal level at time of explosion (n = 510) (pg/g fat) 46.6 (24.3–104.0)	**Congenital anomalies/disorders, spontaneous abortions, birth weight, gestational age** No association of log10TCDD in samples collected close to the explosion with spontaneous abortions (adj-OR=0.8; 95% CI=0.6–1.2), with birth weight (adj-β=–4g; 95% CI=–68-60), or with births that were small for gestational age (adj-OR=1.2; 95% CI=0.8–1.8). Associations with birth weight (adj-β=–92g; 95% CI=–204–19) and with small for gestational age (adj-OR=1.4; 95% CI=0.6–2.9) were stronger for pregnancies within first 8 years after exposure. TCDD associated with 1.0–1.3 day non-significant adjusted decrease in gestational age. TCDD associated with a 20-50% non-significant increase in the odds of preterm delivery. Risk of bias tier: 1
Wesselink et al. (2014). Maternal dioxin exposure and pregnancy outcomes over 30 years of follow-up in Seveso Seveso Women's Health	Cohort 30 years follow-up	617 mothers, 1,211 pregnancies M, F Average (SD) age at exposure: 16.9	TCDD Blood (serum) Lipid adjusted	Median (IQR) (n = 617) (pg/g fat) 55.0 (27.0–184.0) Estimated TCDD levels at	**Spontaneous abortion, fetal growth, birth weight and birth defects** No association between estimated maternal serum TCDD at pregnancy and spontaneous abortion, foetal growth or gestational length.

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Study (SWHS) (Italy, Seveso)		(9.0), at pregnancy: 29.9 (5.5) 1976, 1996–1998		pregnancy: 9.9 (4.3–29.6)	Non-significant inverse association between maternal serum TCDD in 1976 and birth-weight. Risk of bias tier: 1
Michalek et al. (1998). Paternal dioxin, preterm birth, intrauterine growth retardation, and infant death. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)	Cohort 11–33 years Children were followed-up from pregnancy to 18 years of age	2,134 fathers serving in South-East Asia, 2,082 children M, F Age at outcome assessment: children born between 1959–1992 1987, 1992	TCDD Blood Not lipid adjusted	Paternal TCDD Median (range) (pg/g fat) Comparison: 3.7 (0–10) Background: 5.6 (0–10) 'Low': 39 (11.1–78.8) 'High': 153.4 (79.2–1,424.8) Initial TCDD levels at conception estimated using a constant half-life of 8.7 years. Cut-point of 79 pg/g fat as the median initial TCDD for Ranch Hand children having an initial TCDD level.	**Preterm birth, intrauterine growth retardation, infant death** Preterm birth: risk increased at the 'High' (RR=1.3) and 'Background' (RR=1.4) exposure groups. Intrauterine growth: risk not increased in any exposure category Infant death: risk increased in all Ranch Hand children. Greatest increase in the 'High' exposure group (RR=4.5) and 'Background' group (RR=3.2). Risk of bias tier: 2
Schnorr et al. (2001). Spontaneous abortion, sex ratio, and paternal occupational exposure to 2,3,7,8-tetrachlorodibenzo-	Cross-sectional n/a	502 (281 workers, 260 referents), 1,339 pregnancies (632 from workers' wives, 707 from	TCDD Blood (serum) Lipid adjusted	Paternal TCDD at conception [Median (range)] (pg/g fat):	**Pregnancy history and outcomes** No association between paternal TCDD level at time of conception and spontaneous abortion observed among pregnancies fathered by

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
p-dioxin. National Institute for Occupational Safety and Health (NIOSH) (USA, New Jersey and Missouri)		referents wives) M, F Mean (SD) age of wives at 1st pregnancy: Referents: 22.3 (4.2) Workers: 21.8 (4.2) 1987–1988		Referent: 6 (2–19) Workers: - before exposure: 6 (all pre-exposure births assigned median referent value of 6) - during exposure: 254 (3-16,340)	workers with TCDD levels of: < 20 ppt (OR=0.77, 95% CI=0.48–1.22) 20 to < 255 ppt (OR=0.81, 95% CI=0.40–1.63) 255 to < 1,120, (OR=0.69, 95% CI=0.30–1.58) ≥1,120 ppt (OR=0.95, 95% CI=0.42–2.17) compared to pregnancies fathered by referents. Risk of bias tier: 2
Vafeiadi et al. (2013). In Utero Exposure to Dioxins and Dioxin-like Compounds and Anogenital Distance in Newborns and Infants. European NewGeneris project: Rhea study (Greece, Crete, Heraklion) and Hmar study (Spain, Barcelona)	Cross-sectional n/a	121 newborns (62 boys, 59 girls), 462 young children M (239), F (223) Median (range) age at outcome assessment: 16 (1–31) months 2007–2008	CALUX determined BEQ levels Blood (serum) Lipid adjusted	Maternal levels (n = 700) Median (range) (pg BEQ/g fat) Newborns: ALL: 53.6 'Low'-level group: 42.5 (6–53.6) 'High'-level group: 66.1 (53.7–106.3) Young children: ALL: 50.3 'Low'-level group: 34.7 (range, 6–50.2) 'High'-level group: 63.5 (50.4–225.7) * Values above median	**Anogenital distance (AGD), anoscrotal distance (ASD), and penis width (PW)** in boys (119 newborn and 239 young boys) **Anoclitoral (ACD) and anofourchetal distance (AFD)** in girls (118 newborn and 223 young girls) After adjusting for potential confounders, the AGD was -0.44 mm (95% CI -0.80, -0.08) per 10 pg BEQ/g fat. No associations were found in girls. Risk of bias tier: 1

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
				were categorized as 'high' whereas values below median were categorized as 'low' in both age groups	
Vafeiadi et al. (2014). In Utero Exposure to Compounds with Dioxin-like Activity and Birth Outcomes European NewGeneris project (Greece, Spain, Norway, Denmark, UK)	Cross-sectional n/a	967 mother-child pairs M, F 48% boys among those with cord plasma 50% boys among those with maternal plasma 2006–2010	CALUX determined BEQ levels Blood (serum), cord blood Lipid adjusted	Mean / Median (pg BEQ /g fat) Cord blood samples (n = 269): 38.0 / 34.2 Maternal blood samples (n = 791): 39.0 / 38.3	**Birth weight, length, head circumference** Gestational age (weeks) Lowest tertile: Reference Medium tertile: -0.1 (95% CI, -0.5 to 0.3) Highest tertile: -0.4 (95% CI, -0.8 to -0.1) Test for trend: p-value =0.029 No significant trends for birth weight (p=0.22) or head circumference (p=0.41) Risk of bias tier: 1

AGD: anogenital distance; ASD: anoscrotal distance; PW: penis width; ACD: anoclitoral distance; AFD: anofourchetal distance; FYD: Foetal Yusho Disease; n/a: not applicable.

A.8.4. Studies on thyroid disease and thyroid hormones

Table 68. Epidemiological studies on the association between exposure to PCDD/Fs and DL-PCBs and **thyroid disease and thyroid hormones**. Details about the risk of bias appraisal can be found in **Annex A.9.4**.

Reference **Trial or Study name (geography)**	**Study type** **Duration**	**Participants in the study** **Sex (M/F)** **Age at outcome assessment (years)** **Year of tissue sampling**	**Compounds** **Measurement of exposure**	**Levels of exposure**	**Parameters measured and Measures of effect** **Risk of bias tier**
STUDIES IN ADULTS					
Calvert et al. (1999). Evaluation of diabetes mellitus, serum glucose, and thyroid function among United States workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. n/a (USA, New Jersey and Missouri)	Cross-sectional Exposure during employment: 1951-1969 and between 1958-1972	541 (281 workers from two TCP plants, 260 referents from area) M (mostly), F Mean (SD) age at outcome assessment: Workers: 55.4 (10.3) Referent group: 56 (10.5) 1987–1988	TCDD Blood (serum) Lipid adjusted	Mean (range) (pg/g fat) Workers: 220 (ND–3,400) Referents: 7 (ND–20) ($p<0.001$) Estimated TCDD when occupational exposure stopped (back-extrapolated): 1,900 (ND–30,000)	**TSH, T4, free T4 index** No association between TCDD exposure and TSH or T4. Only (positive) association with free T4 index. Risk of bias tier: 1
Johnson et al. (2001). Serum hormone levels in humans with low serum concentrations of 2,3,7,8-TCDD.	Cross sectional n/a	32 workers having sprayed herbicides M	TCDD Blood (serum) No information about lipid adjustment	Mean <10 pg/g Estimated historical: 50–100 pg/g	**TSH, T4, T3** Inverse associations between estimated historical TCDD and TSH and T3. Risk of bias tier: 2

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
n/a (Australia, Victoria)		Mean (range) age at outcome assessment: 48 (29-76) Year of tissue sampling: not clear.			*Comments*: Small study. Non informative.
Pavuk et al. (2003). Serum 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) levels and thyroid function in Air Force veterans of the Vietnam War. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)	Cross-sectional and Longitudinal 11–35 years	1,009 exposed (Ranch Hand) and 1,429 internal referents (comparison veterans) M Mean (SD) age at outcome assessment: Comparison: 48.8 (7.7) Background: 49.9 (7.4) Low TCDD: 50.2 (7.7) High TCDD: 46.3 (7.2) 1987, 1992, 1997	TCDD Blood (serum) Lipid adjusted Sampling/analysis dates: 1982, 1985, 1987, 1992, 1997 (serum was analysed in 1987, 1992, 1997)	Mean (SD) in 1987 (pg/g fat) Comparison: 4.6 (2.9) Background: 5.8 (2.3) 'Low': 15.6 (4.1) 'High': 69.4 (67.9) Mean (SD) extrapolated levels at the end of the last tour of duty in Vietnam using a constant half-life of 8.7 years 'Low': 55.0 (18.0) 'High': 302.5 (327.3)	**TSH, T4, T3 uptake, free T4 index** TSH slightly but significantly higher in 'High' exposed group. Risk of bias tier: 1

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Foster et al. (2005). Dioxin-like activity and maternal thyroid hormone levels in second trimester maternal serum. n/a (South Western Ontario, Canada,)	Cross-sectional n/a	150 F (pregnant) Age (SD) at outcome assessment: 38.0 (0.2) 2002–2003	CALUX determined BEQ levels Blood (serum) Lipid adjusted	pg BEQs/g fat Mean (SEM): 0.34±0.01 Median (range): 0.27 (0.15–0.73)	**TSH, T4** No association with CALUX-BEQs. Risk of bias tier: 2 *Comments*: Very low TEQs. Non-informative.
Bloom et al. (2006). Chronic exposure to dioxin-like compounds and thyroid function among New York anglers. New York State Angler Cohort Study (NYSACS) (New York State, USA)	Cross sectional n/a	38 (22 having consumed Ontario Lake fish-high PCB, 15 non-consumers of sportfish) M, F Median (range) age at outcome assessment/blood collection: 39.5 (29-45) 1993–1994	17 PCDD/Fs 4 DL-PCBs (-77, -81, -126, -169) Blood (serum) No information about lipid adjustment	Median (range) (pg WHO_{1998}-TEQ/g) Upper bound 0.141 (0.050–0.302)	**TSH, free T4, free T3** No association with WHO-TEQs. Risk of bias tier: 2 *Comments*: Small study. Non informative.
Turyk et al. (2006). Associations of organochlorines with endogenous hormones in	Cross-sectional n/a	56 M	17 PCDD/Fs, 10 DL-PCBs (-77, -81, -126, -169, -105, -114, -118, -123, -157, -167)	Mean (Min, Max) (pg WHO_{1998}-TEQ/g fat) Sport caught fish eaters:	**T3, T4, TSH, SHBG** Inverse association observed between total TEQ and TSH. Chance finding cannot be

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
male Great Lakes fish consumers and nonconsumers. n/a (Lakes Michigan, Huron and Erie, USA)		Mean age at outcome assessment: Sport caught fish eaters: 49.6 Referents: 48.0 1993–1994	Blood (Serum) Lipid adjusted	46 (19, 105) <u>Referents:</u> 21 (11, 42)	excluded (this was the only significant finding for total TEQ out of 10 outcomes tested). Risk of bias tier: 1 *Comments*: Limited quality due to small sample size and possible chance finding.
Chevrier et al. (2014). Serum Dioxin concentrations and thyroid hormone levels in the Seveso Women's Health Study. Seveso Women's Health Study (SWHS) (Italy, Seveso)	Cohort Follow up to 2008	724–909 F Average (SD) age at outcome assessment: 19.7 (11.2) 1976 (n=981) 1996 (n=260)	TCDD Blood (serum) Lipid adjusted TCDD serum levels: 1976 and 1996. Thyroid hormones: 1996 and 2008.	Median (IQR) (pg/g fat) 1976: 60.2 (28.5–163.0) 1996: 7.0 (4.2–12.9) Median total WHO_{2005}-TEQ 1996: 25.6 (19.7–35.8)	**TSH, T4, free T3, free T4** Inverse association between 1976 TCDD and T4, but not with free T4, free T3 or TSH. Risk of bias tier: 1
STUDIES IN NEWBORNS OR CHILDREN					
Nagayama et al. (1998). Postnatal exposure to chlorinated dioxins and related chemicals on thyroid hormone status in Japanese breast-fed infants. n/a (Japan)	Cross-sectional n/a	36 (children) Sex not specified Age at outcome assessment: 1 Year of human	TEQ (17 PCDD/Fs, DL-PCBs, congeners not specified) Estimated intake human milk Lipid adjusted	Estimated mean total intake: 34 (6–84) ng TEQ/Kg bw	**TSH, T4, T3, TBG** T3 and T4 inversely associated with estimated intake. Risk of bias tier: 2 *Comments*: Small study. Non informative.

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		milk sampling: not reported			
Matsuura et al. (2001). Effects of dioxins and polychlorinated biphenyls (PCBs) on thyroid function in infants born in Japan - The second report from research on environmental health. Dioxins and PCBs in human milk (Japan)	Cross-sectional n/a	390 (children: 337 breast-fed infants and 53 bottle-fed infants) Sex not specified Age at outcome assessment: 1 1998–1999	17 PCDD/Fs, 12 DL-PCBs Human milk (at 30 days postpartum) Lipid adjusted	Mean (pg WHO_{1998}-TEQ/g fat) 20-25	**TSH, T4, free T4, T3** No association with exposure Risk of bias tier: 2
Nagayama et al. (2001). Effects of contamination level of dioxins and related chemicals on thyroid hormone and immune response systems in patients with "Yusho" Yusho Cohort (Japan)	Cross-sectional 26–29 years	16 (3 males, 13 females) Age at outcome assessment: 28–75 1994–1995	17 PCDD/Fs, 12 DL-PCBs Blood Lipid adjusted	Median (range) (pg WHO_{1998}-TEQ/g fat) 222.4 (27.8–1048.5)	**T3, T4, TSH** T3, T4, free T4 and TSH at their normal levels except for one subject in which T4 was slightly higher than normal. No significant correlation between the blood TEQ concentrations and the serum levels of T3, T4 or TSH. Risk of bias tier: 2
Wang et al. (2005). In utero exposure to dioxins and polychlorinated biphenyls and its relations to thyroid function and growth hormone in newborns.	Cross-sectional Infants < 3 months of age.	118 newborns M, F Mean (SD) age of mother: 29 (4)	17 PCDD/Fs, 12 DL-PCBs Placenta Lipid adjusted	pg WHO_{1998}-TEQ/g fat Mean (SD): 16.20 (6.14)	**TSH, T4, free T4, T3, TBG** Positive associations between total TEQs and T3 and TBG in female newborns. No significant associations with free T4 or TSH.

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Part of a prospective study of dioxins/PCBs for the general population (Taiwan)		Infants: newborns 2000–2001			Risk of bias tier: 2 *Comments*: Data analysed in several ways and with various TEQs.
Maervoet et al. (2007). Association of Thyroid Hormone Concentrations with Levels of Organochlorine Compounds in Cord Blood of Neonates. n/a (Flanders, Belgium)	Cross-sectional	138 newborns M, F Age at outcome assessment: after birth 2002–2004	CALUX determined BEQ levels Cord blood Lipid adjusted	pg BEQs/g fat Mean (SD): 30.6 (20.6) Median (5th, 95th %): 26.3 (7.4, 64.9)	**TSH, free T4, free T3** Inverse associations with free T4 and free T3, but not TSH Risk of bias tier: 1
Nagayama et al. (2007a). Concentrations of organochlorine pollutants in mothers who gave birth to neonates with congenital hypothyroidism. n/a (Fukuoka, Japan)	Case-control 2 years (2002–2004)	124 (22 cretinism cases, 102 normal controls) M, F Aged at outcome assessment: 5-20 days 2001–2004	17 PCDD/Fs, 12 DL-PCBs Human milk (approx 4 weeks postpartum) Not lipid adjusted	Mean (SD) in 34 human milk samples (pg WHO_{1998}-TEQ/g whole weight) Cretinism 0.62 (0.44) Normal 0.28 (0.15)	**Incidence of cretinism** Significantly lower TEQ levels in breast milk of mothers who had normal children versus those whose children were diagnosed with cretinism. Risk of bias tier: 1
Wilhelm et al. (2008). The Duisburg birth cohort study: Influence of the prenatal exposure to PCDD/Fs and dioxin-like PCBs on thyroid	Cross-sectional 2 years (2000–	80 (maternal serum), 60 (human milk) newborns	17 PCDD/Fs, 12 DL-PCBs Maternal blood (serum), human milk	Median (min, max) (pg WHO_{2005}-TEQ/g fat) Blood (serum): 19.3 (3.77, 58.36)	**TSH, T4, free T4, T3, free T3** No significant associations with exposure Risk of bias tier: 1

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
hormone status in newborns and neurodevelopment of infants until the age of 24 months Duisburg Cohort (Duisburg, Germany)	2002)	M, F Age at outcome assessment: mothers: 32.1, infants: after birth. 2002–2004	Lipid adjusted	Human milk: 19.67 (2.62, 52.37)	*Comments*: Low power.
Baccarelli et al. (2008). Neonatal thyroid function in Seveso 25 years after maternal exposure to dioxin. Seveso Cohort (Seveso, Italy)	Ecological, Cross-sectional 25 years	1,014 in the residence based (ecological) study 51 in the maternal blood sub-study M, F Age at outcome assessment: newborns (1994-2005) to mothers from 3 zones 1992–1998	TCDD, 17 PCDD/Fs, 12 DL-PCBs Blood (plasma) Lipid adjusted	Median 1977-1978: 447(A), 94(B) 1993-1995: 61(A), 18(B), 6 (Reference) Mean (95% CI) (pg WHO_{2005}-TEQ/g fat) b-TSH ≤ 5 µU/mL: TCDD: 5.2 (4.1–6.7) Total WHO-TEQ: 29.2 (25.7–33.5) b-TSH ≥ 5 µU/mL: TCDD: 39.0 (8.9–173) Total WHO-TEQ: 84.5 (16.7–427.8)	**TSH** Ecological/Residence based study: higher TSH in children born by mothers from zones A and B. Maternal blood sub-study: significant association between TCDD and TSH in the plasma sub-study (β=0.47, p<0.001). Risk of bias tier: 1 *Comments*: Strong findings in the residence based study. Sub-study findings more uncertain.
Han et al. (2011). Correlations of PCBs, dioxin, and PBDE with TSH in	Cross-sectional	369 children from an e-waste area (195 exposed and	17 PCDD/Fs, 12 DL-PCBs	Mean (SD) PCDD/Fs (ng/g fat):	**TSH** Higher in the control area (aluminium

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Children's Blood in Areas of Computer E-waste Recycling n/a (China, Luqiao (E-waste recycling area), Longyou (control))	n/a	174 controls) M, F Age at outcome assessment: 6-8 years. Year of tissue sampling: not reported	Blood (serum) Lipid adjusted	Exposed E-waste area: 26.00 (19.58) Control: 39.64 (31.86)	smelter). Weak negative correlation with PCDD/Fs in Luqiao (r=-0.15) but positive correlation in Longyou (r=0.64). PCBs had strong positive correlation with TSH in Luqiao (r=0.61) and Longyou (r=0.75). Risk of bias tier: 2 *Comments*: No TEQs. No good control group. Non informative.
Leijs et al. (2012). Thyroid hormone metabolism and environmental chemical exposure. Amsterdam/Zaandam Cohort (The Netherlands)	Longitudinal Children followed-up for 14–19 years	29 adolescents M, F Age at outcome assessment: 14–19 years 1987–1991	17 PCDD/Fs, 3 DL-PCBs (-77, -126, -169) Human milk (perinatal exposure), blood (serum) Lipid adjusted	Mean (range) Human milk: (pg I-TEQ/g fat) 32.6 (9.05-88.8) Serum (current): (pg WHO_{2005}-TEQ/g fat) PCDD/Fs: 2.2 (0.4–6.1) DL-PCBs: 2.2 (0.04–7.8)	**TSH, T4, free T4, T3, TBG** No associations for total TEQ. Risk of bias tier: 2 *Comments*: Small study. Non informative
Croes et al. (2014). Monitoring chlorinated persistent organic pollutants in adolescents in Flanders	Cross-sectional	200 M, F Age at outcome	CALUX determined BEQ levels Blood serum	Geometric mean (pg BEQ/g fat) PCDD/Fs: 108 (101, 114)	**T3, T4, TSH** DL-PCB- and PCDD/F-BEQs positively correlated with free T4.

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
(Belgium): Concentrations, trends and dose-effect relationships (FLEHS II). Flemish Environment and Health Study FLEHS II (Belgium, Hotspots: Genk-Zuid and Menen)		assessment: 13.6–17.0 2008–2011	Lipid adjusted	DL-PCBs: 32.1 (30.1, 34.2)	TSH negative correlation with PCDD/Fs (p = 0.02 after Ln transformation). No significant relationships with free T3. Risk of bias tier: 2
Xu et al. (2014). Association of PCB, PBDE and PCDD/F body burdens with hormone levels for children in an e-waste dismantling area of Zhejiang Province, China. n/a (China, Luqiao (exposure) and Tiantai (control))	Cross-sectional n/a	45 M, F Age at outcome assessment: 8 Year of tissue sampling: not reported	17 PCDD/Fs, 12 DL-PCBs Blood (serum) Lipid adjusted	Median, Mean (SD), (pg WHO_{2005}-TEQ/g fat) PCDD/Fs Exposed: 155.20, 206.17 (156.68) Control: 139.20, 160.27 (102.09) DL-PCBs Exposed: 16.07, 16.02 (3.32) Control: 5.86, 6.68 (3.05)	**Free T3, Total T3, free T4, total T4, TSH** No associations were found between PCDD/F or DL-PCB levels and thyroid hormones. Risk of bias tier: 1
Su et al. (2015). Thyroid and growth hormone concentrations in 8-year-old children exposed *in utero* to dioxins and polychlorinated biphenyls. Part of a prospective study of	Cohort 2000–2009	56 (23 males, 33 females) M, F Age at outcome assessment: 8	17 PCDD/Fs, 12 DL-PCBs Placenta Lipid adjusted	(pg WHO_{1998}-TEQ/g fat) Mean (SD) 15.41 (5.5) Median (Min – Max) 14.83 (6.75 – 29.07)	**T3, T4, free T4, TSH, TBG** No consistent associations with T3, T4, free T4, TSH and TBG. Risk of bias tier: 2

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
dioxins/PCBs for the general population (Taiwan)		2009		'High' group: ≥ 14.83	

TSH: thyroid stimulating hormone; TBG: thyroxin-binding globuline; n/a: not applicable.

A.8.5. Studies on type 2 diabetes and obesity

Table 69. Epidemiological studies on the association between exposure to PCDD/Fs and DL-PCBs and **diabetes and obesity**. Details about the risk of bias appraisal can be found in **Annex A.9.5**.

Reference **Trial or Study name (Geography)**	**Study type** **Duration**	**Participants in the study** **Sex** **Age at outcome assessment (years)** **Year of tissue sampling**	**Compounds** **Measurement of exposure**	**Levels of exposure**	**Parameters measured and Measures of effect** **Risk of bias tier**
Michalek et al. (1999a). Serum dioxin, insulin, fasting glucose, and sex hormone-binding globulin in veterans of operation Ranch Hand. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)	Cohort 11–22 years	1,992 M Mean (SD) age at outcome assessment: Comparison: 53.4 (7.4) Background: 54.3 (6.9) 'Low': 55.0 (7.4) 'High': 50.9 (7.2) 1987, 2002	TCDD Blood (serum) Lipid adjusted	Median (range) in 1987 and 2002 (pg/g fat): Comparison (n = 1,121): 3.9 (0–10) Background (n = 376): 5.7 (0–10) 'Low' (n = 247): 15.0 (10–26.6) 'High' (n = 248): 45.8 (18–618.8) Mean (range) extrapolated levels at the end of the last tour of duty in Vietnam (using a constant half-life of 8.7 years) (pg/g fat): 'Low': 52.8 (27.7–94.6) 'High':195.3 (94.7–3,290.2)	**Insulin and fasting glucose** Among non-diabetic veterans: - insulin significantly increased in 'High' TCDD category. - relation between SHBG and insulin interacted significantly with TCDD category on log scale within strata defined by age and % body fat. Among young (≤ 53 years old), lean (% body fat ≤ 25%) non-diabetic veterans: - slope relating log-SHBG and log-insulin significantly decreased in the 'High' category. **Sex hormone-binding globulin (SHBG):** Diabetic and Non-diabetic veterans: no significant differences with the comparison category with regard to the mean of the logarithm of SHBG. Risk of bias tier: 2
Steenland et al. (1999). Cancer, heart disease, and diabetes in workers exposed to	Cohort Around 15–57	3,538 M	TCDD Cumulative	Cumulative exposure scores were calculated for each production plant	**Diabetes** Number of deaths: 26

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
2,3,7,8-tetrachlorodibenzo-*p*-dioxin n/a (USA)	years	Age at outcome assessment: not reported. Year of tissue sampling: unclear.	exposure scores based on Job Exposure Matrix, calibrated against serum TCDD in subgroup		SMR (95% CI): 1.18 (0.77–1.73) Risk of bias tier: 2
Cranmer et al. (2000). Exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is associated with hyperinsulinemia and insulin resistance. n/a (USA, Arkansas, Jacksonville (near the Vertac/Hercules Superfund site)	Cohort 20–33 years	69 M, F TCDD <15 pg/g fat group: 51 (13.2) TCDD >15 pg/g fat group: 55 (11.6) 1991, 1994, 1995	TCDD Blood Lipid adjusted	Range (n = 69) (pg/g fat) 2–95 Highest decile: >15 (n=7) Lower levels: <15 (n=62)	**Hyperinsulinemia and insulin resistance** OR (95% CI) for high insulin subjects with TCDD>15 pg/g fat (n=7) compared to subjects with TCDD<15 pg/g fat (n=62). Fasting (insulin level >4.5 µIU/mL): 8.5 (1.49–49.4) 30 min (insulin level >177 µIU/mL): 7 (1.26–39.0) 60 min (insulin level >228 µIU/mL): 12 (2.23–70.1) 120 min (insulin level >97.7 µIU/mL): 56 (5.7–556) Risk of bias tier: 2 *Comments:* Small study with only 7 individuals in the highest decile.
Longnecker and Michalek	Cross-	1,197 (Comparison	TCDD	TCDD levels in 1987	**Fasting serum glucose, post-challenge**

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
(2000). Serum dioxin level in relation to diabetes mellitus among Air Force veterans with background levels of exposure. Air Force Health Study (AFHS) (Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)	sectional n/a	veterans) M Median age at outcome assessment in 1995: 53 1987, 1992, 1997	Blood (serum) Lipid adjusted	(pg/g fat) Median: 4.0 Quartile 1: < 2.8 Quartile 2: < 4 Quartile 3: < 5.2 Quartile 4: ≥ 5.2	**serum glucose and insulin** Crude OR (95% CI) / Adjusted OR (95% CI) / Adjusted OR (95% CI) (in addition to the above, serum TGs) Quartile 1 (cases: 26, controls: 272) 1 / 1 / 1 Quartile 2 (cases: 25, controls: 280) 0.93 (0.53–1.66) / 0.89 (0.48–1.63) / 0.91 (0.50–1.68) Quartile 3 (cases: 57, controls: 238) 2.51 (1.53–4.11) / 1.88 (1.11–3.19) / 1.77 (1.04–3.02) Quartile 4 (cases: 61, controls: 238) 2.68 (1.64–4.38) / 1.71 (1.00–2.91) / 1.56 (0.91–2.67) Risk of bias tier: 1
Steenland et al. (2001a). Dioxin and diabetes mellitus: an analysis of the combined NIOSH and Ranch Hand data Air Force Health Study (AFHS, Operation Ranch Hand), NIOSH (USA)	Cross-sectional Ranch Hand: 16–25 years NIOSH: 35 years of	Ranch Hand: 990 Ranch Hand veterans, 1,275 referents NIOSH: 259 chemical workers, 227	TCDD Blood (serum) Lipid adjusted	Median (range) (pg/g fat) NIOSH (1987–1988) (n=259): 75 (2–3,388) Ranch Hand (1987, 1992)	**Diabetes mellitus** Prevalence of diabetes: Combined exposed groups did not differ from the combined non-exposed groups: OR (95% CI): 1.17 (0.92–1.48), with no evidence of heterogeneity of exposure effect between studies.

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
	occupationally exposure	referents M Mean age at outcome assessment: Rand Hand: 53 NIOSH: 56 NIOSH: 1987–1988 Ranch Hand: 1987, 1992		(n=990): 12 (0–618) NIOSH referents (assigned): 6.1 (2.0–19.7) Ranch Hand Comparison (>10 pg/g fat excluded): 4.0	Fasting serum glucose: No difference between combined exposed and non-exposed groups in mean fasting serum glucose (difference in log serum glucose 0.002, 95% CI .0.006–0.010). Little evidence in either study of a dose-response trend for fasting serum glucose. Increasing trend (p=0.0001) in prevalence of diabetes with increased TCDD (at the time of examination or at time of last exposure) among the Ranch Hand subjects, with excess risk largely confined to the highest 8% of the exposed group (>78 pg/g fat) (3.21 (1.81–5.72) versus those with <10 pg/g fat. No positive dose-response in the NIOSH subjects. Risk of bias tier: 1
Johnson et al. (2001). Serum hormone levels in humans with low serum concentrations of 2,3,7,8-TCDD. n/a (Australia, Victoria)	Cross-sectional n/a	32 M Mean (range) age at sampling: 48 (29–76) Year of tissue sampling: not clear.	TCDD Blood (serum) No information about lipid adjustment	(pg/g) (n = 32) TCDD < 20 Mean level: 2.6 – 8.1 pg/g	**Insulin glucagon** TCDD positively correlated with glucagon. No correlation with insulin. Risk of bias tier: 2

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Fierens et al. (2003). Dioxin / polychlorinated biphenyl body burden, diabetes and endometriosis: findings in a population-based study in Belgium. n/a (Belgium: Cockerill (iron and steel plant), Mont-Saint-Guibert (waste dumping site), Pont-de-Loup (MWSI), Thumaide (MWSI), Rural areas in Southern Belgium)	Cross-sectional 1 year duration	257 (9 cases, 248 controls) M, F Age at outcome assessment: Cases: 56.0 Controls: 51.5 2000–2001	17 PCDD/Fs, 4 DL-PCBs (-77, -81, -126, -169) Blood Lipid adjusted	Mean (pg WHO_{1998}-TEQ/g fat) PCDD/Fs: Cases: 46.6 (34.7–62.5) Controls: 25.2 (23.6–26.8) DL-PCBs: Cases: 16.2 (9.47–27.7) Controls: 7.2 (6.65-7.73) Total TEQ: Cases: 64.2 (46.7-88.3) Controls: 32.8 (30.8-35.0)	**Diabetes** After adjustment for age and other covariates, serum total TEQs in diabetics were 62% (p=0.0005) and 39% (p=0.0067) higher, respectively, than in controls. Risk of diabetes significantly increased in subjects in the top decile: OR (95% CI): PCDD/Fs: 5.07 (1.18–21.7) DL-PCBs: 13.3 (3.31–53.2) Risk of bias tier: 2
Kern et al. (2004). Insulin sensitivity following agent orange exposure in Vietnam veterans with high blood levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in	Cross-sectional 11–37 years	58 (1997 study), 142 (2002 study) M Mean (SD) age at outcome assessment: 1997 study: Cases: 56.6 (6.4)	TCDD Blood (serum) Lipi adjusted	Mean (range) (pg/g fat) 1997 study: Cases (n = 29): 45.3 (22.6–186) Comparison (n = 29): 3.6 (1.2–9.0) 2002 study:	**Insulin sensitivity, quantitative insulin sensitivity check index (QUICKI)** An 18-fold increase in blood TCDD resulted in a 10% change in insulin sensitivity in the 29 matched pairs. Risk of bias tier: 1

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Southeast Asia during Vietnam War)		Comp: 56.8 (6.1) 2002 study: Cases: 57.6 (4.1) Comp: 58.4 (4.6) 1987, 1992, 1997		Cases (n = 71): 25.4 (10.3–58) Comparison (n = 71): 3.7 (0.5–8.7)	
Baccarelli et al. (2005). Health status and plasma dioxin levels in chloracne cases 20 years after the Seveso, Italy accident. Seveso study (Italy, Seveso)	Case control 17–22 years after the Seveso incident	312 (101 chloracne cases, 211 controls) M, F Age at explosion: Cases: 6 months–46 years Controls: 3 months–48 years Age at outcome assessment: Cases: 17–22 years older than at time of exposure 1993–1998	TCDD Blood Lipid adjusted	(pg/g fat) (n = 293) < 10 (n = 215) > 10 (n = 78)	**Diabetes** Only one diabetes case among the chloracne cases and two among the controls. Risk of bias tier: 2
Michalek and Pavuk (2008). Diabetes and cancer in veterans of Operation Ranch Hand after adjustment for calendar period, days of spraying, and time spent	Cohort study 11-40 years	2,583 M Age at outcome	TCDD Blood (serum) Lipid adjusted	Median extrapolated levels at the end of the last tour of duty in Vietnam using a constant half-life of 7.6 years (pg/g fat)	**Diabetes** Associations between TCDD and diabetes stratified by calendar period of service, days of spraying, and the combination of calendar

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
in Southeast Asia. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)		assessment: not reported 1987, 1992, 1997, 2002		Vietnam service: Comparisons: 4 Ranch Hand: 12.6 No Vietnam service: Comparison: 3.9 Ranch Hand: 10.6 Days of spraying: Comparison: 3.9 Ranch Hand: ≥90 days: 13.3 <90 days: 5.9	period of service and days of spraying, respectively. Ranch Hand **Comp Backgr Low** **High** Diabetic (%): 259 (17.9) 49 (11.0) 62 (21.7) 69 (24.0) RR 0.86 1.45 1.68 Stratified by calendar period of service **≤1969** RR 1.26 1.87 1.97 95% CI 0.8–1.98 1.21–2.89 1.26–3.06 **>1969** RR 0.47 1.08 1.22 95% CI 0.23–0.93 0.63–1.85 0.67–2.24 Stratified by days of spraying **≥ 90 days** RR 0.97 1.45 1.58 95% CI 0.66–1.43 1.04–2.02 1.12–2.24 **<90 days** RR 0.59 0.73 0.35

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					95% CI 0.26–1.32 0.17–3.05 0.05–2.65 Stratified by calendar period of service and days of spraying **≤1969 and ≥90 days** RR 1.37 1.99 2.12 95% CI 0.85–2.22 1.28–3.09 1.36–3.3 **Complement** (Not during/ before 1969, ≥90 days of spraying) RR 0.48 0.98 0.98 95% CI 0.26–0.87 0.58–1.67 0.54–1.79 Risk of bias tier: 2
Chen et al. (2008). Relationship between insulin sensitivity and exposure to dioxins and polychlorinated biphenyls in pregnant women n/a (Taiwan)	Cross sectional n/a	40 F Mean (SD, range) age at outcome assessment: 28.21 (3.92, 21-39). 2004	17 PCDD/Fs, 12 DL-PCBs Blood (serum) Lipid adjusted	Mean (SD) Total-TEQs (pg WHO-TEQ/g fat): 14.91 (2.82) * TEF scheme not reported	**Fasting serum insulin and glucose levels** PCB-123, -126, and -169 significantly correlated with insulin activity. However, except for 1234678-HpCDD, no PCDD or PCDF congener were correlated with the insulin, insulin sensitivity or QUICKI measures. No significant correlations between concentration-based total-TEQ and insulin, insulin sensitivity or quicki. Risk of bias tier: 2

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Uemura et al. (2008). Associations of environmental exposure to dioxins with prevalent diabetes among general inhabitants in Japan. n/a (Japan)	Cross sectional 4 years	1,374 M, F Age range at outcome assessment: 15-73 2002–2006	17 PCDD/Fs, 12 DL-PCBs Blood Lipid adjusted	Mean, Median (25%, 75%) (pg WHO_{1998}-TEQ/g fat): Total TEQs: 24.08, 20.00 (12.00, 31.00) PCDD/F-TEQs: 13.96, 12.00 (7.70, 18.00) DL-PCB-TEQs: 10.15, 7.60 (4.40, 13.00)	**Prevalent diabetes** <20.00 pg WHO_{1998}-TEQ/g fat (reference category) Cases/total: 9/666 ≥20.00 and <31.00 pg WHO_{1998}-TEQ/g fat Cases/total: 17/353 Non-adjusted OR (95% CI): 3.69 (1.67–8.75) Adjusted OR (95% CI): 2.10 (0.87–5.39) ≥31.00 pg WHO_{1998}-TEQ/g fat Cases/total: 39/355 Non-adjusted OR (95% CI): 39 9.01 (4.51–20.0) Adjusted OR (95% CI): 3.81 (1.56–10.1) Risk of bias tier: 1
Uemura et al. (2009). Prevalence of metabolic syndrome associated with body burden levels of dioxin and related compounds among Japan's general population. n/a (Japan)	Cross-sectional 4 years	1,374 M, F Age (range) at outcome assessment: 15-73 years 2002–2006	17 PCDD/Fs, 12 DL-PCBs Blood Lipid adjusted	Median (25, 75%) (pg WHO_{1998}-TEQ/g fat) Total TEQs: 20 (12, 31) PCDD/F-TEQs: 12 (7.7–18) DL-PCB-TEQs: 7.6 (4.4–13)	**Metabolic syndrome (BMI, serum triglycerides, serum HDL, systolic blood pressure, diastolic blood pressure, HbA1c)** <12.00 pg WHO_{1998}-TEQ/g fat (reference category) Cases/total: 10/303 ≥20.00 and <19.00 pg WHO_{1998}-TEQ/g fat Cases/total: 22/318 Non-adjusted OR (95 % CI): 2.2 (1.0–4.9)

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					Adjusted OR (95% CI): 2.2 (0.98–5.0) ≥19.00 and <30.00 pg WHO_{1998}-TEQ/g fat Cases/total: 35/345 Non-adjusted OR (95% CI): 3.3 (1.7–7.2) Adjusted OR (95%CI): 3.2 (1.4–7.6) ≥30.00 pg WHO_{1998}-TEQ/g fat Cases/total: 55/343 Non-adjusted OR (95% CI): 5.6 (2.9–12) Adjusted OR (95% CI): 5.1 (2.1–13) p for trend <0.01 Risk of bias tier: 2
Pelclova et al. (2009). Chronic health impairment due to 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin exposure. n/a (Not reported)	Cross-sectional 44 years	11 M Exposure between 1965 and 1968 Age (SD) at outcome assessment: 64.4 (1.5) 2008	TCDD Blood (serum) Lipid adjusted	Mean (SD, range) (pg/g fat) 274.0 (181.2, 53–756)	**Diabetes type 2** The proportion of diabetes type 2 was 55%. Risk of bias tier: 2
Burns et al. (2011). Serum dioxins and polychlorinated biphenyls are associated with	Cohort 3 years	473 Age (range) at	17 PCDD/Fs, DL-PCBs and NDL-PCBs	Median (25^{th} - 75^{th} percentile) sum PCDD/Fs and non-*ortho* PCBs (pg WHO_{2005}-TEQ/g fat)	**BMI, height, height velocity** Boys in highest TEQ exposure quintile had a

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
growth among Russian boys. Russian Children's Study (Russia, Chapaevsk)		enrolment: 8–9 2003–2005	 Blood serum Lipid adjusted	(n=468): 21.1 (14.4, 33.2)	significant decrease in mean BMI z-scores of 0.67 compared with boys in the lowest quintile. For PCB[1] exposure, the BMI z-score reduction was 1,04. PCDD/Fs-and DL-PCB TEQ was not significantly associated with height z scores or height velocity Higher serum PCB concentrations at age 8-9 were associated with significantly lower height z scores (mean decrease 0.41) and height velocity (mean decrease 0.19 cm/year) after 3 years. Risk of bias tier: Tier 1
Yi et al. (2013). Serum 2,3,7,8-tetrachlorodibenzo-*p*-dioxin levels and their association with age, body mass index, smoking, military record-based variables, and estimated exposure to Agent Orange in Korean Vietnam veterans. Korean Veterans Health Study (KVHS) (Korea)	Cross-sectional 30-40 years	105 M Average age at outcome assessment in 2001: 56.5 (3.7) 2001	TCDD Blood (serum) Lipid adjusted	pg/g fat Mean: 1.2 Median 0.9	**BMI** No significant relationships between serum TCDD concentration, and age, BMI, and smoking in the Korean Vietnam veterans studied. Risk of bias tier: 2
Warner et al. (2013). Diabetes, Metabolic Syndrome, and Obesity in Relation to	Cohort 32 years	833 F	TCDD Blood (serum)	Median (IQR) pg/g fat 55.9 (28–157)	**Metabolic syndrome, waist circumference, triglycerides, HDL-C, blood pressure, glucose**

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Serum Dioxin Concentrations: The Seveso Women's Health Study. Seveso Women's Health Study (SWHS) (Italy, Seveso)		Average (SD) age at outcome assessment: 54.9 (9.4) 1976	Lipid adjusted	Geometric mean (SD) Subjects with diabetes: 7.9 (3.9) Non-cases: 71.1 (4.2)	10-fold increase in serum TCDD (log_{10}TCDD) not associated with: Diabetes: Adj HR (95% CI)=0.76 (0.45-1.28) Obesity: Adj OR (95% CI)=0.80 (0.58-1.10) Metabolic syndrome: Adj OR (95% CI)=1.05 (0.78-1.43) However, TCDD associated with metabolic syndrome among women ≤12-years of age at time of explosion: Adjusted OR (95% CI) = 2.03 (1.25-3.29). Risk of bias tier: 1
Delvaux et al. (2014). Prenatal exposure to environmental contaminants and body composition at age 7-9 years Flemish Environment and Health Study (FLEHS I) (Belgium)	Cohort study 9 years follow-up	114 M, F Mean (SD) age at outcome assessment: 8.43 (0.43) 2011	CALUX determined BEQ levels Cord blood (plasma) No information whether lipid adjusted	Median (P25, P75) (pg BEQs/L) Participants: Boys: 0.05 (0.02, 0.08) Girls: 0.04 (0.02, 0.06) Total: 0.05 (0.02, 0.07) Non-participants Total: 0.05 (0.02, 0.07)	**Anthropometric parameters (height, weight, BMI, sum of four skinfolds), waist circumference and waist/height ratio)** No significant associations found for pre-natal CALUX-BEQs after adjustment for confounders/covariates. Risk of bias tier: 2
Iszatt et al. (2016). Perinatal exposure to dioxins and dioxin-like compounds and infant growth and body mass index at	Cohort	96 (FLEHS I), 207 (Slovak PCB), 64 (HUMIS)	CALUX determined BEQ levels	Mean (SD) (pg BEQ/g fat) FLEHS I (n=96):	**Postnatal growth** Perinatal BEQ exposure associated with increased growth between 0 and 24 months (β

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
seven years: a pooled analysis of three European birth cohorts. HUMIS (Norway), FLEHS I (Belgium), Slovak PCB cohort (Slovakia)		M, F Age at outcome assessment: 24 months FLEHS I, Slovak PCB: 2002-2004 HUMIS: 2002-2009	Human milk (HUMIS, Slovak PCB), cord serum (FLEHS I) Lipid adjusted	31.2 (19.2) HUMIS (n=64): 7.9 (2.6) Slovak PCB (n=207): 15.5 (9.5)	= 0.07, 95% CI: −0.01, 0.14). At 7 years, exposure was associated with a statistically significant increase in BMI in girls (β = 0.49, 95% CI: 0.07, 0.91) but not in boys (β = −0.03, 95% CI:−0.55, 0.49) (p-interaction = 0.044). Girls had a 54% (−6%, 151%) increased risk of overweight at 7 years (p-interaction = 0.023). Risk of bias tier: 2
Leijs et al. (2017). Alternations in the programming of energy metabolism in adolescents with background exposure to dioxins, dl-PCBs and PBDEs. Amsterdam/Zaandam Cohort (The Netherlands)	Cohort 14–19 years follow-up	33 M, F Age at assessment: 14–19 years 1987–1991, 2005/2006	17 PCDD/Fs, 3 DL-PCBs (PCB-77, -126, -169) Human milk (perinatal exposure), blood (serum)	Mean (range) Human milk: (pg I-TEQ/g fat) 32.6 (9.05–88.8) Serum (current): (pg WHO_{2005}-TEQ/g fat) PCDD/Fs: 2.2 (0.4–6.1) DL-PCBs: 2.2 (0.04–7.8)	**Fasting glucose, insulin, HbA1c, leptin** Prenatal PCDD/F exposure positively correlated to the glucose:insulin ratio (p=0.024), and negatively correlated to the fasting insulin concentration (p=0.017). Postnatal lactational PCDD/F intake negatively correlated to fasting insulin concentration (p=0.028). Current serum levels of PCDD/Fs and total TEQ positively correlated to the fasting serum glucose concentration (p=0.015 and p=0.037, respectively).

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					Risk of bias tier: 2

MSWI: Municipal solid waste incinerator.

A.8.6. Studies on cardiovascular effects

Table 70. Epidemiological studies on the association between exposure to PCDD/Fs and DL-PCBs and **cardiovascular effects**. Details about the risk of bias appraisal can be found in **Annex A.9.6**.

Reference **Trial or Study name (geography)**	**Study type** **Duration**	**Participants in the study** **Sex (M/F)** **Age at outcome assessment (years)** **Year of tissue sampling**	**Compounds** **Measurement of exposure**	**Levels of exposure**	**Parameters measured and Measures of effect** **Risk of bias tier**
Calvert et al. (1998). Evaluation of cardiovascular outcomes among US workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. n/a (USA, New Jersey, Newark and Missouri, Verona)	Cross sectional 15 years after exposure	541 (281 workers from two TCP plants, 260 referents from the area) M (mostly), F Age (SD) at outcome assessment: Referents: 56 (10.5) years All workers: 55.4 (10.3) years 1987	TCDD Blood (serum) Lipid adjusted	Mean (SD) (pg/g fat) All workers: 220 (434) Referents: 7 (2) Back-extrapolated: 1,900	**Various cardiovascular diseases (e.g. heart disease, hypertension)** No significant association with TCDD exposure. Risk of bias tier: 1 *Comments*: Low power.
Pesatori et al. (1998). Dioxin exposure and non-malignant health effects: a mortality study. Seveso study (Italy, Seveso)	Cohort 15 years	About 45 000 in three zones M, F Age at outcome assessment: all	TCDD Blood (serum) (from another study) Lipid adjusted	Median (pg/g fat) 1976-1977: Zone A: 447 Zone B: 94 Zone R: 48	**Cardiovascular mortality** RR (95% CI) Zone A: 1.1 (0.8–1.5), 21 deaths Zone B: 0.9 (0.8–1.1), 228 deaths Risk of bias tier: 2

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		ages 1976/1977		1992-93 (geometric mean), Zone A (n=7): 53.2 Zone B (n=51): 11.0 Reference area (n=55): 4.9	*Comments*: Low power
Steenland et al. (1999). Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. n/a (USA)	Cohort Follow up of round 15–57 years	3,538 workers from 12 plants (e.g. PCP) M Age at outcome assessment: Not reported Year of tissue sampling: unclear.	TCDD Cumulative exposure scores based on JEM, calibrated against serum TCDD in subgroup	Estimated back-calculated levels about 200,000 ppt-years in septile 6–7 (e.g. 10 000 pg/g x 20 years)	**Ischemic heart disease (IHD) mortality** RR (95% CI) (>400 deaths) (Ref Septile 1) Septile 6: 1.57 (0.96–2.56) Septile 7: 1.75 (1.07–2.87) Risk of bias tier: 2 *Comments*: No information on potential confounders. Lung cancer increased
Bertazzi et al. (2001). Health effects of dioxin exposure: A 20-year mortality study. Seveso study (Italy, Seveso)	Cohort 20 years	About 45,000 in three zones M, F Age at outcome assessment: all ages 1976/1977, 1993/1994	TCDD Blood (plasma) from another study Lipid adjusted	Median (pg/g fat) Zone A 1976-77: 447.0 1993-94:73.7 Zone B 1976-77: 94.0 1993-94: 12.4 Zone R: 48.0 Reference: 5.5	**Cardiovascular mortality** RR (95% CI) Zone A: 1.1 (0.8–1.5), 37 deaths Zone B: 0.9 (0.8–1.1), 228 deaths Risk of bias tier: 2 *Comments*: Increased cardiovascular mortality only in early observation period
Ketchum and Michalek (2005). Postservice mortality of	Cohort	1,262	TCDD	Measured in sub-group, back-extrapolated	**Cardiovascular mortality**

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Air Force veterans occupationally exposed to herbicides during the Vietnam War: 20-year follow-up results. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)	28–37 years	M The median birth year and age range is indicated in Table VII. The median age range at exposure can be calculated 1987, 1992, 1997	Blood (serum) Lipid adjusted	Median (range) (pg/g fat) High: 245 Low: 65 Background: <32 Comparison group: 4.0 (0.4-54.8) Background: 5.7 (0.6–10.0) Low: 15.0 (10.0–29.2) High: 47.4 (18.0–617.8) Serum level extrapolated to the end of service in Vietnam Low: 65.0 (32.2–117.4) High: 244.8 (117.9–4,221.9)	RR (95% CI) with internal non-exposed referents: Overall: 1.3 (1.0–1.6), 88 deaths. Ground crew: 1.7 (1.2–2.4), 40 deaths RR for subgroup with serum TCDD (29 deaths) were 1.3 (all) 1.5 (high), 1.8 (low) and 0.8 (background). Risk of bias tier: 2
Kang et al. (2006). Health status of Army Chemical Corps Vietnam veterans who sprayed defoliant in Vietnam Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)	Cohort 28-35 years	1,499 exposed (including 662 sprayers), and 1,428 non-Vietnam referents M Age at outcome assessment: 53. 1999–2000	TCDD Blood (serum) in subgroup Lipid adjusted	Mean (pg/g fat)[(a)] Vietnam service self-reported herbicide spraying (n=357): 4.3 Vietnam service self-reported no herbicide spraying (n=413): 2.7 No Vietnam service (n=87): 2.1	**Self-reported heart conditions** No difference between Vietnam staff and referents. Within the Vietnam veterans OR was 1.4 (95% CI 1.1–1.9) for those who had sprayed versus those who had not. Risk of bias tier: 2 *Comments*: Adjusted for confounders. Low

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					exposure contrast.
Pelclova et al. (2007). 2,3,7,8-TCDD exposure, endothelial dysfunction and impaired microvascular reactivity. n/a (The Czech Republic)	Cross sectional 39	15 workers from Czech TCP plant, 14 referents M Mean (SD) age at outcome assessment: Exposed: 59 (3) Referents: 54 (2) 1996, 2001	TCDD Blood (serum), based on 1996 and 2001 measurements Lipid adjusted	(pg/g fat) Exposed men median (range): 110 (7–380) Back-calculated levels: 120–9,000	Microvascular function worse in the exposed group. Risk of bias tier: 2 *Comments* : Small study. Referents not comparable. Non-informative.
Pelclova et al. (2009). Chronic health impairment due to 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin exposure. n/a (The Czech Republic)	Cohort 44 years	11 workers from a Czech TCP plant M Age at exposure assessment: 64.4 (1.5) 2008	TCDD Blood (serum) Lipid adjusted	Mean (SD, range) (pg/g fat) 274.0 (181.2, 53–756)	Hyperlipidaemia, hypertension, and increased IMT was common. Risk of bias tier: 2 *Comments*: Small study, no referent group. Non-informative.
Boers et al. (2010). Cause-specific mortality of Dutch chlorophenoxy herbicide manufacturing workers. n/a (The Netherlands)	Cohort 10–41 years	2,016 workers from two Dutch plants for phenoxi herbicides M	TCDD Blood (serum) estimated from small group sampled	High exposure group: mean 600 in 1993, back-extrapolated 1,800 Sample of workers in 1993 (pg/g fat)	**Cardiovascular mortality** Hazard ratios close to 1.0 based on about 100 cases Risk of bias tier: 2

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		Mean (SD) age at entry of the exposed workers from factories A and B: around 32 (9.55). 1993	(Predictive exposure model based on back-extrapolation of TCDD from a sample of exposed workers (n=47) from factory A in 1993) Not reported whether lipid adjustment	Low exposure: < 7.1 Medium exposure: 7.1–124.1 High exposure: >124.1	*Comments*: No confounder adjustment.
Manuwald et al. (2012). Mortality study of chemical workers exposed to dioxins: follow-up 23 years after chemical plant closure. n/a (Germany, Hamburg)	Cohort 23 year follow up after a chemical plant closure	1,589 workers at a German chemical plant (e.g. 2,4,5-T) M, F Age at outcome assessment: Unclear Year of tissue sampling: unclear (adults).	TCDD Blood (serum) Lipid adjusted	Cumulative exposure estimated from work histories and serum TCDD (lipid adjusted) in subgroup. Median: 77 pg/g fat Upper quartile: >335	**Cardiovascular mortality** SMR (95% CI): 1.05 (0.9-1.2), 309 deaths Ref. Hamburg population. No trend across quartiles of cumulative exposure. Risk of bias tier: 2 *Comments*: No information about potential confounders.
Lin et al. (2012b). Environmental exposure to dioxin-like compounds and the mortality	Cohort 4.63 (range:	2,361 M, F	17 PCDD/Fs, 9 DL-PCBs (3 non-*ortho* and 6	(pg WHO-TEQ/g fat) Median: 19.2	**Mortality risk** Deaths during the follow-up period: n=242,

Reference Trial or Study name (geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
risk in the U.S. population. NHANES (USA)	<1–7.67)	Age at baseline ranged from 40 to 5+ 1999	mono-*ortho* PCBs) Blood (serum) Lipid adjusted	IQR: 13.3–27.9	including: - 75 from cardiovascular disease Increased mortality risk associated with logarithmically expressed total TEQs for all-cause deaths (HR=1.19, 95% CI 1.02-1.39, p=0.02). Similar graded dose-response trends were found for cardiovascular mortality. Risk of bias tier: 1
Cypel et al. (2016). Herbicide Exposure, Vietnam Service, and Hypertension Risk in Army Chemical Corps Veterans	Cohort Work categories (herbicide spray history) during military service (1965-1971) used as proxy for exposure	3,086 M Age at outcome assessment: unclear. 1999–2000	TCDD Blood serum Lipid adjusted	Mean (range) (n = 636) Vietnam-herbicide sprayers: 3.5 (0.5–30.6) Vietnam-non sprayers: 2.5 (0.7–17.7)	**Hypertension Risk** ORadjusted [95% CI] 1.74 (95%CI: 1.44,2.11)] Risk of bias tier: 2

(a): Units confirmed by the authors of the study.

A.8.7. Studies on hepatic disorders and digestive effects

Table 71. Epidemiological studies on the association between exposure to PCDD/Fs and DL-PCBs and **hepatic disorders and digestive effects**. Details about the risk of bias appraisal can be found in **Annex A.9.7**.

Reference **Trial or Study name (Geography)**	**Study Type** **Duration**	**Participants in the study** **Sex** **Age at outcome assessment (years)** **Year of tissue sampling**	**Compounds Measurement of exposure**	**Levels of exposure**	**Parameters measured and Measures of effect** **Risk of bias tier**
Neuberger et al. (1999). Persistent health effects of dioxin contamination in herbicide production. n/a (Austria, Linz)	Cohort 21–27 years	50 M, F Average (SD) age at outcome assessment: 57.8 (6.8) 1996	17 PCDD/Fs, 7 DL-PCBs (-126, -169, -105, -118, -156, -157, -180) Blood (plasma) Lipid adjusted	pg I-TEQ/g fat TCDD Median: 280.0 Mean: 465.5 Maximum: 2,900.0	**Symptom prevalence rates, Stomach trouble, Levels of γ-GT, SGOT (AST) and SGPT (ALT)**. γ-GT (U/L) Exposed: 42.2 ± 44.3 Controls A: 19.1 ± 11.9 Controls B: 21.3 ± 29.1 SGOT (U/L) Exposed: 16.7 ± 16.5 Controls A: 12.2 ± 3.6 Controls B: not analysed. SGPT (U/L) Exposed: 20.6 ± 14.8 Controls A: 15.1 ± 5.9 Controls B: not analysed. Comparison of SGOT and SGPT levels, together with urinary coproporphyrin I/III ratios suggest disturbed liver function associated with higher TCDD plasma levels and independent of alcohol consumption. Good association with chronic liver dysfunction but no direct evidence of liver disease per se. Fewer numbers in study than others Risk of bias tier: 1

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Michalek et al. (2001a). Serum dioxin and hepatic abnormalities in veterans of Operation Ranch Hand. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)	Cohort study 11 to 30 years	2,130 M Age at outcome assessment: unclear (adults) 1982, 1985, 1981, 1992	TCDD Blood (serum) Lipid adjusted	pg/g fat Background: ≤10 'Low': >10 and initial ≤94.1 'High': > 10 ppt and > 94.1 Year 1992 Background levels (n=401) 5.7 (0-10) 'Low' (n=264) Median (range): 15 (10-27) 'High' (n=266) Median (range): 45.7 (18-618) Serum level extrapolated to the end of service in Vietnam: 'Low': 52.6 (28-94) 'High': 194.8 (94-3,290)	**Hepatic abnormalities and indices of hepatic function** Adjusted OR (95% CI) **Hepatomegaly** Comparison: 1.0 Background: 0.7 (0.3, 1.6) 'Low': 0.4 (0.1, 1.2), 'High': 1.4 (0.7, 3.1) **Non-alcoholic chronic liver disease and cirrhosis** Comparison: 1.0 Background: 2.1 (0.7, 6.0) 'Low': 1.3 (0.3, 4.7), 'High': 1.4 (0.5, 4.3) **Other liver disorders** Comparison: 1.0 Background: 1.0 (0.8, 1.4) 'Low': 1.1 (0.8, 1.4), 'High': 1.6 (1.2, 2.1) **Unspecified disorders of the liver** Comparison: 1.0 Background: 0.8 (0.4, 2.0) 'Low': 1.0 (0.4, 2.4), 'High': 1.1 (0.4, 2.7) **Nonspecific elevation of transaminase or LDH** Comparison: 1.0 Background: 0.8 (0.4, 1.8) 'Low': 1.0 (0.4, 2.3), 'High': 2.7 (1.4, 5.1) **Other nonspecific abnormal results of function studies**

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					of the liver Comparison: 1.0 Background: 1.0 (0.7, 1.3) 'Low': 0.9 (0.6, 1.4), 'High': 1.4 (1.0, 2.0) *Comments*: Association with liver dysfunction but not established that is causal. Link not clear between liver dysfunction and disease. Risk of bias tier: 1
Baccarelli et al. (2005). Health status and plasma dioxin levels in chloracne cases 20 years after the Seveso, Italy accident. Seveso study (Italy, Seveso)	Case control study 17-22 years after the Seveso incident.	293 M, F Age at outcome assessment: 17-22 years older than at time of exposure 1993-1998	TCDD Blood (plasma) Lipid adjusted	< 10 pg/g fat (n=215) > 10 pg/g fat (n=78)	**Gastrointestinal diseases** Summary on history of health conditions in cases: gastrointestinal (9.9%). Controls: no significant difference was observed between cases and controls in the unadjusted analysis, as well as in the analysis adjusted for age and sex (95% CIs were large, and P-value estimates were not significant). Risk of bias tier: 1
Ketchum and Michalek (2005). Postservice mortality of Air Force veterans occupationally exposed to herbicides during the Vietnam War: 20-year follow-up results.	Cohort study 28– 37 years	2,452 M The median birth year and age range is indicated in Table VII. The median age range	TCDD Blood (serum) Lipid adjusted	Median (range) (pg/g fat) Comparison group: 4.0 (0.4–54.8) Background: 5.7 (0.6–10.0) 'Low': 15.0 (10.0–29.2)	**Post service mortality – Digestive diseases** No evidence of increased mortality due to disease of digestive system. The RRs of death caused by diseases of the digestive system was not significantly increased (based on 10 deaths) Number of deaths (%): Ranch Hand = 10 (0.8), Comparison = 89 (0.5)

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)		at exposure can be calculated. 1987, 1992, 1997		'High': 47.4 (18.0–617.8) Serum level extrapolated to the end of service in Vietnam: 'Low': 65.0 (32.2–117.4) 'High': 244.8 (117.9–4221.9)	RR (95% CI): 1.6 (0.8–3.0), p = 0.17 Risk of bias tier: 2
Boers et al. (2010). Cause-specific mortality of Dutch chlorophenoxy herbicide manufacturing workers. n/a (The Netherlands)	Cohort study 10-41 years	2016 M Mean age at entry of the exposed workers from factories A and B: around 32 years (SD: 9.55). 1993	TCDD Blood (serum) Lipid adjusted	Back extrapolation of TCDD measurements in serum collected from a sample of exposed workers (n = 47) from factory A in 1993. Low exposure: TCDD < 7.1 pg/g fat Medium exposure: 7.1-124.1 pg/g fat High exposure: > 124.1 pg/g fat	**Cause of death (**all causes and some specific cancers, Infectious and bacterial diseases, Disease of endocrine system and blood, Mental disorders, Disease of nervous system and sense organs, Diseases of circulatory system, Diseases of respiratory system**, Digestive system,** Genital-urinary system, Ill-defined and unspecified causes, Accidents, poisoning and violence**)** **Digestive system** Factory A: Exposed/non-exposed: 6/6 HR (95% CI): 0.60 (0.18 to 2.01) Factory B: Exposed/non-exposed: 0/4 HR (95% CI): approximately zero Risk of bias tier: 2 *Comments*: Potentially many confounding exposures. No association with digestive system cancers

A.8.8. Studies on effects in the immune system

Table 72. Epidemiological studies on the association between exposure to PCDD/Fs and DL-PCBs and effects on the **immune system**. Details about the risk of bias appraisal can be found in **Annex A.9.8**.

Reference **Trial or Study name (Geography)**	**Study Type** **Duration**	**Participants in the study** **Sex** **Age at outcome assessment (years)** **Year of tissue sampling**	**Compounds** **Measurement of exposure**	**Levels of exposure**	**Parameters measured and Measures of effect** **Risk of bias tier**
STUDIES IN ADULTS					
Jung et al. (1998). Immunologic findings in workers formerly exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and its congeners n/a (Germany, Mainz and Hamburg)	Case control 2 years duration of study	192 workers, 28 controls M, F Median (range) age at outcome assessment: 56 (27–83) Exposed: 55.5 (37–69.3) Control: 53.8 (42.8–65.3) 1992–1994	TCDD Blood Lipid adjusted	Median (range): 103.7 (11.1–1,153.1) 95%: 592.3 pg I-TEQ /g fat Highly exposed group: Median (range): 217 (33.6–2,252) Median I-TEQ: 425.9 Control group: Median (range): 3.9 (2.9–6) Median I-TEQ: 15.4	**IgA, IgG, IgM, specific and natural autoantibodies, monoclonal antibodies, L-Chains in urine, lymphocyte surface markers, lymphocyte proliferation, tetanus antibodies following vaccination** No correlation of frequency of infectious diseases and PCDD/Fs were noted. No correlation between TCDD or TEQ levels and tetanus antibodies, and between TCDD or TEQ levels and autobodies were observed. Significant correlations of T lymphocytes proliferative responses, but restricted to tetanus vaccinated individuals with logTEQ, logTCDD were observed. Risk of bias tier: 2
Halperin et al. (1998). Immunological markers among workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-	Cross-sectional Exposure in New Jersey plants: 1951–	259 M Age (range) at	TCDD Blood (serum) Lipid adjusted	pg/g fat Referents (n=243): 0-19	**Enumeration of circulating leukocyte and lymphocyte populations, proliferative responses of circulating lymphocytes to mitogens and antigens, serum concentrations of the major immunoglobulins, complement**

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
dioxin. National Institute for Occupational Safety and Health (NIOSH) (USA, New Jersey and Missouri)	1969 Missouri plant: 1968–1972 Duration of follow up: 15–36 years	outcome assessment: 31–77 years 1987–1988		Workers: Overall range: 0-3,389 Category: <20 (n=65) 20-51 (n=47) 52-125 (n=49) 126-297 (n=49) 298-3389 (n=49)	**factor C3** Increased odds of lower counts of CD26 cells (activated T cells) were observed in all exposure categories except the lowest. <20 OR=1.0, 95% CI 0.5–1.8 20-51 OR=1.6, 95% CI 0.8–3.2 52-125 OR=2.7, 95% CI 1.4–5.1 126-297 OR=2.6, 95% CI 1.4–4.9 298-3389 OR=2.4, 95% CI 1.3–4.6 Spontaneous proliferation of cultured lymphocytes was reduced, but increased of responses to concanavalin and pokeweed in lymphopcytes from workers in the high TCDD category were observed. Age, cigarette smoking, and alcohol were significant predictors of several immunological outcomes. Risk of bias tier: 2
Michalek et al. (1999b). Serum dioxin and immunologic response in veterans of Operation Ranch Hand. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia	Cohort 11–30 years	2,100 M Mean age at outcome assessment: background: around 55 low: around 55	TCDD Blood (serum) Not lipid adjusted	(pg/g fat) Background: <10 'Low': >10 and <94 'High': > 10 and >94 Median (range) Background: 5.7 (0–10) 'Low': 52.8 (28–94) 'High': 194.7 (94–3,290)	**Abnormal skin tests, average lymphocyte populations, average quantitative immunoglobulin concentrations, autoantibody panel and monoclonal immunoglobulins.** Some statistically significant differences in lymphocyte subpopulations (CD20 B cells and CD16+CD56+CD3+ cells) were observed. No differences in immunoglobulin concentrations,

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
during Vietnam War)		High: 51.2 1987, 1992		Comparison group: 4 (0–10)	pattern of autoantibodies were noted. Overall, no evidence of a consistent relation between TCDD exposure and immune system alteration was shown. Risk of bias tier: 2
Kitamura et al. (2000). Health effects of chronic exposure to polychlorinated dibenzo-*p*-dioxins (PCDD), dibenzofurans (PCDF) and coplanar PCB (Co-PCB) on municipal waste incinerator workers. n/a (Osaka prefecture, Japan)	Cross-sectional n/a	92 (M, 88 with blood analysis), 4 (F) M, F Mean age at outcome assessment: 40±16 10 years exposure 1998	17 PCDD/Fs, 3 DL-PCBs (PCB-77, -126, -169) Blood (plasma) Lipid adjusted	Total TEQ Mean (range) (pg TEQ/g fat) 100 (7–831)	**Lymphocyte distribution, ConA, PHA proliferation, NK activity** Significant decrease of PHA proliferation and NK activity Risk of bias tier: 2
Nagayama et al. (2001). Effects of contamination level of dioxins and related chemicals on thyroid hormone and immune response systems in patients with "Yusho".	Cohort 26–29 years	16 M, F Mean (range) age at outcome assessment: 55.0 (28–75) years	17 PCDD/Fs, 12 DL-PCBs Blood Lipid adjusted	Median (range) (pg WHO_{1998}-TEQ/g fat) 222.4 (27.8–1,048.5) (about seven times higher than that of healthy Japanese people)	**Lymphocyte subsets, serum immunoglobulin and autoantibodies** Ratios of CD4 to CD8 positive lymphocytes were not associated to blood TEQs. Serum IgA, IgG and IgM were not markedly different in the three blood TEQ groups. Respective correlation coefficients between blood TEQ levels and serum

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Yusho study (Japan)		1994–1995			concentrations were IgA - 0.115 , IgG - 0.039 and IgM - 0.077, absolute values were very small, and none of them statistically signifficant. No significant differences in expression of antinuclear antibody were noted. Rheumatoid factor seemed to proportionally increase with total TEQ levels in the blood (3.8% in the lowest TEQ group, 16.7% in the middle one and 21.1% in the highest one), but this was not statistically significant. LE factor was not detected in the serum of any Yusho patient. Risk of bias tier: 2
Baccarelli et al. (2002). Immunologic effects of dioxin: New results from Seveso and comparison with other studies. Seveso study (Italy, Seveso)	Case control 20 years	121 M, F Age at outcome assessment: not reported 1992–1994	TCDD Blood (plasma) Lipid adjusted	(pg/g fat) Range: 1.2-89.9 Quintiles: 1.2-3.5 (n=21) 3.6-6.0 (n=21) 6.1-9.3 (n=23) 9.4-20.0 (n=22) 20.1-89.9 (n=22)	**Immunoglobulins: IgG, IgM, IgA, Complement components: C3, C4** Plasma IgG levels were decreased with increasing plasma-TCDD (r=–0.35, p=0.0002). Median IgG concentration decreased from 1,526 mg/dL in group with lowest (<3.5 ppt) TCDD levels to 1,163 mg/dL in group with highest (20.1–89.9 ppt) TCDD levels (p=0.002). The association was significant (p=0.0004) after adjusting for age, sex, smoking, and consumption of domestic livestock and poultry. Association persisted after exclusion of subjects with inflammatory diseases

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					and those using antibiotics or nonsteroidal anti-inflammatory drugs. IgM, IgA, C3, and C4 plasma concentrations did not exhibit any consistent association with TCDD levels. Risk of bias tier: 2
Baccarelli et al. (2004). Aryl-hydrocarbon receptor-dependent pathway and toxic effects of TCDD in humans: a population-based study in Seveso, Italy. Seveso study (Italy, Seveso)	Cohort 20 years after exposure	121 (62 study subjects, 59 controls) Sex not specified Age outcome assessment: not reported 1992–1994	TCDD Blood (plasma) Lipid adjusted	Range (pg/g fat) 3.5–90	**Plasma IgG levels, AHR dependent markers in lymphocytes** Subjects from the zones contaminated by TCDD showed lower plasma IgG levels compared to subjects from the surrounding reference area (non-ABR). Median IgG levels were: Zone non-ABR (n=58): 1403 mg/dL Zone B (n=55): 1,294 mg/dL, P=0.03 versus non-ABR Zone A (n=7): 1,142 mg/dL, P=0.01 versus non-ABR Plasma IgG progressively decreased with increasing lipid-adjusted TCDD plasma concentration (r =−0.35; P=0.0002). After adjusting for age, sex, smoking, and consumption of domestic livestock, the inverse association between plasma TCDD and IgG remained highly significant (P=0.0004). IgM, IgA, and complement component C3 and C4 plasma concentrations did not exhibit a consistent

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					association with TCDD plasma levels AhR mRNA levels in uncultures lymphocytes negatively associated with plasma TCDD (p=0.03). Risk of bias tier: 2
Baccarelli et al. (2005). Health status and plasma dioxin levels in chloracne cases 20 years after the Seveso, Italy accident. Seveso study (Italy, Seveso)	Case control 17-22 years after the Seveso incident.	293 M, F Age at outcome assessment: 17–22 years older than at time of exposure 1993–1998	TCDD Blood (plasma) Lipid adjusted	< 10 pg/g fat (n=215) > 10 pg/g fat (n=78)	**Allergic diseases, Infectious diseases,** No significant difference between cases and controls for allergic, gastrointestinal, and infectious diseases, either unadjusted or adjusted for age and sex, were observed. Risk of bias tier: 2
Saberi Hosnijeh et al. (2011). Long-term effects on humoral immunity among workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Dutch herbicide cohort (The Netherlands)	Cross-sectional n/a	153 M Mean (SD) age at outcome assessment: Factory A: Exposed: 69.7 (7.03) Non-exposed: 68.8 (7.9)	TCDD Blood Lipid adjusted	Mean (SD) (pg/g fat) Current: Factory A -Exposed: 3.3 (7.7) -Non-exposed: 1.2 (5.4) Factory B - Non-exposed: 0.4 (5.1) Back-extrapolated to the time of last exposure using a one-compartment first order kinetic model with a TCDD half-life of	**Serum immunoglobulin (IgG, IgM, IgA, IgD, IgE) and complement factors (C3, C4)** Borderline significant negative association were observed between current and predicted TCDD levels and C4 complement (β=-0.02; 95% CI=-0.04-0.01; β=-0.02; 95% CI=-0.03-0.00, respectively). Occurrence of eczema significantly associated with current TCDD levels. Risk of bias tier: 2

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		Factory B: 59.2 (9.1) Tissue sampling: approx 35 years after last exposure		7.1 years: Factory A - Exposed: 81.9 (35.6) - Non-exposed: 8.9 (26.6) Factory B - Non exposed: 0.4 (5.1)	
Saberi Hosnijeh et al. (2012). Changes in lymphocyte subsets in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Dutch herbicide cohort (The Netherlands)	Cross-sectional Followed up until 31st December 2006	85 M Age (SD) at study: High exposed: 69.07 (7.45) Low exposed: 68.55 (7.93) Tissue sampling: approximately 35 years after the last exposure	TCDD Blood (plasma) Lipid adjusted	Mean (SD) (pg/g fat) Current: High exposed: 3.25 (7.43) Low exposed: 1.07 (6.42) Back-extrapolated to the time of last exposure (using a one-compartment first order kinetic model with a TCDD half-life of 7.1 years): High exposed:79.82 (33.28) Low exposed: 7.53 (32.14)	**Haematological parameters (white and red blood cells number and proportion, granulocytes, monocytes, platelets, haemoglobin concentration and haematocrit)** Cell counts and lymphocyte subsets were similar between high- and low-exposed workers and increase in CD4/CD8 ratio in high-exposed workers. Most lymphocyte subsets, especially B-cells, showed a decrease with increasing TCDD. Risk of bias tier: 2
Saberi Hosnijeh et al. (2013). Circulating soluble CD27 and CD30 in workers exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD). Dutch herbicide cohort (The Netherlands)	Cross-sectional n/a	85 M Age at study: High exposed: 69.07 (7.45) Low exposed: 68.55 (7.93)	TCDD Blood (plasma) Lipid adjusted	Mean (SD) (pg/g fat) Current: High exposed: 3.25 (7.43) Low exposed: 1.07 (6.42) Back-extrapolated to the time of last exposure (using a one-compartment first order kinetic model with a TCDD half-life of	**sCD27, sCD30 and IL1RA blood markers** Dose-response showed no significant association between blood levels of sCD27/30 and TCDD levels at time of last exposure. IL1RA showed borderline significant decrease with increasing plasma TCDD. Risk of bias tier: 2

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		Tissue sampling: approximately 35 years after the last exposure		7.1 years): High exposed:79.82 (33.28) Low exposed:7.53 (32.14)	
Nakamoto et al. (2013). Association between blood levels of PCDDs/PCDFs/dioxin-like PCBs and history of allergic and other diseases in the Japanese population. n/a (Japan)	Cross-sectional 8 years duration	2,264 M, F Age at first exposure: unknown Mean age (SD): M: 43.5 (13.6) F: 45.3 (14.0) 2002–2010	17 PCDD/Fs 12 DL-PCBs Blood Lipid adjusted	Percentiles (pg WHO_{2005}-TEQ/g fat) 5%: 4.8 25%: 9.7 50%: 16 75%: 25 95%: 45	**Asthma, Atopic dermatitis, Allergic rhinitis,** TEQs of PCDD/Fs and total PCDD/Fs and DL-PCBs showed a significant inverse dose-response relationships with atopic dermatitis (after adjustment). Risk of bias tier: 2
Croes et al. (2014). Monitoring chlorinated persistent organic pollutants in adolescents in Flanders (Belgium): Concentrations, trends and dose-effect relationships (FLEHS II). Flemish Environment and Health Study (FLEHS II) (Belgium)	Cross-sectional Duration: 2008-2009: reference group 2010: region Genk-Zuid 2010-2011: region Menen	200 M, F Age at outcome assessment: 13.6–17.0 2008–2011	CALUX determined BEQ levels Blood serum Lipid adjusted	Geometric mean (pg BEQ/g fat) PCDD/Fs: 108 (101, 114) DL-PCBs: 32.1 (30.1, 34.2)	**Allergy** DL-PCBs observed to be positively associated with the development of animal allergy (p=0.02, OR=1.46) A borderline non-significant correlation of DL-PCBs with development of hay fever (p=0.11, OR=1.23 after correction for age, active smoking and familial history of hay fever) and with eczema (p=0.10, OR=0.73, after correction for age, active smoking and familial history of eczema) were noted. Higher levels of PCDD/Fs were associated with a

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					higher risk for development of animal allergy (p=0.03, OR=1.60 after Ln transformation) and asthma (p=0004, OR=1.42). The percentage thrombocytes in the blood was negatively associated with DL-PCBs (p=0.02) and PCDD/Fs (p=0.0005). Risk of bias tier: 2
Dinse et al. (2016). Associations Between Selected Xenobiotics and Antinuclear Antibodies in the National Health and Nutrition Examination Survey, 1999-2004. NHANES (USA)	Cross-sectional n/a	4,340 M, F Age at outcome assessment: 12-55+ 1999–2004	17 PCDD/Fs, 9 DL-PCBs Blood (serum) Lipid adjusted	Individual concentrations reported in table 2 of the study	**Antinuclear antibodies (ANA)** No associations with autoantibodies were noted. Risk of bias tier: 1
STUDIES ON EXPOSURE DURING DEVELOPMENT					
Nagayama et al. (1998). Postnatal exposure to chlorinated dioxins and related chemicals on lymphocyte subsets in Japanese breast-fed infants. Japan	Cross-sectional n/a	36 M, F Age at outome assessment: 1 year old Year of human milk sampling: not	17 PCDD/Fs, DL-PCBs (congeners not specified) Human milk Lipid adjusted	Mean (min, max) (pg TEQ/g) 27.1 (15.2, 48.5) Estimated total TEQ intake via human milk: Mean (range): 34 (6–84) ng/kg bw	**Lymphocytes (CD3, CD4, CD8, CD16, CD20, HLA-DR)** Total TEQ intake from human milk was observed to be positively correlated with the % of CD4+ T cells (p=0.079), and negatively correlated with those of CD8+ Tcells (p=0.072), hence a tendency to increase CD4/CD/ ratios. Risk of bias tier: 2

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		reported			
Weisglas-Kuperus et al. (2000). Immunologic effects of background exposure to polychlorinated biphenyls and dioxins in Dutch preschool children. Dutch PCB/Dioxin Study (The Netherlands)	Cohort 42 months	175 (health questionnaire) 85 (immunological markers) M, F Age at outcome assessment: 42 months 1990	17 PCDD/Fs, 12 DL-PCBs Human milk Lipid adjusted	Median (min-max) pg WHO_{1998}-TEQ/g fat <u>Non-*ortho* PCBs</u> Questionnaire (n= 81): 14.9 (4.4–45.7) Immuno marker (n= 30): 17.1 (5.9–45.7) <u>Mono-*ortho* PCBs</u> Questionnaire (n= 85): 14.0 (3.2–44.4) Immuno marker (n= 30): 14.0 (6.4–25.45) <u>PCDD/Fs</u> Questionnaire (n=71): 35.8 (10.2–87.2) Immuno marker (n=24): 35.1 (15.6–66.6)	**Infectious diseases (**Middle-ear infections, Recurrent middle-ear infections, Pneumonia, Scarlatina, Chicken pox , Other infectious diseases, Hospital admissions for infectious diseases**), allergic diseases (**Eczema, Allergic reaction, Asthma or bronchitis, Coughing, chest congestion, or phlegm lasting for 10 days or more**), Attacks of shortness of breath with wheeze** Associations with antibody levels were observed for the NDL-PCBs in blood. PCDD/Fs and DL-PCBs were not examined in blood (). Dioxins and DL-PCBs were measured in milk but do not show a relation with the levels of antibodies or illnesses investigated in this study (breast-fed infants were accidentally underrepresented in this subgroup). At 18 months of age the number of CD8+ (cytotoxic) and TcR αβ+ T cells correlated best with the PCDD/F-TEQ levels, while at 42 months of age there was no significant relation with the PCDD/Fs-TEQ levels (Pearson correlation 0.11 and 0.16). Risk of bias tier: 1
Van Den Heuvel et al. (2002). Immunologic biomarkers in relation to exposure markers of	Cross-sectional 18 years	200	CALUX determined BEQ levels	Geometric mean (95% CI) (pg BEQ/g fat) <u>Girls</u>:	**IgG, IgA, IgM, IgE, RAST, eosinophil count, reported allergies** Negative association of eosinophils, natural killer cells,

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
PCBs and Dioxins in Flemish adolescents (Belgium). Environment and Health Study (Belgium)		M (n=80), F (n=120) Age at outcome assessment: 17–18 1999	Blood Lipid adjusted	28.59 (24.93–32.80) Boys: 34.89 (28.66–42.46) *p*-value: 0.09	specific IgE, and reported allergies. Increase IgA. Risk of bias tier: 1
Nagayama et al. (2007b). Immunologic effects of perinatal exposure to dioxins, PCBs and organochlorine pesticides in Japanese infants n/a (Japan)	Cohort 10 months	92 infants M, F Mean age at outcome assessment: 10.1 months 1994–1996	17 PCDD/Fs, 3 DL-PCBs (congeners not specified) Human milk Lipid adjusted	Median (min, max) (pg WHO_{1998}-TEQ/g fat) 23 (3.4, 49)	**Lymphocyte subsets (CD16+, HLA-DR+, CD4+, CD4+8+, CD8+, CD3+ and CD20+ cells)** Significant increased in ratio CD4/CD8 cells and percentage of CD3 cells, but clinical relevance unclear. Risk of bias tier: 1
Leijs et al. (2009). Effects of Dioxins, PCBs, and PBDEs on immunology and hematology in adolescents. Amsterdam/Zaandam cohort (The Netherlands)	Cohort Birth cohort followed-up in childhood and adolescents. Duration of follow-up: mean (range) age at follow-up: 15 (14-	33 M, F Mean (range) age at outcome assessment: 15 (14-18.7) years. 1987–1991	17 PCDD/Fs, 3 DL-PCBs (-77, -126, -169) Blood (serum), human milk Lipid adjusted	Mean (range) (pg I-TEQ/g fat) Prenatal exposure: 32.6 (9.05–88.8) Lactational exposure: I-TEQ (ng): 66.9 (4.34–279) Current serum (pg WHO_{2005}-TEQ/g fat)	**Haematological and immunological parameters in serum/blood: Thrombocytes, Haemoglobin, Thrombopoietin, HbA1C, Leukocytes, Polymorphic neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils.** Negative effect on polymorphic neutrophils found in adolescents with higher current DL-PCB levels (p=0.021). In the neonatal period this negative effect was seen with prenatal PCDD/F exposure. No relationship observed between neutrophils and

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
	18.7) years			PCDD/Fs: 2.2 (0.4–6.1) DL-PCBs: 2.2 (0.04–7.8)	perinatal or current dioxins levels in serum. Risk of bias tier: 2
Miyashita et al. (2011). Effects of prenatal exposure to dioxin-like compounds on allergies and infections during infancy. Hokkaido Study on Environment and Children's Health (Japan)	Cohort study 3 years duration	364 M, F Mothers age at delivery: 31±4.5 years Gestational age: 39.5±1.5 weeks 2002–2005	17 PCDD/Fs 4 DL-PCBs (-77, -81, -126, -169) Blood (serum) Lipid adjusted	Median (min, max) (pg WHO_{2005}-TEQ/g fat) Total TEQs: 13.89 (3.17, 43.35) PCDDs-TEQs: 6.92 (1.65, 29.32) PCDFs-TEQs: 2.38 (0.64, 7.77)	**Food allergy, eczema, asthma, otitis media** After adjustment for confounders, relatively higher levels of PCDFs were associated with a significantly increased risk of otitis media, especially among male infants (OR=2.5, 95% CI 1.1–5.9). In addition, relatively higher levels of 23478-PeCDF were associated with significantly increased risk of otitis media (OR=5.3, 95% CI 1.5–19). Weak association between dioxin-like compound levels and allergic symptoms in infancy. Risk of bias tier: 1
Stolevik et al. (2011). Prenatal exposure to polychlorinated biphenyls and dioxins is associated with increased risk of wheeze and infections in infants. BraMat (MoBa sub-cohort, Norway)	Cohort study Follow-up: 1 year	195 M, F Age at outcome assessment: 1 2007	17 PCDD/Fs, 12 DL-PCBs Validated FFQ (MoBa Cohort)	Dietary intake (pg WHO_{2005}-TEQ/kg bw/day) Median (min, max) 0.58 (0.15, 3.07) IQR: 0.45–0.81 80th percentile: 0.90	**Wheeze, otitis media, gastric flu, chicken pox, upper respiratory tract infection (URTI), Exanthema subitum** Prenatal exposure to PCDD/Fs and DL-PCBs was associated with increased risk of wheeze and exanthema subitum, and also with increased frequency of upper respiratory tract infections. **Eczema:** Increased prenatal exposure to PCDD/Fs and DL-PCBs lowered the risk of eczema or itchiness in bivariate logistic regression analyses when the

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					levels of exposure were categorized using the tertiles. When adjusted for maternal BMI in the final models, associations were not significant: 1st vs 2nd tertile: 0.49 (0.20–1.22) 0.127 1st vs 3rd tertile: 0.76 (0.32–1.78) 0.521 Risk of bias tier: 2
Stolevik et al. (2013). Prenatal exposure to polychlorinated biphenyls and dioxins from the maternal diet may be associated with immunosuppressive effects that persist into early childhood. BraMat (MoBa sub-cohort, Norway)	Cohort study 3 years follow-up	180 M, F Mean (range) age at outcome assessment: 36 (33-43) months 2007	17 PCDD/Fs 12 DL-PCBs Maternal dietary intake by validated FFQ	Maternal dietary intake during pregnancy (pg WHO_{2005}-TEQ/kg bw/day) Median (min-max): 0.59 (0.15–3.07). IQR: 0.46–0.81 80th percentile: 0.89	**Antibody responses to four vaccines: attenuated measles, rubella, tetanus toxoid, *Haemophilus influenzae* type b (Hib)** Maternal dietary exposure to PCBs/dioxins was associated with increased risk of wheeze and URTI. Maternal dietary exposure to PCBs/dioxins was associated with reduced antibody response to measles vaccine. Positive association of antibody responses to vaccination to measles with maternal dietary exposure were observed. No effects on immunophenotypes, allergic sensitisation and vaccine-induced antibody response to other vaccines were noted. Risk of bias tier: 2

n/a: not applicable.

A.8.9. Studies on effects on the nervous system

Table 73. Epidemiological studies on the association between exposure to PCDD/Fs and DL-PCBs and effects on the **nervous system**. Details about the risk of bias appraisal can be found in **Annex A.9.9**.

Reference **Trial or Study name (Geography)**	**Study type** **Duration**	**Participants in the study** **Sex (M/F)** **Age at outcome assessment** **Year of tissue sampling**	**Compounds** **Measurement of exposure**	**Levels of exposure**	**Parameters measured and Measures of effect** **Risk of bias tier**
NEURODEVELOPMENT IN CHILDREN					
Lanting et al. (1998). Neurological condition in 42-month-old children in relation to pre- and postnatal exposure to polychlorinated biphenyls and dioxins. Dutch PCB/dioxin cohort (Rotterdam and Groningen, The Netherlands)	Cohorts 1990-1992	170 with PCDD/Fs, 186 with DL-PCBs M, F Age at outcome assessment: 42 months 1990	17 PCDD/Fs, 6 DL-PCBs (PCB-77, -126, -169, -105, -118, -156) Lipid adjusted	Median (p5, p95) (ng TEQ/kg fat) PCDD/Fs: 28.8 (14.9, 51.5) No-*ortho* PCBs: 14.5 (6.8, 31.9) Mono-*ortho* PCBs: 14.2 (6.9, 24.8) * TEF scheme not clear	**Neurological Examination** focused on observation of **motor function** (prehension, sitting, crawling, standing, walking) in free-field situation, leading to clinical diagnosis 'normal', 'mildly abnormal', 'abnormal'. **Neurological optimality score**. Quality of movements evaluated separately as a **fluency cluster score**. Exposure to PCDD/Fs and DL-PCBs was not found to be related to neurological conditions. Risk of bias tier: 1
Patandin et al. (1999). Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age Dutch PCB/dioxin cohort (Rotterdam, The Netherlands)	Cohort Age at follow up: 42 months	209 breastfed M, F Age at outcome assessment: 42 months 1990–1992	17 PCDD/Fs, 6 DL-PCBs (-77, -126, -169, -105, -118, -156) Human milk Lipid adjusted	WHO_{1998}-TEQ (PCDD/Fs+DL-PCBs) (ng/kg fat) Median (P5, P95) Mono-*ortho* PCBs (n=195): 14.2 (6.8, 24.8)	**Cognitive abilities, measured by the Dutch version of Kaufman Assessment Battery for Children (K-ABC), yelding the sequential scale and the simultaneous processing scale, and a combined score of these.** **Verbal comprehension measured by the Dutch version of the Reynell Developmental Language Scales (RDLS) in the Rotterdam branch of the cohort only.**

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
				Non-*ortho* PCBs (n=194): 14.5 (7.1, 31.7) PCDD/Fs (n=176): 33.4 (17.0, 59.8)	**Alls scores standardized to a mean of 100 and SD of 15.** No association between prenatal exposure and K-ABC or RDLC in covariate adjusted analyses. . Lactational exposure (calculated concentration in breast milk multiplied with duration of breast-feeding) was also not associated with the outcomes. Risk of bias tier: 1
Vreugdenhil et al. (2002). Effects of perinatal exposure to PCBs and dioxins on play behavior in Dutch children at school age Dutch PCB/dioxin cohort (Rotterdam, The Netherlands)	Cohort 1990–1992	*105* 53 M, 32 F Age at outcome assessment: 7.5 (0.4) 1990–1992	17 PCDD/Fs, 6 DL-PCBs (-77, -126, -169, -105, -118, -156) Human milk Lipid adjusted	WHO_{1998}-TEQ (PCDD/Fs+DL-PCBs) (ng/kg fat) Median (range) Total: 68.1 (27.7–135.2) Breast-fed boys: 68.1 (27.7–135.2) Breast-fed girls: 67.1 (28.1–108.9)	**Play behaviour (Dutch version of the Pre-School Activity Inventory, PSAI). Contains 24 questions that are answered by 5 points scales, addressing three aspects: i) Type of toys, ii) activities and iii) child characteristics. Gives a masculine, feminine and composite scale (feminine-masculine).** Higher ln PCDD/F-TEQ was by adjusted linear regression associated with higher scores on the feminine scale in the total group of boys and girls (p=0.048), indicating more feminized play behavior in both sexes. No significant differences between boys and girls. Of note sum of PCBs in milk was associated with masculine play behaviour, which is in opposite direction from the PCDD/F-TEQs. Postnatal exposure (calculated as [concentration of PCDD/Fs and DL-PCBs (TEQ) in milk] × [duration of

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					breastfeeding]) not related to play behavior in the total breast fed group or in boys and girls separately. Risk of bias tier: 1 *Comment:* Limited power because of small n.
Nakajima et al. (2006). Effects of prenatal exposure to polychlorinated biphenyls and dioxins on mental and motor development in Japanese children at 6 months of age. Hokkaido Study on Environment and Children's Health (Japan, Sapporo)	Cohort 6 months	134 M, F 2002–2004	17 PCDD/Fs, 12 DL-PCBs Maternal blood (serum) Lipid adjusted	pg WHO_{1998}-TEQ/g fat Mean: Total TEQ: 18.8 PCDD-TEQ: 7.7 PCDF-TEQ: 4.2 DL-PCB-TEQ: 6.9	**Mental developmental index (MDI) and Psychomotor developmental index (PDI) with the Bayley Scale of Infant Development II, translated to Japan.** After adjustment for potential confounding variables, total TEQ, PCDD/F-TEQ or DL-PCB-TEQ not associated with MDI or PDI. Risk of bias tier: 1
Wilhelm et al. (2008). The Duisburg birth cohort study: Influence of the prenatal exposure to PCDD/Fs and dioxin-like PCBs on thyroid hormone status in newborns and neurodevelopment of infants until the age of 24 months Duisburg cohort study (Duisburg, Germany)	Cross-sectional 2 years	182 M, F Age at outcome assessment: 2 weeks, 12, 18 and 24 months 2000–2002	17 PCDD/Fs, 12 DL-PCBs Maternal blood (serum), human milk Lipid adjusted	pg WHO_{2005}-TEQ/g fat Median (min, max) Blood (n=182): 19.33 (3.77, 58.36) Human milk (n=149): 19.67 (2.62, 52.37)	**Neurological optimal score (NOS) at 14 days (postural tone, reflexes), and 18 months (spontaneous motor behaviour). Psycomotor and cognitive development at 12 and 24 months by Bayley Scale of Infant Development (BSID II).** No associations between maternal (prenatal) exposure to total TEQs and NOS or BSID was found. Risk of bias tier: 1
Halldorsson et al. (2009). Dioxin-like activity in plasma	Cohort	77 with outcome	CALUX determined BEQ	pg BEQs/g fat	**Infant developmental milestones at 6 months**

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
among Danish pregnant women: dietary predictors, birth weight and infant development. Danish National Birth Cohort (Denmark)	n/a	 M, F Age at outcome assessment: 5.7 and 7 months 1996–2002	levels Maternal blood Lipid adjusted	Geometric mean: 46.0. 5-perc, 50-perc, 95-perc, 7.0, 38.2, 134.6	Among four milestones on motor development and two on non-motor development, only "Cannot crawl" was associated, adj. OR (95% CI) 3.01 (1.05, 8.61). Also the combined score on motor development was significantly associated (adj. OR 4.72 (1.05, 21.2). Risk of bias tier: 2 *Comment*: *Authors state that bioassay results must be interpreted with care, may be confounded by PAHs since exposure was associated with high fat/meat consumption.*
Sioen et al. (2013). Prenatal exposure top environmental contaminants and behavioural problems at age 7-8 years. Flemish Environment and Health Study FLEHS I (Belgium, Flanders)	Cohort 7–8 years	270 M, F Age at outcome assessment: 7-8 2002–2006	CALUX determined BEQ levels Cord blood Lipid adjusted	Median (P25, P75) (pg BEQs/g fat) All (n=270): 24.4 (12.3, 37.6) Boys (n=130): 25.2 (13.2, 43.2) Girls (n=140): 24.1 (11.9, 33.5)	**Parent reported behavioural problems (Strenghts and Difficulties Questionnaire, SDQ)** No significant associations between cord blood BEQ considered as continuous variables and abnormal SDQ values at age 7–8 years in children. When exposure was analysed in tertiles, there was statistically significantly (p=0.016) lower OR in highest vs lowest tertile for high hyperactivity score (OR, 95%CI: 0.493, 0.164-0.727). This finding was opposite of the research hypothesis. Risk of bias tier: 1 *Note: The LOD for BEQ was higher than the P25 in cord blood, weakening the conclusions based on analysis in tertiles.*

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Winneke et al. (2014). Behavioral Sexual Dimorphism in School-Age Children and Early Developmental Exposure to Dioxins and PCBs: A Follow-Up Study of the Duisburg Cohort. Duisburg birth cohort study (Germany, Duisburg)	Cohort 6-8 years	121 (61 M, 60 F) Children's age mean (SD): 6.6 (0.5) years 2000–2002	17 PCDD/Fs, 12 DL-PCBs, Maternal blood and milk Lipid adjusted	(pg WHO_{2005}-TEQ/g fat) Blood (n=118) mean (SD) 21.5 (9.6) Milk (n=101) Mean (SD) 20.5 (9.1)	**Pre-School Activities Inventory (PSAI) grouped into three categories: preferred toys, preferred activities and behaviour characteristics. Used to derive feminine, masculine, and difference (feminine – masculine) scores** Log_2-transformed TEQ-weighted sum (PCDD/Fs+DL-PCBs,) β (95% CI) *p*-Value **Masculine score** Maternal blood, boys: 2.48 (-0.58, 5.51) 0.11 Maternal blood, girls: -1.72 (-3.81, 0.37) 0.11 Sex × exposure from milk: 0.19 Maternal milk, boys: 2.88 (-0.59, 6.35) 0.10 Maternal milk, girls: -2.59 (-5.16, -0.02) 0.05 Sex × exposure: 0.02 **Feminine score** Maternal blood, boys: 2.62 (0.52, 4.71) 0.02 Maternal blood, girls: -2.20 (-4.69, 0.29) 0.08 Sex × exposure: 0.06

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					Maternal milk, boys: 3.90 (1.74, 6.06) <0.01 Maternal milk, girls: -4.22 (-7.24, -1.19) 0.01 Sex × exposure: <0.01 Similar results for PCDD/F-TEQ. Risk of bias tier: 1 *Comments: Relative small sample size, but robust associations still detected. PSAI developed for pre-school children, but subjects were >6 years old. Questions raised as to whether PSAI fully reflects behavioural aspects of sexual dimorphism.*
Nowack et al. (2015). Influence of Low-Level Prenatal Exposure to PCDD/Fs and PCBs on Empathizing, Systemizing and Autistic Traits: Results from the Duisburg Birth Cohort Study. Duisburg birth cohort study (Germany, Duisburg)	Cohort 10 years follow-up	116 M, F Age at completion of EQ-SR: 8-11 years Age at completion of SRS: 9–12 years 2000–2002	17 PCDD/Fs, 12 DL-PCBs Maternal blood Lipid adjusted	Total TEQs (pg WHO_{2005}-TEQ/g fat) Median: 19.85 Geom mean: 20.10 95% CI: 18.31–21.91	**Gender-specific cognitive style assessed by parent reported Empathy-Systemizing Quotient (ESQ) questionnaire. Autistic traits assessed by parent reported Social Responsive Scale (SRS) questionnaire (giving a total score and five subscales). Higher score indicates more severe deficits.** Less impairment with increasing exposure was reported. Significant ($p<0.05$) negative associations between PCDD/F TEQ in maternal blood and SRS total scores in whole group (β, 95% CI) =-6.66, -11.88, -1.44). Similar results for PCDD/Fs+dl-PCB TEQ, but not significant for

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					dl-PCB TEQ alone. Significant interaction sex * exposure. Significant negative association between total TEQ and total SRS score in girls alone (β=-11.21 (95% CI -19.86, -2.57), in several SRS subscales in girls and in one SRS subscale in boys. No association between exposure levels and sex-typical behaviour. Risk of bias tier: 1 *Comments: Cohort was 231 mother-child pairs. 136 and 133 mothers invited to follow up, not described how selected. 73-75% loss to follow up of the invited, possible selection bias. Parent reported child's behaviour. Sample might not be representative of general population. Parents were informed of their exposure levels at an early stage, which might have influenced parenting behaviour. Regression on SRS scores included 41 boys and 39 girls (low n).*
Neugebauer et al. (2015). The influence of low level pre- and perinatal exposure to PCDD/Fs, PCBs, and lead on attention performance and attention-related behavior among German school-aged children: Results from the	Cohort Follow-up: 8 or 9 years	117 M, F KITAP: 8.5±0.30 years FBB-ADHS	17 PCDD/Fs, 12 DL-PCBs Maternal blood Maternal milk Lipid adjusted	(pg WHO_{2005}-TEQ/g fat) Median blood PCDD/F-TEQ: 12.99 Median DL PCB-TEQ: 6.64	**Computerized test battery for attention performance in children (KITAP): distractibility, alertness, flexibility, divided attention, go/no go, divided attention, flexibility.** **Parent rating scale for attention-deficit hyperactivity disorder (FBB-ADHS): inattention, hyperactivity, impulsivity, overall ADHD.**

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Duisburg Birth Cohort Study. Duisburg Birth Cohort Study (Germany, Duisburg)		questionnaire: 9.5±0.40 years 2000			Increasing maternal blood PCDD/F TEQ and PCB TEQ significantly ($p < 0.05$) associated with more omission errors in the subtest Divided Attention (47% and 42%; 95% CI 1.08–2.00 and 1.07–1.89, respectively). Small and non-significant associations in other KITAP subtests Reduction in hyperactivity scale (gMR 0.86; 95% CI 0.78–0.95) and on overall ADHD scale (gMR: 0.90; 95% CI 0.82–0.99) with increasing maternal blood PCB TEQ. Risk of bias tier: 2 *Comments: Low n. 50% loss to follow up, similar exposure in participants and non-participants, but possible selection bias. Parents were informed of their exposure levels at an early stage. Intercorrelation between compounds moderate to high. KITAP not validated.*
Caspersen et al. (2016a). Maternal dietary exposure to dioxins and polychlorinated biphenyls (PCBs) is associated with language delay in 3 year old Norwegian children. MoBa Cohort (Norway)	Cohort Ongoing duration/ 3 years follow up from birth	44,092 M, F Children: mean age of 37 months for language test 1999–2008	17 PCDD/Fs, 12 DL-PCBs FFQ during gestational week 22 See Caspersen et al 2013. Dietary exposure to dioxins and PCBs	Maternal dietary exposure generally low: 98% of women had intakes of PCDD/Fs and DL-PCBs ≤14 pg WHO_{2005}-TEQ/kg bw/week.	**Grammar complexity measured with grammar rating. Receptive/expressive communication skills assessed by ages and stages questionnaire (ASQ).** High maternal exposure (>14 pg WHO_{2005}-TEQ/kg bw/week) associated with higher odds of incomplete grammar (boys/girls: OR=1.1) and severe language delay in girls (OR=2.9, 95% CI 1.4-5.9). High maternal exposure also associated with moderate language delay (OR=1.4, 95% CI 1.0-2.0) and ASQ

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
			in a large cohort of pregnant women: results from the Norwegian Mother and Child Cohort Study (MoBa).		(OR=1.4, 95% CI 1.1-1.9) in girls. Risk of bias tier: 2 *Comments: General limitations of assessing dietary intake using FFQ. Adjusted for dietary mercury exposure.*
Caspersen et al. (2016b). The influence of maternal dietary exposure to dioxins and PCBs during pregnancy on ADHD symptoms and cognitive functions in Norwegian preschool children. ADHD Study (MoBa subcohort, Norway)	Cohort 3.5 years	1,024 Age at outcome assessment: 3.5 2007–2011	17 PCDD/Fs, 12 DL-PCBs FFQ during gestational week 22 See Caspersen et al. (2013). Dietary exposure to dioxins and PCBs in a large cohort of pregnant women: results from the Norwegian Mother and Child Cohort Study (MoBa).	Maternal dietary exposure generally low: 98% of women had intakes of PCDD/Fs and DL-PCBs ≤14 pg WHO_{2005}-TEQ/kg bw/week	**ADHD symptoms and cognitive functioning in pre-schoolers (IQ, expressive language, and executive functions)** Maternal dietary exposure to PCDD/Fs and DL-PCBs was not significantly associated with any of the outcome measures when analyses were performed for boys and girls together. After stratifying by sex, adjusted analyses indicated a small inverse association with language in girls (1 SD increase in exposure was associated with a reduction in language score of -0.2 [CI -0.5, -0.1]) but not in boys. The difference between sex-specific associations was not statistically significant (p-value=0.13). No sex-specific effects were observed for ADHD-symptoms, IQ scores, or executive functions. Risk of bias tier: 2
Nakajima et al. (2017). Sex-specific differences in	Cohort	190 children at 6 months of	17 PCDD/Fs, 12 DL-PCBs	Median (P25, P75) (pg WHO_{2005}-TEQ/g fat)	**Bayley's scale of infant development (BSID-II) expressed by Mental developmental indeces (MDI)**

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
effect of prenatal exposure to dioxin-like compounds on neurodevelopment in Japanese children: Sapporo cohort study. Sapporo Cohort (part of the Hokkaido Study on Environment and Children's Health) (Japan, Sapporo)		age, 121 children at 18 months of age Age at outcome assessment: 6 and 18 months 2002–2005	Mother's blood Lipid adjusted	15.1 (11.2, 19.6) in mothers of the 18 months olds (n=121)	**and psychomotor developmental indeces (PDI).** MDI and PDI were not significantly associated with maternal total TEQ or PCDD/F-TEQ at 6 or 18 months in boys or girls. Breast feeding duration (mean 10.9 months) was not taken into consideration. Mean score on MDI (82.2) and PDI (85.2) was lower than the standardized 100. Maternal intellectual performance was not taken into consideration at 6 months. Risk of bias tier: 2
Ikeno et al. (2018). Effects of low-level prenatal exposure to dioxins on cognitive development in Japanese children at 42months Sapporo Cohort (part of the Hokkaido Study on Environment and Children's Health) (Japan, Sapporo)	Cohort (prospective)	141 mother-child pairs Age at outcome assessment: 42 months 2002–2005	17 PCDD/Fs, 12 DL-PCBs Mother's blood Lipid adjusted	Median (P25, P75) (pg WHO_{2005}-TEQ/g fat) 15.1 (11.0, 20.3)	**Cognitive development at 42 months with Kaufman Assessment of Battery for Children (K-ABC). Mental processing scale (MPCS) and a scale measuring acquired knowledge and application of skills (AS) were used.** No negative associations between maternal prenatal PCDD/Fs and DL-PCBs TEQ and the outcomes. Positive association between total TEQ and AS in girls (B: 30.33, 95% CI 12.95, 47.72). Risk of bias tier: 1
Hui et al. (2016). Prenatal dioxin exposure and neurocognitive development in Hong Kong 11-year-old children	Cohort (prospective)	161 Age at outcome assessment: 11 years	CALUX determined BEQs Human milk Lipid adjusted	Mean (SD), IQR (pg BEQ/g fat) 14.9 (76.0), 10.9-18.7 (n=128)	**Neurocognitive function in 11-year old children (Wechsler Intelligence Scale for Children-IV, the Hong Kong List Learning Test, the Tests for Everyday Attention for Children and the Grooved Pegboard Test)**

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
n/a (Hong Kong, China)		2002			BEQs in human milk was not significantly associated with measures of neurocognitive function in terms of full scale IQ, fine motor coordination, verbal and non-verbal reasoning, verbal learning and recall and attention at 11 years of age. Risk of bias tier: 1
OCCUPATIONAL STUDIES					
Michalek et al. (2001b). Serum dioxin and peripheral neuropathy in veterans of Operation Ranch Hand. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during the Vietnam War)	Cohort 11–35 years	2101 M Age at exposure: 23.9–33.7 Age at outcome assessment (1997): 26–35 years older than at the time of exposure (1962-1971). 1982	TCDD Blood (serum) No lipid adjustment	Comparison: Non- Ranch Hand Air Force veterans Ranch Hand Veterans in three levels: Background: <10 pg/g fat 'Low': >10–94 pg/g fat 'High': > 94 pg/g fat	**Neurological status (1982, 1985, 1987, 1992, 1997), nerve conduction (1982), vibrotactile threshold (1992, 1997)** No change in the mean nerve conduction velocities or distal latencies. No change in odds for vibrotactile abnormality OR of symmetrical peripheral abnormality significantly increased in the high category in 1997 (OR=1:8, 95% CI 1.2–2.7) with a significant p for trend with increasing exposure. OR of possible peripheral neuropathy significantly increased in the 'High' category in 1997 (OR=1.8, 95% CI 1.2–2.7) with a significant trend with increasing exposure. OR of probable peripheral neuropathy increased with increasing exposure (significant p for trend) and showed

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					borderline significance in the 'High' category in 1992 (OR=2.5, 95% CI 0.9–6.6). The high category was significantly increased in 1997 (OR=5:0, 95% CI 2.2–11.2) and with significant p for trend with increasing exposure. OR of diagnosed peripheral neuropathy was significantly increased in the high category in 1992 (OR=4.9, 95% CI 1.5–15.3) and 1997 (OR 5.8, 95% CI 2.0–17.1) and with significant p for trend both years. Of note, it was a strong relation between diabetes and all the outcomes, as well a reported relation between dioxin and diabetes in Ranch Hand veterans, which complicate the interpretations. Risk of bias tier: 2
Barrett et al. (2001). Serum dioxin and cognitive function among veterans of Operation Ranch Hand. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during the Vietnam War)	Cohort 11–20 years	1,989 (937 Ranch Hand veterans, 1,052 comparisons) M Age at outcome assessment: Ranch Hand: 10.9–45.1 Comparison: 43.9	TCDD Blood Lipid adjusted	TCDD (pg/g fat) Median (range) Comparison: 4.0 (0–10) in 1987 or 1992 Background: 5.7 (0–10) in 1987 or 1992	**Cognitive functioning (Halstead-Reitan neuropsychological test battery, Wechsler adult intelligence scale-revised (WAIS-R), Wechsler memory scale (WMS) Form I, reading subtest of the wide range achievement test (WRAT))** Overall, there were few significant differences, but Ranch Hand veterans in the 'High' category scored lower than the comparison veteran on the immediate recall trial (difference in mean score; 95%CI: -0.5; -0.91, -0.09, P=0.02) and the delayed recall trial (-0.42; -0.8, 0.03,

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		1987, 1992		'Low', back-calculated*: 53.2 (27–94) 'High', back-calculated*: 194.9 (94–3,920) * Initial TCDD levels at the end of last tour of duty calculated based on TCDD measured in 1987 and 1992 using a half-life of 8.7 years.	P=0.04) of the WMS logical memory test. These findings were consistent with findings from alternative analysis in quintiles of exposure of the combined cohorts of veterans and comparisons. The decrement was relatively small and of unknown clinical significance. Risk of bias tier: 2
Pelclova et al. (2001). Biochemical, neuropsychological, and neurological abnormalities following 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) exposure. n/a (The Czech Republic)	Cross-sectional study About 30 years follow up in 1996 Exposure 1965–1968	13 M Average age at follow-up: 48–61 1996	TCDD Blood Lipid adjusted	Mean (range) in 1996 (pg/g fat) 256 (14–760) Back-estimation at the time of exposure: approx 5,000	**Neuropsychological variables (8 tests) and standard clinical neurological examination with 3 electrophysiological methods.** Significant correlation between TCDD in 1996 and several neuropsychological variables. Normal neuropsychological findings in only two subjects that had low TCDD in blood (94 and 74 pg TCDD/g fat). Abnormal EEG in 7 subjects. Clinical polyneuropatic signs in 5 men. Electromyographic (EMG) results abnormal in 3 men. Frequency of polyneurophatic EMG was significantly decreased form 1970s (38%) to 1996 (23%). Since this parameter is expected to increase by aging, the decrease may be related to decreasing TCDD levels. Risk of bias tier: 2
Pelclova et al. (2002). Lipid	Cohort	12	TCDD	Mean (range)	**Neuropsychological variables (8 tests)**

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
metabolism and neuropsychological follow-up study of workers exposed to 2,3,7,8- tetrachlordibenzo-*p*-dioxin. n/a (The Czech Republic)	About 35 years follow up in 2001 Exposure 1965-1968	M Age at follow up: 35-61 1996	Blood (*results taken from a previous study Pelclova et al 2001*) Lipid adjusted	(pg/g fat) 256 (14–760) Back-estimation at the time of exposure: approx 5,000	Correlations between neuropsychological variables and blood TCDD seen in 1996 had the same direction but were no longer statistically significant in 2001. Normal findings (absence of organic psychosyndrome, organic psychosyndrome mild grade or pseudoneurasthenic syndrome) in three out of the 12 subjects. According to the authors, no substantial changes were noticed in the subjects in comparison with the neuropsychological findings in 1996. Risk of bias tier: 2
Michalek et al. (2003). Serum dioxin and psychological functioning in U.S. Air Force veterans of the Vietnam War Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during the Vietnam War)	Cohort 11-30 years	2122 M Exposure in 1962-1971. Mean age at outcome assessment: 51-55. 1982	TCDD Blood No lipid adjustment	Comparison: Non- Ranch Hand Air Force veterans. For Ranch Hand veterans three levels: Background: <10 pg/g 'Low': 10-94 pg/g 'High': >94 pg/g	**Psychological assessment using self-administered questionnaires:** The Minnesota Mutiphasic Personality Inventory (MMPI) is used to evaluate personality status and emotional adjustment; the Million Clinical Multiaxial Inventory for basic personality charcteristics and clinical disorders (MCMI) There were few consistent psychological abnormalities associated with serum dioxin levels, and possibly related to the fear of possible health effects of dioxin exposure. Risk of bias tier: 2

Reference Trial or Study name (Geography)	Study type Duration	Participants in the study Sex (M/F) Age at outcome assessment Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Urban et al. (2007). Neurological and neurophysiological examinations on workers with chronic poisoning by 2,3,7,8-TCDD: follow-up 35 years after exposure. n/a (The Czech Republic)	Cohort 38-39 years follow up in 2003–2004 Exposure between 1965–1968	15 M Mean age (SD) at outcome assessment in 2003–2004: 60 (3) years 1996	TCDD Blood (plasma) Lipid adjusted	(pg/g fat) Arithmetic mean: 128 Geometric mean: 78 Range: 7-380	**Neurological examination through standardized clinical examination and 8 neuropsychological end-points** **Neurological examination:** Clinical signs of polyneuropathy: 9 subjects. Mean TCDD in subjects with and without signs were 169 and 67 pg/g fat (P=0.08). No association with neurasthenic syndrome. **Neuropshycological examination (n=13)**: Two variables (number of errors in the Category Test and the percentage of non-perseverative errors in the Wisconsin Card Sorting Test) and the frequency of abnormal neurophysiological tests in individual patients correlated with TCDD plasma level. Risk of bias tier: 2
Pelclova et al. (2009). Chronic health impairment due to 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin exposure. n/a (The Czech Republic)	Cohort 44 years follow up Exposure between 1965–1968	11 M Age (SD) at outcome assessment: 64.4 (1.5) 1996	TCDD Blood (serum) Lipid adjusted	Mean (SD, range) (pg/g fat) In 2008: 274.0 (181.2, 53–756)	**Neurological examination through standardised clinical examination, nerve conduction, brain perfusion and 8 neuropsychological endpoints** Four of 11 patients had normal neurological results. No significant correlation between TCDD and neuropsychological status appeared in the 8 patients examined. Risk of bias tier: 2

n/a: not applicable.

A.8.10. Studies on effects on teeth and bone

Table 74. Epidemiological studies on the association between exposure to PCDD/Fs and DL-PCBs and **effects on teeth and bone**. Details about the risk of bias appraisal can be found in **Annex A.9.10**.

Reference **Trial or study name (Geography)**	**Study type** **Duration**	**Participants in the study** **Sex** **Age at outcome assessment (years)** **Year of tissue sampling**	**Compounds** **Measurement of exposure**	**Levels of exposure**	**Parameters measured and Measures of effect** **Risk of bias tier**
EFFECTS ON TEETH					
Alaluusua et al. (2002). Natal and Neonatal Teeth in Relation to Environmental Toxicants n/a (Helsinki and Turku, Finland)	Case control (cross-sectional) n.a	26 (14 cases, 12 controls) M, F Age at outcome assessment: Newborn to one month 1997–2000	17 PCDD/F, 12 DL-PCBs Human milk Lipid adjusted	Median (P25, P75) (pg WHO_{1998}-TEQ/fat) Cases: PCDD/Fs: 11.9 (7.02, 14.1) DL-PCB: 7.24 (4.55, 9.54) Controls: PCDD/Fs: 8.58 (6.03, 9.99) DL-PCB: 5.26 (3.49, 6.20)	**Prevalence of natal and neonatal teeth** 34,457 newborns from four hospitals located in the Helsinki and Turku area, of which 29 with natal teeth. The prevalence of natal teeth was 1:1188 and of neonatal teeth 1:1013. Concentration of PCDD/Fs and DL-PCBs in milk from 14 mothers (Helsinki 11, Turku 3) of children with natal or neonatal teeth was not significantly different from that of 12 control mothers from the Turku area. Risk of bias tier: 1
Wang et al. (2003). Neonatal and childhood teeth in relation to perinatal exposure to polychlorinated biphenyls and dibenzofurans: observations of the Yucheng children in Taiwan.	Case control (cross-sectional) n/a	148 (73 Yucheng children, 75 matched controls) M, F	2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF Child blood (serum) Lipid adjusted	Mean (SE), range (pg TEQ/g fat) Cases Low (n=16): 233 (27.2), 84.9-455 High (n=15):	**Dental defects and related factors** Parents reported 9.6% (7/73) bearing teeth during the neonatal period in the exposed group and none in the control group. The percentages of children with congenitally

Reference Trial or study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Yucheng cohort (Taiwan, Qigu District, Yucheng)		Mean (rage) age at outcome assessment: 9.3 (SEM 0.2) 1991–1992		1,780 (266), 481-3,830 Control 12.0 (pooled serum of control children)	missing tooth germ and rotated teeth were significantly increased in the exposed group (P<0.05). The developmental defects combined (fusion, microdontia, pigmentation, enamel hypoplasia, and impaction) increased with exposure (P=0.01). Risk of bias tier: 1
Alaluusua et al. (2004). Developmental dental aberrations after the dioxin accident in Seveso. Seveso Cohort (Italy, Seveso)	Cohort 25 years follow-up	113 (ABR: 48, non-ABR:65) M, F Mean (range) age at outcome assessment: 29 1976–1977	TCDD Blood (serum) Lipid adjusted	Median 476 (pg/g fat) Zone ABR: T1: 31–226 T2: 238–592 T3: 700–26,000 Zone non-ABR: Not available. Concentration was indicated by two pooled samples from children (0-12 years) with 33.4 and 47.6 ng TCDD/g fat (Eskenazi et al., 2004).	**Enamel defects, lesions, caries, hypodontia** Enamel defects: 27 of the 113 subjects had enamel defects. 93% of these (25/27) had been <5 years of age at time of accident. Prevalence of defects in those who were <5 years of age was 42% (15/36) in zone ABR subjects and 26% (10/39) in zone non-ABR subjects. Enamel defects correlated with serum TCDD levels (only available for ABR; T1: 1/10, T2: 5/11, T3 9/15, p=0.016). Of note, the prevalence was higher in non-ABR children than in T1. The overall difference in prevalence between ABR and non-ABR was due to teeth with enamel hypoplasia (zone ABR 19.4%, zone non-ABR 5.1%). The OR (95% CI) for enamel defects in the two higher TCDD tertiles: 2.4 (1.3–4.5) non-ABR children as referent population.

Reference Trial or study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					Hypodontia: Lateral incisors or second premolars were missing in 12.5% (6/48) of subjects from zone ABR and in 4.6% (3/65) of non-ABR subjects. Frequency increased with serum TCDD level (p=0.05). Caries, periodontal disease, gingival pigmentation and salivary flow rate was not associated with exposure. Risk of bias tier: 1
EFFECTS ON BONE					
Eskenazi et al. (2014). Serum Dioxin Concentrations and Bone Density and Structure in the Seveso Women's Health Study. Seveso Women's Health Study (SWHS) (Italy)	Cohort 32	339 F Age at outcome assessment: 30-52 2008	TCDD Blood (serum) Lipid adjusted	pg/g fat All women: Median 73.2 IQR: 33.1–193.0 Premenopause women: median: 78.9 IQR: 40.9–209.0 Perimenopause/menopause women: Median: 43.1 IQR: 21.9–129.0	**Bone mineral density** at the lumbar spine and left proximal femur (neck, throcanter, intertrochanter and total hip) using DXA**. Hip structural analysis (HSA)** using mineral content and dimentional data from hip DXA images at three thin regions traversing the proximal femur, where bone size, cross sectional area and bone strength and bending strength is estimated (HSA program). Overall, TCDD exposure was not associated with adverse effects on adult bone health. A 10-fold increase in TCDD was positively associated with some measures of bone strength

Reference Trial or study name (Geography)	Study type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					and size, but differed somewhat by whether exposure occurred before or after peak bone mass. Risk of bias tier: 1
Fukushi et al. (2016). Effects of dioxin-related compounds on bone mineral density in patients affected by the Yusho incident. Yusho Cohort (Japan)	Cohort n/a	489 (262 women, 227 men) M, F Average age at outcome assessment: Women: 66.3 Men: 66.9 2010	17 PCDD/Fs, 12 DL-PCBs Blood (serum) Sampled in 2004-2007, 36-39 years after incidence Lipid adjusted	Individual congeners reported in pg/g fat, stratified by men and women (for women wih and without osteoporosis medication)	**Bone mineral density** No significant associations between single congeners and bone mineral density after adjustment for confounders, with exception of 1,2,3,4,6,7,8-HpCDD which was negatively associated with bone mineral desity in women. This congener was not increased after the contamination incidence. Risk of bias tier: 2

n/a: not applicable

A.8.11. Studies on cancer

Table 75. Epidemiological studies on the association between exposure to PCDD/Fs and DL-PCBs and **cancer**. Details about the risk of bias appraisal can be found in **Annex A.9**.

Reference **Trial or Study name (Geography)**	**Study Type** **Duration**	**Participants in the study** **Sex** **Age at outcome assessment (years)** **Year of tissue sampling**	**Compounds** **Measurement of exposure**	**Levels of exposure**	**Parameters measured and Measures of effect** **Risk of bias tier**
INDUSTRIAL ACCIDENTS OR CONTAMINATION INCIDENTS					
Bertazzi et al. (2001). Health effects of dioxin exposure: A 20-year mortality study. Seveso Cohort (Italy, Seveso)	Cohort 20 years	232,745 M, F Age at outcome assessment: all ages 1976–1977	TCDD Blood (plasma) Lipid adjusted	Median (pg/g fat) <u>Zone A</u> 1976–77: 447.0 1993–94: 73.7 <u>Zone B</u> 1976–77: 94.0 1993–94: 12.4 <u>Zone R</u> 1976–77: 48.0 <u>Reference</u> 1993–94: 5.5	**Evidence of latency of effects from 10–15 years** Mortality among men in Zones A and B increased from: - All cancers: RR=1.3, 95% CI 1.0–1.7 - Rectal cancer: RR=2.4, 95% CI 1.2–4.6 - Lung cancer: RR=1.3, 95% CI 1.0–1.7 Increased in RR after 15 years for lung and rectal cancer. Excess of lymphohaematopoietic neoplasms in both genders (RR=1.7, 95% CI 1.2–2.5) Hodgkin's disease risk elevated in first 10 years observation period (RR=4.9, 95% CI 1.5–16.4), whereas highest increase for non-Hodgkin's lymphoma (RR=2.8, 95% CI 1.1–7.0) and myeloid leukaemia (RR=3.8, 95% CI 1.2–12.5) occurred after 15 years. No soft tissue sarcoma cases found in the zones

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					Risk of bias tier: 2
Warner et al. (2002). Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. Seveso Women's Health Study (SWHS) (Italy, Seveso)	Cohort 20 years follow-up	981 F Age at outcome assessment: 20–29 (n=191) 30–39 (n=284) 40–49 (n=244) ≥50 (n=262) 1996	TCDD Blood (serum) (1976–1981), some back extrapolated with $t_{1/2}$ 9 yrs Lipid adjusted	Median (pg/g fat) Breast cancer cases (n=15): 71.8 Non-cancer cases (n=981): 55.1	**Breast cancer** HR for breast cancer associated with a 10-fold increase in serum TCDD levels (log_{10}TCDD) significantly increased to 2.1 (95% CI 1.0–4.6). Covariate-adjusted results were not different. Risk of bias tier: 1 *Comments: Only some results reported. Some selection bias.*
Pesatori et al. (2008). Aryl hydrocarbon receptor-interacting protein and pituitary adenomas: a population-based study on subjects exposed to dioxin after the Seveso, Italy, accident. Seveso Cohort (Italy, Seveso)	Cohort 0-20 years	45,369 M, F Age (range) at outcome assessment: all ages 1976	TCDD Blood (serum) (1977–78) Lipid adjusted	Median (pg/g fat): Zone A (n=296): 447 Zone B (n=80): 94 Zone R (n=48): 48 Number based on Pesatori et al. (2009)	**Pituitary adenoma** Small sample size but a tendency for increased risk. No statistically significant increase in pituitary adenoma incidence in subjects exposed to high and intermediate TCDD concentrations in comparison with the non-exposed reference population. Eight tumours identified between 1986-1996 in 5 F and 3 M (non-functioning pituitary tumours n=4, prolactin secreting adenoma n=4). Tendency toward s a higher risk of pituitary tumours:

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					Zone A: RR=6.2, 95% CI 0.9–45.5, P=0.07 Zone B: RR=1.9, 95% CI 0.5–7.7, P=0.39 Risk of bias tier: 2
Consonni et al. (2008). Mortality in a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow-up. Seveso Cohort (Italy, Seveso)	Cohort 25 year follow-up	278,108 M, F Age at outcome assessment: all ages 1976–1977, 1992–1996	TCDD Blood (serum) Lipid adjusted	Median (pg/g fat) Zone A: 1976–77 (n=296): 447.0 1992–96 (n=7): 73.3 Zone B: 1976–77 (n=80): 94.0 1992–96 (n=51): 12.4 Zone R: 1976–77 (n=48): 48.0 1992–96: n/a Reference: 1976–77: n/a 1992–96 (n=52): 5.5	Increased risk of lymphatic and haematological cancer in both exposed zones but the number of cases is small: Zone A (6 deaths): RR=2.23, 95% CI 1.00–4.97 Zone B (28 deaths): RR=1.59, 95% CI 1.09–2.33. Risk of bias tier: 2
Pesatori et al. (2009). Cancer incidence in the population exposed to dioxin after the "Seveso accident": twenty years of follow-up. Seveso Cohort (Italy, Seveso)	Cohort 20 years follow-up	2,122 M, F Age at outcome assessment not reported	TCDD, 17 PCDD/Fs, 12 DL-PCBs (as WHO_{2005}-TEQ) Blood (serum) Lipid adjusted	Median TCDD (pg/g fat) Zone A: 1976 (n=296): 447.0 1993–94 (n=7): 73.3 Zone B: 1976 (n=80): 94.0	**Cancer incidence** All cancer incidences did not differ from expectations in any of the contaminated zones. Increased risk of lymphatic and haematological cancer in both exposed zones but the number of cases is small

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		1976, 1993–1994		1993–94 (n=51): 12.4 Zone R: 1976 (n=48): 48.0 1993–94: n/a Reference: 1976: n/a 1993–94 (n=52): 5.5 Median (pg WHO_{2005}-TEQ/g fat) Zone A (1993–94): 94.0 Zone B (1993–94): 43.2 Zone R (1993–94): n/a Reference (1993–94): 38.8	- Zone A (4 cases): RR=1.39, 95% CI 0.52–3.71 - Zone B (29 cases): RR=1.56, 95% CI 1.07–2.27 Increased risk of breast cancer in zone A (F) after 15 years since the accident (5 cases: RR=2.57, 95% CI 1.07–6.20). No cancer cases observed among subjects diagnosed with chloracne early after the accident. No cases of soft tissue sarcomas occurred in the most exposed zones (A and B, 1.17 expected). Risk of bias tier: 2
Warner et al. (2011). Dioxin Exposure and Cancer Risk in the Seveso Women's Health Study. Seveso Women's Health Study (SWHS) (Italy, Seveso)	Cohort 32 years (following explosion in 1976)	833 F Age (mean, SD) at outcome assessment: 50.8 (11.8)	TCDD Blood Lipid adjusted	Mean (SD) (pg/g fat) Cancer cases: 95.3 (4.0) Non-cancer cases: 67.9 (4.2) (p=0.06)	**All cancers and breast cancer** Adjusted HR associated with a 10-fold increase in serum TCDD for all cancers combined significantly increased (adj HR=1.80, 95% CI 1.29–2.52). For breast cancer, the HR was increased, but not significantly (adj HR=1.44, 95% CI 0.89–2.33).

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		1976–1977 (n=894), 1978–1981 (n=59), 1996–1997 (n=28)			Increased Risk for breast cancer seen in earlier studies not sustained. Most women not yet in 50s so cancer risk may increase with longer follow up. Risk of bias tier: 1
OCCUPATIONAL STUDIES					
Heederik et al. (1998). Modelling of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin levels in a cohort of workers with exposure to phenoxy herbicides and chlorophenols. n/a (The Netherlands)	Cohort 1963 (exposure due to accident)–1991	47 M, F Age at outcome assessment: not reported 1993	17 PCDD/Fs, 4 DL-PCBs (-77, -81, -126, -169) Blood (serum) Lipid adjusted	(pg/g fat) TCDD Mean (SD): 37.3 (53.1) TCDD Median (range): 8.2 (1.9-194) Levels back-extrapolated TCDD at the time of occupational exposure (using three different half-life of 5.8 years, 7.1 years and 11.3 years) also provided.	**Relative risks of selected causes of death from occupational exposure for male workers with medium and high TCDD levels compared to workers with low levels based on model predicted $TCDD_{max}$ ($t_{1/2}$=7.1 years)** RR (95% CI) Low levels Medium levels High levels **All causes** 1.0 1.9 (1.2–2.8) 1.9 (1.3–2.8) **Malignant neoplasms** 1.0 4.8 (2.0–11.3) 4.4 (1.9–10.4) Trachea, bronchus, lung 1.0 6.4 (0.8–53.1) 6.8 (0.9–54.4) Respiratory organs 1.0 7.7 (1.0–63.2) 7.7 (1.0–61.1) Urinary organs

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					1.0 8.5 (1.0–71.7) 1.0 (0.1–16.5) Non-Hodgkin's lymphoma 1.0 1.2 (0.1–19.7) 2.4 (0.2–27.5) Predicted levels were positively associated with increased (cause-specific) mortality. Risk of bias tier: 1
Becher et al. (1998). Quantitative cancer risk assessment for dioxins using an occupational cohort. n/a (Hamburg, Germany)	Cohort 1952–1984 (follow up 1992)	1,189 M Age at outcome assessment: not reported (adults) Year of tissue sampling: not reported	TCDD Blood Lipid adjusted	Exposure verified in sample of 275 workers Mean (pg/g fat) 101.3 (2-2,252) Integrated TCDD concentration over time	**Total cancer mortality** Quantitative cancer RA Increased SMR for total cancer 1.41, 95% CI 1.17–1.68. Interval of 10^{-3} – 10^{-2} additional cancer lifetime risk under daily intake 1 pg/kg bw/day from dose response model Risk of bias tier: 1
Collins et al. (2009a). Mortality rates among trichlorophenol workers with exposure to 2,3,7,8-tetrachlorobidenzo-*p*-dioxin. n/a (Michigan, US)	Cohort Follow-up: 1942–2003	1,615 Mean age at start of follow-up: 29.6 Year of blood sampling not reported	TCDD Blood Not reported whether lipid adjusted	Blood samples were analysed from 17% of the subjects (n=280). Historical exposures based on these to estimate the TCDD levels of all workers.	1 compartment model No increase in SMR for all cancer combined (SMR=1.0, 95% CI 0.8–1.1). No increase in lung cancer (SMR=0.7, 95% CI 0.5–0.9). Four deaths from soft tissue sarcoma (SMR=4.1, 95% CI 1.1–10.5) Risk of bias tier: 1

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Collins et al. (2009b). Mortality rates among workers exposed to dioxins in the manufacture of pentachlorophenol. n/a (Michigan, US)	Cohort Exposure 1937-1980	773 128 blood samples 196 exposed Year of tissue sampling: not reported	TCDD Blood Not reported whether lipid adjusted	Historical exposures based on these to estimate the TCDD levels of all workers.	1 compartment model No increase in SMR for all cancer combined using low, medium and high TCDD 8 deaths from NHL (SMR 2.4 95% CI1.0-4.8) Risk of bias tier: 2
Flesch-Janys et al. (1998). Estimation of the cumulative exposure to polychlorinaterd dibenzo-*p*-dioxins/furans and standardised Mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort n/a (Germany)	Cohort	1,189 M Age at outcome assessment: Unclear Year of tissue sampling: not reported.	TCDD Blood (serum) from 275 Measured blood in M and F	Estimation of cumulative job exposure to TCDD 413 deaths	SMR all cancer 1.41 95% CI 1.17–1.68 Trend for increasing effect only significant for total cancer combined Risk of bias tier: 2
Steenland et al. (2001b). Risk assessment for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) based on an epidemiologic study. n/a (US)	Cohort	170 M 1988 Age at outcome assessment: Unclear Year of tissue	TCDD Blood (serum) Lipid adjusted	Levels back-calculated using a half-life of 8.7 years Estimated TCDD concentration from dose response using cumulative serum level Estimated serum	**All cancer mortality** Positive trend (p=0.003) between estimated log cumulative TCDD serum level and cancer mortality. For males excess lifetime risk of dying of cancer at intake of 1 pg/kg bw/day was 0.05–0.9% against a lifetime risk of 12.4% Risk of bias tier: 1

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		sampling: 1988		level at end of follow-up: Median (range): 9 (5–52,681) Mean (SD): 343 (2,223) Estimated serum level at end of exposure: Median: 98 (6-210,054) Mean (SD):1,589 (8,208)	
Ketchum et al. (1999). Serum dioxin and cancer in veterans of Operation Ranch Hand. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)	Cohort Follow-up measured in 1987 or 1992	2,255 M Mean (SD) age at outcome assessment: Comparison group: 53.5 (7.6) Ranch Hand: Background: 54.6 (7.2) 'Low': 54.6 (7.6) 'High': 50.9 (7.4) 1987, 1992	TCDD Blood (serum) Unclear if lipid adjusted	Median (range) (pg/g) Comparison: 4.0 (0-10) Ranch Hand (Levels measured): Background: 5.7 (0–10) 'Low': 52.3 (27–94) 'High': 195.7 (94–3,290) Serum levels also back-calculated to at	**Skin cancer by cell type, cancers at sites other than the skin, specific cancer among veterans, cancer latency** There is no consistent dose response and no significant increase in cancer risk in the 'High' dioxin exposed group. Cancer risk at sites other than skin increased in low TCDD exposed group but results inconsistent. Some effects (latency) concluded not to be associated with TCDD exposure. Risk of bias tier: 2 Comments: *This study had low power to detect an effect for specific or rare cancers.*

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		1962–1971		the end of service in Vietnam using a constant half-life of 8.7 years.	
Akhtar et al. (2004). Cancer in US Air Force veterans of the Vietnam War. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)	Cohort n/a	2,438 M Median age at examination in 1982: Comparison: 43.3 Ranch Hand Background: 45.1 'Low': 45.5 'High': 37.2 1987, 1992, 1997	TCDD Blood (serum) Lipid adjusted	Median (range) (pg/g fat) (1987, 1992 or 1997): 'Low': 15.2 (10–29.2) 'High': 47.7 (18–617.8) Back-extrapolated to end of service in Vietnam using a constant half-life of 7.6 years: 'Low': 66 (32.2–118.5) 'High': 245.5 (119.3–4221.9)	**Cancer incidence, cancer mortality** White Ranch Hand veterans increased incidence prostate and melanoma but restricted to <2 years of service in Southeast Asia. Risk of bias tier: 2
Pavuk et al. (2005). Did TCDD exposure or service in southeast Asia increase the risk of cancer in air force Vietnam veterans who did not spray agent orange?	Cohort 20 years	1,482 M Age at outcome assessment: not	TCDD Blood (serum) Lipid adjusted	Median (range) (pg/g fat) 3.8 (5.2–54.8)	**Cancer incidence** All sites cancer risk increased with TCDD (RR=1.6, 95% CI 1.2–2.2) Risk of prostate cancer increased with years of

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)		clear 1987			service in Southeast Asia but not with TCDD exposure. TCDD and years of service in Southeast Asia interacted with all sites cancer. Risk was greatest in those with highest TCDD levels and longest time served in Southeast Asia. Risk of bias tier: 2 *Comments:* Some confounding variables noted but potential for mixed exposures not considered
Ketchum and Michalek (2005). Postservice mortality of Air Force veterans occupationally exposed to herbicides during the Vietnam War: 20-year follow-up results. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)	Cohort 28–37 years	2,452 M The median birth year and age range is indicated in Table VII. The median age range at exposure can be calculated 1987, 1992, 1997	TCDD Blood (serum) Lipid adjusted	Median (range) in 1987, 1992, 1997 (pg/g fat) Comparison: 4.0 (0.4–54.8) Background: 5.7 (0.6–10.0) 'Low': 15.0 (10.0–29.2) 'High': 47.4 (18.0–617.8) Median (range) TCDD extrapolated levels at the end of the last tour of duty in Vietnam using a	**Post service mortality** The risk of death caused by cancer was not increased (RR=1.0). Highest exposure group had increased risk of mortality but circulatory disease rather than cancer. Risk of bias tier: 2

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
				constant half-life of 7.6 years (pg/g fat) 'Low': 65.0 (32.2–117.4) 'High': 244.8 (117.9–4,221.9)	
Kang et al. (2006). Health status of Army Chemical Corps Vietnam veterans who sprayed defoliant in Vietnam. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)	Cohort 28-35 years	1241 M Median age at outcome assessment: Vietnam service: 53 Non-Vietnam service: 51 1999–2000	TCDD Blood (serum) Lipid adjusted	Mean (pg/g fat) [(a)] Vietnam service and self-reported herbicide spraying (n=357): 4.3 (0.5-85.8) Vietnam service and no self-reported herbicide spraying (n=413): 2.7 (0.6–27.7) Non-Vietnam service and self-reported herbicide spraying (n=9): 3.1 (0.8–9.6) Non-Vietnam service and no self-reported	**All cancer and leukaemia** Higher prevalence of cancer in sprayers versus non sprayers but not significant. All cancer prevalence: Vietnam: 108 (7.2%) Non-Vietnam: 53 (3.71%) Adj OR=1.46, 95% CI 1.02–2.10 Risk of bias tier: 2

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
				herbicide spraying (n=87): 2.1 (0.4–12.5)	
Pavuk et al. (2006). Prostate cancer in US Air Force veterans of the Vietnam war. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)	Cohort 21 years	2,516 (Ranch Hand: 1,019, Comparison: 1,497) M Age at outcome assessment: unclear 1987, 1992, 1997, 2003	TCDD Blood (serum) Lipid adjusted	Median (10-90%) in 1987 (pg/g fat) Comparison: 3.9 (1.6-7.1) Ranch Hand: 11.6 (3.6-61.6) 20-years median cumulative TCDD level from the end of exposure in Vietnam to the end of follow-up (pg/g fat): Comparison: 77.2 (32–141) Ranch Hand: 433 (72–3,008)	**Prostate cancer** No overall increase in the risk of prostate cancer in Ranch Hand veterans versus the Comparison group. Positive association in Ranch Hand veterans in the Higher TCDD category who served before 1969 (RR=2.27, 95% CI 1.11–4.66) when more contaminated herbicides were used, but the number of cases was small (n=15). Within-group comparison: in Comparison veterans the time served was associated with an increased risk of prostate cancer (RR=2.18, 95% CI 1.27–3.76). No increase in the risk of prostate cancer within the Ranch Hand group in association with TCDD or time served. Risk of bias tier: 2
Michalek and Pavuk (2008). Diabetes and cancer in veterans of Operation Ranch Hand after adjustment for calendar period, days of	Cohort 11 to 40 years	2,583 M Age at outcome	TCDD Blood (serum) Lipid adjusted	Median (pg/g fat) Vietnam service: Comparisons: 4 Ranch Hand: 12.6	**Cancer** There is only an increased risk of cancer (all) when 3 levels of stratification are taken into account. This means smaller numbers.

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
spraying, and time spent in Southeast Asia. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)		assessment: unclear 1987, 1992, 1997, 2002		No Vietnam service: Comparison: 3.9 Ranch Hand: 10.6 Days of spraying: Comparison: 3.9 Ranch Hand: ≥90 days : 13.3 <90 days : 5.9 Median TCDD extrapolated levels to the end of service in Vietnam using a constant half-life of 7.6 years	Without stratification: no significant increase in the risk of cancer with log(TCDD) in the combined cohort (P=0.24) and no significant increase in the risk of all-site SEER cancer in any of the Ranch Hand TCDD exposure categories. RR significantly increased in the Low category (RR=1.7, 95% CI 1–2.9, P=0.03) and risk of cancer increased significantly with log(TCDD) in the combined cohort (P=0.01) after restriction to those whose last year of service was during or before 1968. Risk of bias tier: 1
Li et al. (2013). High level of dioxin-TEQ in tissue is associated with Agent Orange exposure but not with biochemical recurrence after radical prostatectomy. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)	Case control 34-47 years	93 M Mean age at outcome assessment: 57–60 2005–2009	CALUX determined BEQ levels Abdominal *s.c.* adipose tissue Lipid adjusted	Mean (SD), Median (IQR) (pg BEQ/g fat) 'Low' (n=46): 12.1 (3.5), 13.4 (10.1–15.0) 'High' (n=47): 27.7 (10.4), 24.7 (19.8–31.2)	**Incidence of BioChemical Recurrence (BCR) after radical prostatectomy in prostate cancer patients** Exposure to Agent Orange increases the adipose level of dioxin-TEQ but neither associated with BCR after radical prostatectomy. Risk of bias tier: 2
Landgren et al. (2015).	Cohort	958 (Ranch Hand:	TCDD	Median (IQR)	**Risk of monoclonal gammopathy of**

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
Agent Orange Exposure and Monoclonal Gammopathy of Undetermined Significance: An Operation Ranch Hand Veteran Cohort Study. Air Force Health Study (AFHS, Operation Ranch Hand) (US Veterans that served in Southeast Asia during Vietnam War)	Up to 40 years	479, Comparison: 479) M Median age at outcome assessment in 2002: 65 1987, 1992, 1997, 2002	Blood (serum) Lipid adjusted	(pg/g fat) Ranch Hand: 10.5 (6.2–21.4) Comparison: 4.1 (2.9–5.8)	**undetermined significance (MGUS)** Increased risk of MGUS in veterans exposed to Agent Orange. The supports and association between Agent Orange and myltiple myeloma. No cancer measured. Crude prevalence of overall MGUS: Ranch Hand: 7.1% (34 of 479) Comparison: 3.1% (15 of 479) Risk of bias tier: 2
Hooiveld et al. (1998). Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. Dutch Herbicide Cohort (The Netherlands)	Cohort Mean duration of follow-up: 22.3 years	562 M, F Age at outcome assessment: unclear 1993	TCDD (also PCDD/Fs, DL-PCBs, but relations reported only for TCDD) Blood (serum) Lipid adjusted	Mean measured TCDD levels (n=47) (pg/g fat) Exposed, Accident: No main production: 55.8 Main production: 111.4 Exposed, no accident: No main production: 5.8 Main production: 22.9	**Cancer mortality** Increased risk of NHL (3 cases) (SMR=3.8, 95% CI 0.8–11.0). Positively associated with TCDD level. Increased risk for cancer of respiratory organs (RR=10.3, 95% CI 1.5–72.6). After adjustment for possible confounding factors (age, calendar period at end of follow-up, and time since first exposure/employment), risk still elevated (RR=7.5, 95% CI 1.0–56.1) (no information about smoking habits). Elevated risk for bladder and kidney cancer (SMR=3.9, 95% CI 1.7–7.6). The relative risk compared with non-exposed workers was unstable because there were no cases in the referent group.

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
				Extrapolated mean levels to the time of maximum exposure using a constant half-life of 7.1 years (pg/g fat) <u>Exposed, Accident</u>: No main production: 1,059 Main production: 2,148 <u>Exposed, no accident</u>: No main production: 40.8 Main production: 285.9	Workers exposed as a result of the accident showed a statistically significant increased risk for prostate cancer. Risk of bias tier: 2 *Comments*: Mixed exposure to phenoxyherbicides, chlorophenols and contaminants (TCDD). Cancer mortality increased in exposed group but the exposure mixed. Smoking not considered. Modelled TCDD and used this to make associations but only actually measured TCDD in 47 individuals. Numbers are too small to use.
Boers et al. (2012). Plasma dioxin levels and cause-specific mortality in an occupational cohort of workers exposed to chlorophenoxy herbicides, chlorophenols and contaminants. Dutch Herbicide Cohort (The Netherlands)	Cohort Vital statistics of cohort workers was updated until Dec 2006	2,056 M Age at outcome assessment: not reported Exposure in factory A in 1963 from an accident.	TCDD Blood (plasma) Unclear if lipid adjusted	Plasma TCDD levels (n=187 workers) used to develop a predictive model for TCDD back-extrapolation at the time of last exposure using a half-life of 7.1 years	**Cause-specific mortality (including all cancers and other illness/disease)** There was no association between TCDD exposure and all cancer mortality. There was a possible link to NHL but if factory B (no TCDD) included in the analysis the association disappeared. Risk of bias tier: 2

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		Subjects from Factory B considered as non-exposed. 2007-2008		(pg/g): Background: ≤0.4 Low: 0.4-1.9 Medium: 1.9-9.9 High: ≥9.9	
OTHER STUDIES					
Steenland et al. (1999). Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. n/a (USA)	Cohort Follow up: around 15-57 years	3,538 M Age at outcome assessment: Not reported Year of tissue sampling: unclear.	TCDD Cumulative exposure scores based on JEM, calibrated against serum TCDD in subgroup	Estimated back-calculated levels about 200,000 ppt-years in septile 6–7 (e.g. 10,000 pg/g x 20 years)	**Various cancer types** SMR for all cancers combined: 1.13 (95% CI 1.02–1.25). Statistically significant positive linear trends in SMRs with increasing exposure for all cancers combined and for lung cancer. All cancers combined for the highest exposure group: SRM=1.60, 95% CI 1.15–1.82). Internal analyses with Cox regression found statistically significant trends for cancer (15-year lagtime). Excess cancer limited to the highest exposed group possibly 100-1,000 times normal exposure Analyses showed high TCDD exposure resulted in an excess of all cancers but there was no

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					specificity for any one type. Risk of bias tier: 2
De Roos et al. (2005). Persistent organochlorine chemicals in plasma and risk of non-Hodgkin's lymphoma n/a (USA - Iowa, Los Angeles County, metropolitan areas of Detroit and Seattle)	Case control n/a	200 (100 untreated cases, 100 controls) M, F Age at outcome assessment: unclear. 1998	17 PCDD/Fs, 4 DL-PCBs (-77, -81, -126, -169) Blood (plasma) Lipid adjusted	Levels divided into quartiles: Total pg WHO_{1998}-TEQ/ fat: ≤15.12 >15.12-19.39 >19.39-29.46 >29.46 Different quartiles for PCDDs-TEQ, PCDFs-TEQ and DL-PCBs-TEQ	**Non-Hodgkin's Lymphoma (NHL)** Each PCDF congener associated with risk of NHL, as were total PCDFs, with 3.5-fold increased risk for the highest versus lowest quartile and a significant trend across quartiles (P=0.006). Coplanar PCB congeners -156, -180 and -194 showed increased risk of NHL. Total TEQ associated with NHL, with 35% increased risk per 10 TEQ pg/g fat (95% CI 1.02–1.79). Only 2 cases had detectable TCDD. Risk of bias tier: 2 *Comments*: Used multiple imputation for missing values.
McBride et al. (2009). Mortality in workers exposure to 2,3,7,8-tetrachlordibenzo-*p*-dioxin at a trichlorophenol plant in New Zealand. n/a (New Zealand)	Cohort Worked between 1969 and 1988	1,599 M, F Age at outcome assessment: unclear Year of tissue	TCDD Blood (serum) Not specified whether lipid adjusted	Current serum TCDD levels used to develop cumulative TCDD exposure estimates for the 1,599 workers	196 deaths 61 from cancer No increased mortality due to cancer SMR = 1.1, 95% CI, 0.9–1.4 Risk of bias tier: 2

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		sampling: unclear			
Viel et al. (2011). Increased risk of non-Hodgkin lymphoma and serum organochlorine concentrations among neighbors of a municipal solid waste incinerator. n/a (France, Besançon)	Case control 2	68 M, F Age at outcome assessment: Not reported, however, most subjects were between 55-63 years of age. 2003	17 PCDD/Fs, 12 DL-PCBs Blood (serum) Lipid adjusted	Mean (pg WHO_{1998}-TEQ/g fat) PCDDs: Cases: 13.39 Control 8.73 PCDFs: Cases: 9.44 Controls: 6.27 DL-PCBs: Cases: 33.13 Controls: 20.10 Total TEQ: Cases: 55.96 Control: 35.10	**Non-Hodgkin lymphoma (NHL)** Sum of PCDD showed significant increase in OR (1.12, 95% CI 1.03–1.26) linked to risk of NHL. Serum total WHO_{1998}-TEQ concentrations, at levels experienced by people residing in the vicinity of a polluting MSWI. Risk of bias tier: 3
Manuwald et al. (2012). Mortality study of chemical workers exposed to dioxins: follow-up 23 years after chemical plant closure. n/a (Germany, Hamburg)	Cohort 23 year follow up after a chemical plant closure.	1,589 M, F Age at outcome assessment: Unclear Year of tissue sampling: unclear (adults)	TCDD Blood (serum) Lipid adjusted	Cumulative exposure estimated from work histories and serum TCDD (lipid adjusted) in subgroup. Median: 77 pg/g fat Upper quartile: >335	**Cause-specific standardised mortality ratios** Increase in all-cancer mortality in men (SMR=1.37, 95% CI 1.21-1.56) specific mortality from: - respiratory cancer: SMR=1.64, 95%CI 1.32–2.03, - oesophageal cancer: SMR=2.56, 95%CI 1.27-4.57, - rectum cancer: SMR=1.96, 95% CI 0.98–3.51. For women, increase in breast cancer mortality (SMR=1.86, 95% CI 1.12–2.91).

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					Risk of bias tier: 2 *Comments*: One problem is that when the TCDD content was analysed from a biological sample then the SMR all cause was 0.87 and for all cancer 1.18. Exposure to multiple agents including asbestos (linked to pleural cancer).
Cheng et al. (2006). TCDD exposure-response analysis and risk assessment. National Institute for Occupational Safety and Health (NIOSH) (USA)	Cohort 1942-1993	3,538 M Age at outcome assessment: not reported	TCDD Time-dependent cumulative exposure scores were converted into estimated cumulative serum lipid concentrations (ppt). Lipid adjusted	See Steenland et al. (1999)	**Standardized mortality ratio (SMR) and incremental cancer risks at age 75** Reanalysis of cancer risk in the study by Steenland et al. (1999). Main difference is using a CADM model instead of a one-compartment model to estimate the TCDD levels in workers over time. The CADM model assumes faster elimination when tissue levels are high. The reanalysis still shows an association between TCDD exposure and cancer risk, but a much attenuated slope, i.e. a lower risk per pg/g-year than presented by Steenland et al. (1999) Risk of bias tier: 2
Boers et al. (2010). Cause-specific mortality of Dutch chlorophenoxy herbicide manufacturing workers. n/a (The Netherlands)	Cohort study 10-41 years	2,016 M Mean (SD) age at entry of the	TCDD Blood (serum) Lipid adjusted	(pg/g fat) Back extrapolation of TCDD measurements in serum collected from a sample of	**Cause of death, including all causes and some specific cancers** All cancer mortality increased (HR 1.31; 95%CI 0.86 to 2.01). However, previous increased risk of NHL and respiratory cancer was not confirmed.

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
		exposed workers from factories A and B: around 32 (9.55). 1993		exposed workers (n=47) from factory A in 1993 using a half-life of 7.1 years. Low exposure: 7.6 Medium exposure: 608.2 High exposure: 1,841.8	Increased risks for prostate and urinary organ cancers: Prostate: HR=2.93, 95%CI 0.61-14.15 Bladder and kidney cancer: HR=4.2, 95%CI 0.99-17.89. In factory A increased risk of cancer mortality was found in exposed (accident) and occasionally exposed workers. In factory B increased risk for genital organ cancer. Calculated SMRs (Observed/Expected): Bladder cancer: SMR=3.72, O/E: 9/2.42 Kidney cancer SMR=3.69, O/E: 8/2.17 in exposed workers. Linked to other exposures than TCDD. Risk of bias tier: 2
Lin et al. (2012b). Environmental exposure to dioxin-like compounds and the mortality risk in the U.S. population. NHANES (USA)	Cross sectional study 4.63 (range: <1-7.67)	5,361 M, F Age at outcome assessment: 40–>65 1999	17 PCDD/Fs, 9 DL-PCBs (3 non-*ortho* and 6 mono-*ortho* PCBs) Blood (serum) Lipid adjusted	Median (IQR) pg WHO-TEQ /g fat 19.2 (13.3–27.9)	**Mortality risk** Deaths during the follow-up period: n=242, including: - 72 from cancer. Increased mortality risk associated with logarithmically expressed total TEQs for all-cause deaths (HR=1.19, 95% CI 1.02–1.39, p=0.02). Similar graded dose-response trends were found for cancer mortality which did not reach statistical

Reference Trial or Study name (Geography)	Study Type Duration	Participants in the study Sex Age at outcome assessment (years) Year of tissue sampling	Compounds Measurement of exposure	Levels of exposure	Parameters measured and Measures of effect Risk of bias tier
					significance. Risk of bias tier: 1

(a): Units confirmed by the authors of the study. n/a: not applicable.

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ANNEX A.9. RISK OF BIAS APPRAISAL OF EPIDEMIOLOGICAL STUDIES

A.9.1. Studies on male reproductive effects

Table 76. Risk of bias appraisal of studies on effects in male reproduction (combined score of two independent appraisals). Note: appraisal of individual studies focused only on risk of bias; additional quality aspects were considered when evaluating the overall confidence in the body of evidence (see Section 2.2.1.2 of the opinion).

SPERM QUALITY			
Dhooge et al. (2006)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQ-A** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	+	No individual PCB or PCDD/F congeners measured. The authors stated that inter-laboratory validation is needed for the CALUX-TEQs and that it should be considered as relative measures of exposure within the present population.
Detection	**KQ-C** - Can we be confident in the outcome assessment?	+	Probably blinded, but not stated in the paper.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Participants most probably not aware of their exposure levels but some of them are aware of their fertility status (proven fertile). Out of 2,487 possible male candidates the study ended up with about 100 participants. Not known whether this will results in any selection.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	Results in absence and presence of excluded subjects are presented.
Selective reporting	Were all measured outcomes reported?	++	
Toft et al. (2007)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQ-A** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	-	Lack of information of the applied methodology of the CALUX test
Detection	**KQ-C** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Men from Greenland, Warsaw and Kharkiv were fertile (partner of pregnant woman) but this was not reported for the Swedish fishermen. Participation rate is not clear.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Cok et al. (2008)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQ-A** - Did the study design	-	The authors have information about potential

	or analysis account for important confounding and modifying variables?		confounders but they do not present the distributions among the fertile and infertile groups and, in addition, due to the small numbers of participants, it was not possible to adjust for more than a few numbers of confounders simultaneously.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	++	
Detection	**KQ-C** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Hard to know whether there were differences between the fertile and infertile men regarding characteristics of interest such as socioeconomic status, smoking, etc, as only age was described (similar mean age).
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Mocarelli et al. (2008)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQ-A** - Did the study design or analysis account for important confounding and modifying variables?	+	Other DL-compounds not accounted for, but no reason to believe it is different for exposed and unexposed.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	+	Exposure information of control group not optimal.
Detection	**KQ-C** - Can we be confident in the outcome assessment?	++	Outcome measured in accordance with WHO recommendations and blind by the same two technicians.
Selection	Did selection of study participants result in appropriate comparison groups?	-	Participation rate differed between the exposed group (33%) and the control group (49%). The control group comprised healthy volunteer blood donors which might not represent the general population, and they had higher education than the Seveso participants. The question is whether the men were aware of their reproductive status, for instance if they had fathered a child and whether the fractions differed between the exposed and the control group? This is information is not presented in the paper. On the other hand, the men included in the study were in general relatively young.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	The reason for exclusion of 16 highly exposed men is not explained.
Selective reporting	Were all measured outcomes reported?	++	
Mocarelli et al. (2011)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	The study includes the most important confounders. However, the relatively low number of participants makes it unreasonable to include too many confounders in the statistical models simultaneously.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	The extrapolation makes the exposure characterization more uncertain.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Blind tests were performed by the same two technicians according to the WHO recommendations.
Selection	Did selection of study participants result in	++	Relatively small study with relative high fraction of non-participants among the exposed group as well as in the

	appropriate comparison groups?		control group (as always in male reproductive studies including semen sampling). However, hard to see that this would introduce a bias. The fractions of non-participants were similar in the two groups.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	All outcomes reported.
den Hond et al. (2015)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQ-A** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	-	Unclear description of methods, a large proportion of samples appear to be below the LOQ. Authors report geometric means for PCDD/Fs and PCBs of 0.19 pg BEQ/g and 0.069 pg BEQ/g. Assuming that it is fresh weight and starting with a sample amount of 5 ml with a fat content of 0.3 %, a transformation into fat weight would lead to levels that are below LOQ.
Detection	**KQ-C** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Mínguez-Alarcón et al. (2017)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	Confounding factors (including PCBs) included based on a priori evidence.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Analysed with valid methods at the CDC. Fasting blood collected.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	Double semen sample, analysed with standard methods by one technician who was blinded to the serum OC concentration.
Selection	Did selection of study participants result in appropriate comparison groups?	+	No information about the 'non-participants'
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	Adequately reported and also discussed how some exclusion might affect the results.
Selective reporting	Were all measured outcomes reported?	++	All measured reported. However, surprising that despite high correlations between exposure variables quite different results.
CHRYPTORCHISIM			
Virtanen et al. (2012)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQ-A** - Did the study design	+	Co-exposures not known

	or analysis account for important confounding and modifying variables?		
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	++	
Detection	**KQ-C** - Can we be confident in the outcome assessment?	+	Blinded
Selection	Did selection of study participants result in appropriate comparison groups?	-	Matched controls in Finland, gestational age (used in Finland as matching criterium) was different between cases and controls in Denmark.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Not reported in paper
Selective reporting	Were all measured outcomes reported?	+	All reported
Koskenniemi et al. (2015)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQ-A** - Did the study design or analysis account for important confounding and modifying variables?	+	The study lacks information about e.g. data on the body size of the children and the accuracy of some data might be low. In addition, information is lacking for a great proportion of the participants for specific variables such as smoking. However, there are no indications that this lacks systematically differ between the cases and the controls.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	+	The exposures are analysed with validated methods. However, the exposures are measured at different ages (not during the pregnancy/foetal period) and it was not possible to adjust for lipid content.
Detection	**KQ-C** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	++	Although this is a small study and selected groups due to recruitment of cases and controls at a paediatric surgery and thereby maybe loss of the possibility to generalize the results, this will not result in selection bias.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	Only TEQs and sums were analysed to avoid multiple comparisons which sounds reasonable
PUBERTAL DEVELOPMENT			
Den Hond et al. (2002)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQ-A** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	-	CALUX started with 2.5 ml serum. No LOQ given, but large proportion of the results appear to be at or below the normal LOQ for the method
Detection	**KQ-C** - Can we be confident in the outcome assessment?	+	Indirect that assessors were blinded to exposure. Four physicians performed staging, three of them participated in validation study, kappa in good agreement
Selection	Did selection of study participants result in appropriate comparison groups?	+	58.3 % participation rate. However, no obvious differences between participants and non-participants according to the information in the paper

Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Leijs et al. (2008)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQ-A** - Did the study design or analysis account for important confounding and modifying variables?	-	Confounding not assessed. Due to the small number of participants (n=12) it is not possible to take confounders into account in a proper way.
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	++	
Detection	**KQ-C** - Can we be confident in the outcome assessment?	+	Although some data were collected via a questionnaire which might question the quality of data there are no reason to believe that this will introduce a systematic error.
Selection	Did selection of study participants result in appropriate comparison groups?	+	The fraction of non-participants is relatively high and final number of included participants is low. However, the participants are most probably not aware or the exposure levels.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Not all reported (e.g. testicular volume not shown, just reported as not associated) and reasons why excluded from age at first ejaculation not given. Y axis fig 2 1nd 3 wrong
Selective reporting	Were all measured outcomes reported?	++	
Korrick et al. (2011)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Adjusted for total PCB, adjusted for lead. No obvious confounders are missing.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Samples collected in a standardized way (fasting) and analysed at CDC with well validated methods.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	Standardized physical examinations by a single endocrinologist without knowledge of the boys exposure.
Selection	Did selection of study participants result in appropriate comparison groups?	++	All boys in town invited, high participation rate among the eligible.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Humblet et al. (2011)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQ-A** - Did the study design or analysis account for important confounding and modifying variables?	++	Adjusted for covariates and confounders in different models
Detection	**KQ-B** - Can we be confident in the exposure characterisation?	+	The boy's exposure was measured by maternal blood sample taken at 9-10 years, as proxy for prenatal and lactational exposure. Factors that affect maternal level after giving birth (number of later biths, breastfeeding) was not taken into account. This would however rather

			under- than overestimate any effects.
Detection	**KQ-C** - Can we be confident in the outcome assessment?	++	Analysed with standard methods blinded to the serum OC concentration.
Selection	Did selection of study participants result in appropriate comparison groups?	++	Prospective population cohort, 90% of the eligible families agreed to participate.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Su et al. (2012)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Not described and not reasonable to adjust for in such a small study.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	No information on blinding
Selection	Did selection of study participants result in appropriate comparison groups?	-	Originally n=250. The basis for including only 56 (33 girls) is not explained.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	Insufficient information
Selective reporting	Were all measured outcomes reported?	+	All reported
Croes et al. (2014)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Information about potential confounders provided, age and BMI adjusted.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	DR-CALUX. Incomplete description in this paper. Reference to previous paper.
Detection	**KQC** - Can we be confident in the outcome assessment?	-	Insufficient information of assessment of pubertal development, in particular for males.
Selection	Did selection of study participants result in appropriate comparison groups?	-	Different recruitment protocol and participation rate between the three regions. The regions have different local sources to dioxins and DL-PCBs. Relatively high fraction of non-participants.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Incomplete description
Selective reporting	Were all measured outcomes reported?	+	Only statistically significant associations presented.
Burns et al. (2016)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	Confounding factors included based on a priori evidence and analysed in a proper way (co-exposures with pesticides not assessed).
Detection	**KQB** - Can we be confident	++	Analysed with valid methods at the CDC. Fasting blood

	in the exposure characterisation?		collected.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	Analysed with standard methods by one technician who was blinded to the serum OC concentration.
Selection	Did selection of study participants result in appropriate comparison groups?	+	No information about the "non-participants" (i.e. the initial recruitment to the study).
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	Adequately reported and also discussed how some exclusion might affect the results. Table 1 indicates that the numbers with missing data were relatively few
Selective reporting	Were all measured outcomes reported?	++	All measured reported.

A.9.2. Studies on female reproductive effects

Table 77. Risk of bias appraisal of studies on effects in female reproduction (combined score of two independent appraisals). Note: appraisal of individual studies focused only on risk of bias; additional quality aspects were considered when evaluating the overall confidence in the body of evidence (see Section 2.2.1.2 of the opinion).

ENDOMETRIOSIS			
Pauwels et al. (2001)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	Small study and not possible to take all confounders into account simultaneously.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	There are doubts on the validity of the "CALUX based TEQ levels", because of the high uncertainty associated with low sample weight for analysis (1-1.5 mL). The limit of detection is given as 32 fg TEQ/well. A conversion to pg TEQ/g fat is not reported. The distribution of TEQ-levels depicted in Figure 1 goes down to -20 pg TEQ/g fat.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	++	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Eskenazi et al. (2002a)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	81% participation (n=751). 54 virgins excluded, of cultural reasons. Younger women underrepresented, not sufficiently controlled by age.
Detection	**KQB** - Can we be	+	Co-exposure to other PCDD/Fs and DL-PCBs not

	confident in the exposure characterisation?		accounted for.
Detection	**KQC** - Can we be confident in the outcome assessment?	-	Only 19 cases, by biopsy or ultrasound (validated method). May have missed some cases in the Group of women with uncertain diagnose, may have underestimated the risk.
Selection	Did selection of study participants result in appropriate comparison groups?	+	The recruitment of the cohort is well-defined and clearly described.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	93 women excluded because they refused ultrasound, they may have endometriosis without symphtoms. Laparoscopy performed only on subset of women.
Selective reporting	Were all measured outcomes reported?	++	Both verified and uncertain cases reported
Fierens et al. (2003)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Co-exposure not addressed (may differ for the exposure groups recruited). Not possible to adjust for confounders with so few cases.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	No information about LOQ
Detection	**KQC** - Can we be confident in the outcome assessment?	-	Based on answers from a questionnaire and controls may have endometriosis as well.
Selection	Did selection of study participants result in appropriate comparison groups?	-	Controls may have endometriosis (undiagnosed). Recruited on volunteer basis via a mail. Hard to know who participated.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
de Felip et al. (2004)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Age range between 18 and 40 years is too wide to control for factors related to exposure. Due to the low number of participants and the fact that the samples were pooled it was not possible to adjust for confounding.
Detection	**KQB** - Can we be confident in the exposure characterisation?	- -	Pooled samples, n=6, which means that no individual exposure measures were obtained.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	The outcome was defined according to strict criteria and validated.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Were a priory suspect of different gynaecological conditions. Only women with comparably dietary habits enrolled, no information about those excluded. In addition, to have enough blood individual specimen were pooled into different groups.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	None excluded.
Selective	Were all measured	++	

reporting	outcomes reported?		
Heilier et al. (2005)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Adjusted only for age and BMI, other confounders not significantly associated (smoking, number of children, duration of breast feeding)
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Analysed with validated methods.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Histology provided for all cases. However, Controls may have endometriosis.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Positive that Controls are not from fertility clinic. However, Controls may have endometriosis.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Tsukino et al. (2005)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	May have been affected by high LOQ for some congeners (treated in analyses as LOQ/2) but the LOQ is not given.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	++	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Niskar et al. (2009)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Different sets of covariates adjusted for in different models.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Low volume of blood analyzed (7-15 mL) and low sensitivity. TCDD detected in 7 of 124 samples. (LR) TCDD only detected in 7 out of 124 samples (<6%).
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Half of the controls were not confirmed non-endometriosis. However, separate analysis including only included confirmed controls gave similar results but the power was then even lower.

Selection	Did selection of study participants result in appropriate comparison groups?	+	Participants seeking help for infertility, half of the controls (33) were not confirmed as non-endometriosis (had infertile partner (N=27) or ovulation problems (n=7)). However, including only the 30 confirmed non-endometriosis controls did not affect the outcome.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	All reported or explained
Selective reporting	Were all measured outcomes reported?	++	All reported
Porpora et al. (2009)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	Laparoscopy performed in all participants.
Selection	Did selection of study participants result in appropriate comparison groups?	++	Small differences in age and BMI between cases and Controls adjusted for in analysis.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	None removed.
Selective reporting	Were all measured outcomes reported?	++	
Simsa et al. (2010)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Included only age as a confounder in the analysis due to lack of information about other potentially important confounders.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	CALUX based on only 5 ml plasma. Much lower CALUX TEQ than expected based on pilot study.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	All cases and controls with laparoscopy and histology.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Patients recruited because of infertility and investigation by laparoscopy. Other criteria or response rates not described. Period of sampling not mentioned. No information about non-participants.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	All reported
Selective reporting	Were all measured outcomes reported?	++	All reported
Cai et al. (2011)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis	-	Too few women included in the study for having a chance to adjust for potential confounders in a

	account for important confounding and modifying variables?		reasonable way. Although not statistically significant, the controls were about three years older and have two units higher BMI compared to the controls.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Ascites not commonly analysed, low agreement with blood for PCDD.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Performed in a systematic and well-defined way.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Insufficient information.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Martínez-Zamora et al. (2015)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Low numbers and lack of information on socioeconomic and lifestyle factors.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Adipose tissue, mostly above LOQ.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	Strict criteria for cases and controls.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Next laparscopy patient selected. Similar age in cases and controls.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	Few excluded, well explained
Selective reporting	Were all measured outcomes reported?	++	
Ploteau et al. (2017)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or	++	

	exclusion from analysis?		
Selective reporting	Were all measured outcomes reported?	++	
PUBERTAL DEVELOPMENT			
Warner et al. (2004)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Several confounders considered.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Uncertainty with back-calculation for 20 participants.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Self-reported, but most likely remembered by women.
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Well reported.
Selective reporting	Were all measured outcomes reported?	++	All reported.
Den Hond et al. (2002)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	CALUX started with 2.5 ml serum. No LOQ given, but a large proportion of the results appear to be at or below the normal LOQ for the method.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Indirect that the assessors were blinded to exposure (although probably not regarding geographical areas). Four physicians performed staging; three of them participated in validation study kappa in good agreement.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Participants and non-participants had similar age and sex distribution, parental social class, regional distribution and distance from main pollution source when applicable.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Su et al. (2012)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Not described and not reasonable to adjust for in such a small study.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	

Detection	**KQC** - Can we be confident in the outcome assessment?	+	No information on blinding.
Selection	Did selection of study participants result in appropriate comparison groups?	-	Originally n=250. The basis for including only 56 (33 girls) is not explained. Limited information about participants/non-participants in paper.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	Insufficient information.
Selective reporting	Were all measured outcomes reported?	+	All reported.
Croes et al. (2014)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Information about potential confounders..
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	DR-CALUX. Incomplete description in this paper, Reference to previous paper.
Detection	**KQC** - Can we be confident in the outcome assessment?	-	Insufficient information of assessment of pubertal development.
Selection	Did selection of study participants result in appropriate comparison groups?	-	Different recruitment protocol and participation rate between the three regions. The regions have different local sources to dioxins and DL-PCBs. Relatively high fraction of non-participants and limited information about those.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Incomplete description
Selective reporting	Were all measured outcomes reported?	+	Only statistically significant associations are presented
OTHER EFFECTS IN FEMALE REPRODUCTION			
den Hond et al. (2002)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	CALUX started with 2.5 ml serum. No LOQ given, but large proportion of the results appear to be at or below the normal LOQ for the method..
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Indirect that the assessors were blinded to exposure (although probably not regarding geographical areas). Four physicians performed staging; three of them participated in validation study kappa in good agreement.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Participants and non-participants had similar age and sex distribution, parental social class, regional distribution and distance from main pollution source when applicable.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective	Were all measured	+	

reporting	outcomes reported?		
Eskenazi et al. (2002b)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	TCDD back-calculated to 1976 Levels for 26 out of 301 women. Co-exposure to other dioxins and DL-PCBs not accounted for.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Self-reported menstrual cycle characteristics, but no reason the report should be biased in any direction. How valid are the information about the past year?
Selection	Did selection of study participants result in appropriate comparison groups?	+	Due to different exclusions only 310 out of 981 women were included in the study.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	All reported
Chao et al. (2007)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Placenta samples analysed
Detection	**KQC** - Can we be confident in the outcome assessment?	-	Self-reported and possible recall bias. No knowledge about the dioxin levels.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Insufficient information and only about 27% of the original women were included (randomly selected).
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	Insufficient information.
Selective reporting	Were all measured outcomes reported?	+	Menstrual cycle changes not mentioned as hypothesis/purpose. Some outcomes just reported as no associations and data were not shown.
Warner et al. (2007)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	For 27 women (out of 363), exposure was back-calculated to levels in 1976. What about co-exposures? And what about high back-ground exposure?
Detection	**KQC** - Can we be confident in the outcome assessment?	+	

Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Eskenazi et al. (2010)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Both exposure soon after explosion and calculated to conception gave similar associations. However, accuracy of calculated exposure is unknown. Background exposure comes in addition.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Retrospectively collected. Sometimes many years after. However, "women can fairly accurately report their time to conception" (Joffe)
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Eskenazi et al. (2007)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Co-exposure to other DL-compounds could not be addressed
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Back-calculation of TCDD Level in 1976 performed for 67 of the women out of 956.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Few women that were pre-menarcheal in 1976 have reached an age where leiomyoma can be expected, this may underestimate the risk if these women were in a susceptible age. Self-reported data completed with medical records.
Selection	Did selection of study participants result in appropriate comparison groups?	+	High participation rate in eligible population.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Ultrasound analysed for a subset.
Selective reporting	Were all measured outcomes reported?	++	
Eskenazi et al. (2005)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study	+	Co-exposure from other DL-compounds not fully

	design or analysis account for important confounding and modifying variables?		known.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Serum levels were-back-calculated to 1976 Levels for 41 women. In models re-run excluding women with post-1977 blood samples, associations were strengthened.
Detection	**KQC** - Can we be confident in the outcome assessment?	-	Retrospective recall of age of natural menopause has been reported to have moderately high reliability.
Selection	Did selection of study participants result in appropriate comparison groups?	+	High participation rate, all from Seveso zone A or B.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	

A.9.3. Studies on birth outcomes

Table 78. Risk of bias appraisal of studies on birth outcomes (studies on sex ratio: combined score of two independent appraisals. Studies on birth weight and other birth outcomes: scores corresponding to one appraisal). Note: appraisal of individual studies focused only on risk of bias; additional quality aspects were considered when evaluating the overall confidence in the body of evidence (see Section 2.2.1.2 of the opinion).

SEX RATIO			
Mocarelli et al. (2000)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	There are no strong confounders for sex ratio which could have biased the results in the present study.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Imputation of some missing data, but repeated calculations with only analysed data gave similar results.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	++	Subjects were from the same area and there are no reasons to believe that there would be any selection.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	All recorded by municipalities' censuses.
Selective reporting	Were all measured outcomes reported?	++	
Schnorr et al. (2001)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Confounders assessed
Detection	**KQB** - Can we be confident in the	-	Back calculation to exposure at

	exposure characterisation?		conception does not take liver sequestration into account (I believe). Would give under-estimation of exposure and/or exposure misclassification. Long time span, background changing during the years.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	Child sex easy to remember
Selection	Did selection of study participants result in appropriate comparison groups?	-	Relatively high differences in participants rates between the exposed group and the referents
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Ryan et al. (2002)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Co-exposure in workers different from general population but this is not expected to affect sex ratio.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Long time between exposure and sampling. Level at conception not known. Different sampling time in different cohorts.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	++	Although the study size is relatively small (especially when separate analyses were performed, e.g. for "mother only" in the 2,4,5-T-cohort) there is no obvious risk for selection bias. The comparison group is based on five individual years between the period 1959-1996, i.e. a quite long period, but the sex ratio is very much in line with expected.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	The data is reported in a proper way.
Selective reporting	Were all measured outcomes reported?	++	
't Mannetje et al. (2017)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Levels measured at least 24 years after exposure, high uncertainty associated with back-calculation.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
BIRTH WEIGHT AND OTHER BIRTH OUTCOMES			

Tsukimori et al. (2013)		Risk of bias tier: 2	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Small study, not possible to take all potential into account
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Estimated via back-calculations from samples collected up to 40 years after the pregnancy.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Out of 737 officially registered Yusho patients the study ended up with 64 mothers
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Tsukimori et al. (2012)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Estimated up to 40 years after the pregnancy
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	-	The study has about 50% non-participants.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Konishi et al. (2009)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	There was no association with smoking, which make the quality of the confounding variables questionable.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Little/no information about the non-participants.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	+	
Halldorsson et al. (2009)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	

Detection	**KQB** - Can we be confident in the exposure characterisation?	-	As stated by the authors the CALUX assay can potentially be distorted by contamination from PAHs.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Papadopoulou et al. (2013)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Based on FFQ and dioxin levels in food.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Less than 40 % participated in MoBA.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Papadopoulou et al. (2014)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	CALUX bioassay
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Limited information about non-participants.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Lawson et al. (2004)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	TCDD measured several years after the pregnancies.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Self-reported
Selection	Did selection of study participants result in appropriate comparison groups?	-	Could not calculate a true participation rate for the male referents which raise the question about selection bias.

Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Wohlfart-Veje et al. (2014)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Limited information regarding other pollutants.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Limited information about non-participants.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Vartiainen et al. (1998)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Only about half of those who initially indicated that would participate did participate.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Tajimi et al. (2005)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No associations between smoking and birth weight, which makes the quality of the confounders doubtful.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	-	No information about non-participants or participation rate.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	No information about it.
Selective reporting	Were all measured outcomes reported?	-	The results were presented in two steps and all measured were only presented in step 1.
Govarts et al. (2016)		**Risk of bias tier: 2**	

Bias domain	Question	Score	Judgement
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Based on CALUX
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Tsukimori et al. (2008)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Information collected in different ways (face-to-face interviews, mailed questionnaire, telephone interviews.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Based on back-calculations
Detection	**KQC** - Can we be confident in the outcome assessment?	-	Information collected in different ways (face-to-face interviews, mailed questionnaire, telephone interviews…)
Selection	Did selection of study participants result in appropriate comparison groups?	-	Due to different reasons, relatively many non-participants.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Eskenazi et al. (2003)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Wesselink et al. (2014)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	
Detection	**KQB** - Can we be confident in the	+	The exposure at pregnancy had to rely

	exposure characterisation?		on models
Detection	**KQC** - Can we be confident in the outcome assessment?	+	The outcomes were self-reported and sometimes many years after pregnancy
Selection	Did selection of study participants result in appropriate comparison groups?	++	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Michalek et al. (1998)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Most often based samples collected many years after conception.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Schnorr et al. (2001)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Confounders assessed.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Estimated based in a kinetic model
Detection	**KQC** - Can we be confident in the outcome assessment?	-	Long time since pregnancy and based only on recognized clinical pregnancies
Selection	Did selection of study participants result in appropriate comparison groups?	-	Relatively high differences in participants rates between the exposed group and the referents
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Vafeiadi et al. (2013)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	CALUX bioassay
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or	+	

	exclusion from analysis?		
Selective reporting	Were all measured outcomes reported?	++	
Vafeiadi et al. (2014)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	CALUX bioassay
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	

A.9.4. Studies on thyroid disease and thyroid hormones

Table 79. Risk of bias appraisal of studies on effects in thyroid disease and thyroid hormones (scores corresponding to one appraisal, except for Baccarelli et al. (2008) where the score is the combined scores of two independent appraisals). Note: appraisal of individual studies focused only on risk of bias; additional quality aspects were considered when evaluating the overall confidence in the body of evidence (see Section 2.2.1.2 of the opinion).

STUDIES IN ADULTS			
Calvert et al. (1999)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Adjusted for sex age, race and medication but not other diseases, which is OK.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Individual TCDD data, current and back-extrapolated.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Referents from the area but not from the company, so potential "healthy workers selection". Poor participation rate (28%) in referents.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Johnson et al. (2001)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No confounder adjustment
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Individual TCDD determinations, but 9/32 < DL and extrapolated historical levels somewhat uncertain.

Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	++	Random sample. Participation rate not described.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Pavuk et al. (2003)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Several but not all relevant potential confounders adjusted for. Smoking was assessed for a subgroup (another publication) indicating minor differences.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Individual TCDD data, although only on one occasion about 15 years after exposure. Back-extrapolation.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Participation based on register of staff. All could be followed up. Internal reference group similar to the exposed group.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Foster et al. (2005)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	Impact of potential confounders checked and found not to be present.
Detection	**KQB** - Can we be confident in the exposure characterisation?	- -	Serious doubts about the CALUX bioassay employed. Very low exposure; none of the women had a CALUX-TEQ > 1 pg/g.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	++	Selection clearly described, and participation rate OK in those fulfilling inclusion criteria.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Bloom et al. (2006)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Adjustment for PCB, but no difference if unadjusted. No adjustment for other confounders. Age may be a confounder. Non-consumers (N=15) may be different in other aspects.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	A number of samples <LOD.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	T4 and T3 unreliable due to long term storage.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Selection of anglers with high PCB is OK. Participation rate not described.

Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	One outlier excluded.
Selective reporting	Were all measured outcomes reported?	++	
Turyk et al. (2006)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	BMI, smoking age and medication uses seems appropriate.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Only limited number of characteristics were presented.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	The small size if of major concern as and 1 out of 10 outcomes is significant (total TEQ vs TSH with p=0.04) a chance finding cannot be excluded (has to be interpreted in the context of findings from other studies, which may be supportive). Would not survive adjustment for multiple comparisons
Selective reporting	Were all measured outcomes reported?	++	
Chevrier et al. (2014)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Good confounder control, and rational selection of which to include.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Individual TCDD data.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	++	Participation based on residence. Relatively high participation rate and analyses only performed within the group.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	Few exclusions, and sensitivity analyses performed.
Selective reporting	Were all measured outcomes reported?	++	
STUDIES IN NEWBORNS OR CHILDREN			
Nagayama et al. (1998)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No confounder adjustment. Total intake should be associated with age and weight of children, and grade of breast-feeding. No information on associations with dioxin levels.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Individual intake estimates.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Convenience sample. Participation rate not described.
Attrition/	Were outcome data completely	++	

exclusion	reported without attrition or exclusion from analysis?		
Selective reporting	Were all measured outcomes reported?	++	
Matsuura et al. (2001)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Analyses seem to be unadjusted for age and other potential confounders.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Individual breast milk TEQs.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Selection and participation rate not described, but it was a nationwide study.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Nagayama et al. (2001)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No adjustment for age or sex (which are associated with thyroid hormones), but TCDD TEQs were not associated with sex, however possibly with age.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Individual TCDD data.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	- -	No relevant comparison group.16 patients out of 83 patients examined 2 years earlier participated "voluntarily".
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Wang et al. (2005)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Most analyses seem to be unadjusted for age and other potential confounders.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Individual TCDD data.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Participation rate not described.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Marvoet et al. (2007)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or	++	Several potential confounders were

	analysis account for important confounding and modifying variables?		adjusted for.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Individual breast milk and blood TEQs.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Convenience sample. Participation rate not described.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Nagayama et al. (2007a)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Only age and parity, adjustment for maternal BMI, and lipids in milk would have been appropriate. If there is a heritable component to cretinism that could be a source of confounding.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Presenting lipid adjusted results would have been informative. Blood collected prior to or during pregnancy would have been more optimal in terms of excluding reverse causation. However breast milk samples have been shown to be highly correlated with maternal samples in pregnancy.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	++	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Wilhelm et al. (2008)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	Good description of, and adjustment for, potential confounders.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Individual breast milk and blood TEQs.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Convenience sample. Participation rate not described.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Baccarelli et al. (2008)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important	+	Analyses adjusted for most confounders. Data not available on iodine, but such

	confounding and modifying variables?		confounding unlikely. Information about timing of blood sample collection relative to the outcome assessment is missing.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Individual data only for subgroup, so possible non-differential misclassification. They back their group level findings with dioxin measures in blood but a drawback is 1) small sample size and 2) samples are drawn at different time point in pregnancy. However the results from the two studies (group level exposure and measured exposure) more or less converge.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Timing is not available for those with high TCDD and TSH.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Participation based on residence. Good tracing of children. The groups are similar in relation to the few background variables compared. Lack of information on some lifestyle characteristics.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	There is little information available to evaluate attrition bias here.
Selective reporting	Were all measured outcomes reported?	+	
Han et al. (2011)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	- -	Probably no adjustment for lifestyle factors. Other chemical exposures.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Some pooled samples. Unclear numbers.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Recruitment and participation rate not described.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Not clearly described.
Selective reporting	Were all measured outcomes reported?	+	Difficult to judge. Insufficient information.
Leijs et al. (2012)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No confounder adjustment
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Individual intake estimates.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Convenience sample. Participation rate not described
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	

Croes et al. (2014)		Risk of bias tier: 2	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Adjustment for some potential confounders on individual level but not for area.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Random approach. Low participation rate, but this is not likely to have introduced selection bias.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Xu et al. (2014)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	No confounder adjustment but all children were 8 years old and sex ratio was the same in the two groups.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Selection procedure not described.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Su et al. (2015)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No adjustment were made when comparing mean levels for each outcome across categories of increasing dioxin exposure
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Appears to be the case difficult to evaluate as no comparison is made to other children whose maternal dioxin levels were not quantified
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	

A.9.5. Studies on diabetes and obesity

Table 80. Risk of bias appraisal of studies on effects in type 2 diabetes and obesity (scores corresponding to one appraisal). Note: appraisal of individual studies focused only on risk of bias; additional quality aspects were considered when evaluating the overall confidence in the body of evidence (see Section 2.2.1.2 of the opinion).

Michalek et al. (1999a)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Measured many years after the War ended, assuming a constant half-life.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Steenland et al. (1999)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Lack of information on, e.g. smoking.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Based on job-exposure matrix.
Detection	**KQC** - Can we be confident in the outcome assessment?	-	Death certificate data may be inadequate to study diabetes.
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Cranmer et al. (2000)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Although information is obtained about potential confounders it is not possible to adjust when there are so few subjects in the highest decile.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	

Longnecker and Michalek (2000)		Risk of bias tier: 1	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	++	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Steenland et al. (2001a)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Same laboratory and same method in the studies.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Different methods in the two studies.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Good participation in Ranch Hand, lower in NIOSH. Subsequent telephone interviews with non-participants did not suggest that systematic selection bias were operating.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Johnson et al. (2001)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Small study, not possible to take potential confounders into account
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Fierens et al. (2003)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Too few participants/cases to make reasonable adjustments for potential confounders
Detection	**KQB** - Can we be confident in the	+	

	exposure characterisation?		
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Recruited on a volunteer basis.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Kern et al. (2004)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	The only confounding variables that were taken into account were the matching variables.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Baccarelli et al. (2005)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	The study did only adjust for age and sex (and zone).
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Michalek and Pavuk (2008)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	The exposure was based on a combination of different sources and assumptions, which makes it uncertain.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/	Were outcome data completely	+	

exclusion	reported without attrition or exclusion from analysis?		
Selective reporting	Were all measured outcomes reported?	+	
Chen et al. (2008)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Other exposures (pesticides)?. Small study hard to adjust for confounders.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	80% of all ongoing pregnancies.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Uemura et al. (2008)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	The recruitment was performed via an open call for participants which makes it unclear who actually participate.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Uemura et al. (2009)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Doubtful whether the study focus on the sensitive exposure window.
Detection	**KQC** - Can we be confident in the outcome assessment?	-	BMI, one of criteria for the outcomes, may not rigorously reflect central obesity. In addition, the study lacks data on fasting serum glucose.
Selection	Did selection of study participants result in appropriate comparison groups?	-	Open call
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Pelclova et al. (2009)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**

Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Only 11 subjects which means that it is more or less impossible to take confounding into account
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Only 11 out of 80 were examined in this follow-up study
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	
Selective reporting	Were all measured outcomes reported?	++	
Burns et al. (2011)		Risk of bias tier: 1	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Lack of parental height and weight
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Doubtful whether the study focus on the sensitive exposure window?
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	++	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Yi et al. (2013)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Exposure measured about 40 years after the war.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Limited/no information about participation rate.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Waner et al. (2013)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	

Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Delvaux et al. (2014)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	No postnatal exposure information.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Out of 1173 invitation letters only 281 completed the questionnaires and 114 were included in the present study.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Iszatt et al. (2016)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Different matrixes and different methods used between the populations
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Limited information about the selection of participants.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Leijs et al. (2017)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Small study, which make it not reasonable to consider confounders in a propitiate way
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	No information.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	

A.9.6. Studies on cardiovascular effects

Table 81. Risk of bias appraisal of studies on cardiovascular effects (combined score of two independent appraisals). Note: appraisal of individual studies focused only on risk of bias; additional quality aspects were considered when evaluating the overall confidence in the body of evidence (see Section 2.2.1.2 of the opinion).

Calvert et al. (1998)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Good data on many potential confounders, but not SES.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Individual TCDD data, current and back-extrapolated.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	Might be some 'recall bias' regarding history, but clinical exams were more important for cardiovascular outcomes, and they were blinded.
Selection	Did selection of study participants result in appropriate comparison groups?	-	Referents from the area but not from the company, so potential "healthy workers selection".
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Differential loss of follow-up due to increased mortality in exposed individuals.
Selective reporting	Were all measured outcomes reported?	++	
Pesatori et al. (1998)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	- -	Potential confounders were not assessed on individual level.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Considerable non-differential misclassification, since no individual data were available
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Participation based on residence. 99% could be followed up. It is however likely that populations were not comparable with the reference population.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Steenland et al. (1999)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	- -	Lack of data on potential confounders. Increase in lung cancer in those with highest exposure.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	No individual TCDD data, only estimates by JEM. Another paper supports the ranking and gives serum TCDD levels for part of the individuals.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison	+	Participation based on company registers. Unclear if they were complete. Internal

	groups?		reference group is an advantage.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Differential loss of follow-up due to increased cancer mortality in exposed individuals.
Selective reporting	Were all measured outcomes reported?	++	
Bertazzi et al. (2001)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	- -	Potential confounders were not assessed on individual level.
Detection	**KQB** - Can we be confident in the exposure characterisation?	- -	Considerable non-differential misclassification, since no individual data were available.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Participation based on residence. 99% could be followed up. It is however likely that populations were not comparable with the reference population
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Ketchum and Michalek (2005)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Smoking and other confounders were not assessed on individual level but were available for a subgroup indicating minor differences.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Considerable non-differential misclassification, since individual data were available only in part of the subjects.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	”Recall bias” is possible. Health conditions by interview only.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Differential loss of follow-up due to increased mortality in exposed individuals.
Selective reporting	Were all measured outcomes reported?	++	
Kang et al. (2006)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Smoking and some other confounders could be adjusted for.
Detection	**KQB** - Can we be confident in the exposure characterisation?	- -	Considerable non-differential misclassification, since individual data were available only for a subgroup.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	‘Recall bias’ is possible. Health conditions by interview only.
Selection	Did selection of study participants result in appropriate comparison groups?	-	Participation based on register of military staff. Only 70% could be assessed. An internal reference group similar to the exposed group.
Attrition/ exclusion	Were outcome data completely reported without attrition or	+	Differential loss of follow-up due to increased mortality in exposed individuals.

	exclusion from analysis?		
Selective reporting	Were all measured outcomes reported?	++	
Pelclova et al. (2007)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	The exposed group was not healthy, but the control group was.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Individual TCDD data
Detection	**KQC** - Can we be confident in the outcome assessment?	+	This method is highly dependent on examiner. Hopefully the same person examined exposed and controls.
Selection	Did selection of study participants result in appropriate comparison groups?	- -	Selection of exposed group (N=15) not described. Control group (N=14) not comparable.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Pelclova et al. (2009)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Not adjusted, too low N
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Individual TCDD data.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	- -	Selection of cases (n=11) not described. No control group.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	
Selective reporting	Were all measured outcomes reported?	++	
Boers et al. (2010)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Lack of data on potential confounders, but smoking prevalence was considered similar to referents
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Individual TCDD data only for a subgroup, but the difference between "exposed" and non-exposed is valid. However non-differential misclassification is likely to be large in the ER analyses.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Participation based on complete company registers. External reference group with likely some "healthy worker selection"
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Differential loss of follow-up due to increased mortality in cancer in exposed individuals.
Selective reporting	Were all measured outcomes reported?	++	
Manuwald et al. (2012)		**Risk of bias tier: 2**	

Bias domain	Question	Score	Judgement
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Lack of data on potential confounders, but smoking prevalence was considered similar to referents.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Individual TCDD data only for a subgroup, so likely non-differential misclassification in the ER analyses.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	Participation based on company registers. External reference group with likely some "healthy worker selection".
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Differential loss of follow-up due to increased mortality in cancer in exposed individuals.
Selective reporting	Were all measured outcomes reported?	++	
Lin et al. (2012b)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Age, gender, body mass index, race/ethnicity, cigarette smoking, and alcohol consumption were accounted for. Age was by far the strongest predictor. Given the large age interval (40 to 65+) of the study, not properly reported, residual confounding by age might be a potential problem
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Information on mortality was missing for about 11%.
Selection	Did selection of study participants result in appropriate comparison groups?	-	The large age interval at baseline would have resulted in overrepresentation of older adults among those who are more highly exposed. Most of the mortality are likely to have occurred in this group which makes residual confounding somewhat likely.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Cypel et al. (2016)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Considerable non-differential misclassification. Individual TCDD in only 20%, and only once. Exposure characterisation is crude (previous service status).
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Participation based on register of military staff. Only "survivors" could be included.
Attrition/ exclusion	Were outcome data completely reported without attrition or	+	Only "survivors" included. Differential loss of follow-up.

	exclusion from analysis?		
Selective reporting	Were all measured outcomes reported?	++	

A.9.7. Studies on hepatic disorders and digestive effects

Table 82. Risk of bias appraisal of studies on hepatic disorders and digestive effects (scores corresponding to one appraisal). Note: appraisal of individual studies focused only on risk of bias; additional quality aspects were considered when evaluating the overall confidence in the body of evidence (see Section 2.2.1.2 of the opinion).

Neuberger et al. (1999)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Partial consideration of confounders including age, smoking, alcohol, same physician assessment. Assessments blinded for exposure status.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Exposure to TCDD occupationally and quantitated by certified methods and laboratory close in time to assessment.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Some data from questionnaires
Selection	Did selection of study participants result in appropriate comparison groups?	+	Control group was matched occupational group but not to TCDD. Overall numbers relatively small.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Significant proportion of those originally mailed and known to have been exposed, did not respond or under other physicians. However, not associated statistically with previously known medical history or other parameters. 90% of agreed participants donated blood for clinical chemistry and TCDD measurement.
Selective reporting	Were all measured outcomes reported?	++	
Michalek et al. (2001a)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	Many known confounders of adjusted for.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Although original analyses were acceptable this involved subsequent extrapolations for others. Some exposures very close to detection limit.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Medical examinations and additional plasma chemistry determined but limitation of interpretation without more detailed studies.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Apparently
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	No
Baccarelli et al. (2005)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**

Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Adjusted for age sex and residence.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	TCDD was quantitated by CDC with acceptable technology and accuracy.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Clinical data was acceptable but limited. More in depth investigations might have been invasive but more informative.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Comparison group sizes were acceptable as an indication but larger group sizes would have greatly increased confidence.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Attrition of some data was noted.
Selective reporting	Were all measured outcomes reported?	+	Apparently so given the limited objectives
Ketchum and Michalek (2005)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Not as full as other related studies for this cohort and endpoint
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Although original analyses were acceptable this involved subsequent extrapolations for othes. Some exposures very close to detection limit.
Detection	**KQC** - Can we be confident in the outcome assessment?	-	Minimum data
Selection	Did selection of study participants result in appropriate comparison groups?	+	Within limitations of exposure data
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Boers et al. (2010)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Minimal confounder data
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Probably valid but limited data on some as back extrapolated.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Probably good but limited based on death certificates.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Satisfactory with limited data.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Some attrition. Deaths considered after lack of significant long term exposure excluded.
Selective reporting	Were all measured outcomes reported?	++	

A.9.8. Studies on effects in the immune system

Table 83. Risk of bias appraisal of studies on effects on the immune system (scores corresponding to one appraisal). Note: appraisal of individual studies focused only on risk of bias; additional quality aspects were considered when evaluating the overall confidence in the body of evidence (see Section 2.2.1.2 of the opinion).

STUDIES IN ADULTS			
Jung et al. (1998)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	The subjects in the study are factory workers. Concomitant exposures to other chemicals was not monitored
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Exposure in the selected subject group was available from tests done on blood by CDC-Atlanta. No details on the methods were given, but the stature of CDC and ERGO Hamburg ensures adequacy. For some individuals exposure data at the time of immunologic testing was not available, but these were extrapolated based on earlier measurements and half-life times.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	The outcomes are performed in clinical settings and seem adequate therefore. The chromate sensitivity test on proliferating lymphocytes, the only one showing an immunotoxic effect, is not a well-accepted widely used assay.
Selection	Did selection of study participants result in appropriate comparison groups?	+	There is information that the cases and controls were similar in a number of aspects, i.e. age, social status, smoking.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	The subjects enrolled in the ultimate study were selected from a much bigger group of people, in principle based on volunteering to participate. Of the p[eople eventually enrolled, no people were missing in the analysis.
Selective reporting	Were all measured outcomes reported?	++	All measures foreseen seem to be carried out
Halperin et al. (1998)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Age, smoking, alcohol use were accounted for. Other occupational exposures might have occurred.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	The method for measuring exposure was described in an earlier paper 9Shop et al., 1989). Measures in controls were not executed in all subjects, but just random, and all non-measured subjects were deemed to be within the range of the measured ones.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	Immunologic methods were standard.
Selection	Did selection of study participants result in appropriate comparison groups?	++	Workers of 2 plants were recruited. Exposure over a long time, but cross sectional analysis carried out in 2 years, 1987 and 1988. Matched controls were selected from the same neighborhood as where subjects lived.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Selection results were explained, and there are few subjects missing or excluded.
Selective	Were all measured outcomes	+	There is no indication that outcomes have not

reporting	reported?		been reported.
Michalek et al. (1999b)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	The authors indicate correction for confounders. The paper does not indicate which, and these may be also in Wolfe et al. (1995). However, the authors themselves indicate that there may be confounders that are unknown.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	There is no indication of how dioxin was measured (but there was a reference to Roegner et al., 1991). The measurements on dioxin were made as long as 30 years after exposure in Vietnam, and the time since exposure varied 2- to 3-TCDD half-lives. The measures in 1997 and 1992 were extrapolated to the time in service, to put the subjects into four categories.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Immune tests were well described, although the source of antibodies for immunoglobulin measurement, and autoantibody tests were not given.
Selection	Did selection of study participants result in appropriate comparison groups?	++	Wolfe et al. (1990) provides the details of the subjects.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	The study indicates the low number of subjects removed from the study and the reasons why.
Selective reporting	Were all measured outcomes reported?	++	Whereas the a priori protocol was not provided, it appears that all tests foreseen were done
Kitamura et al. (2000)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	Weight, life style, health status were investigated. Corrections for age, smoking, alcohol were done and had an impact on the outcome.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Exposure assessment was done according standard methods and in the same time frame.
Detection	**KQC** - Can we be confident in the outcome assessment?	-	The outcome measures done seem straightforward, but little information is provided on how these measures are done.
Selection	Did selection of study participants result in appropriate comparison groups?	- -	There was indication of the subjects living in different areas. Workplaces were quite different. Response rates were not given.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Of 96 individuals, 88 were tested. Of 8 the blood clothed and no analyses could be done.
Selective reporting	Were all measured outcomes reported?	+	From the text it seems that all individuals except the 8 mentioned earlier have been tested and data were presented.
Nagayama et al. (2001)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	There is no information on possible confounders.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Blood was collected from Sept 94-Nov 95, and analysed for PCDD/Fs and DL-PCBs, using GC-MS, TEQs were calculated.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	There seems little information on how subpopulations of lymphocytes were determined other than by indirect fluorescence. Antibody

			titres were measured by latex agglutination immunoassay using polyclonal antibodies.
Selection	Did selection of study participants result in appropriate comparison groups?	-	Except for the fact that the subjects were Yusho patients, there is no other information other than the age range.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	83 patients were recruited from which blood was taken to measure exposure. 16 were selected for measurement of thyroid hormones and lymphocyte subpopulations. Immunoglobulins and antibodies were measured in another 69 patients. The rationale for the selection was not indicated.
Selective reporting	Were all measured outcomes reported?	++	It seems that all measures planned were carried out.
Baccarelli et al. (2002) Baccarelli et al. (2004)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	The subjects in the cohorts were sex, age, and cigarette smoking matched. Other confounders may be there but were not reported.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	TCDD exposure in plasma was assessed by CDC according adequate methodology.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Immune parameters were measured according accepted methods.
Selection	Did selection of study participants result in appropriate comparison groups?	-	Two small studies, likely using same subjects and therefore partly overlapping recruited at random from the Seveso Cohort. Although randomly selected no demographic characteristics were given.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	The studies are possibly over overlapping but this is not clearly stated in the publications. In addition, the numbers of subjects are not fully identical. Hence it is not clear if the outcomes were all reported.
Selective reporting	Were all measured outcomes reported?	-	In as far as it can be seen from the reports what was intended to measure, all was performed.
Baccarelli et al. (2005)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Correction for an age was done, information on other confounders was not presented.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	TCDD exposure in plasma was assessed by CDC according adequate methodology.
Detection	**KQC** - Can we be confident in the outcome assessment?	- -	The outcome in terms of immune effects, i.e. questionnaire based allergies. Jaundice and herpes. Respiratory disease is very insensitive and unprecise to draw conclusions on the immune system.
Selection	Did selection of study participants result in appropriate comparison groups?	-	Diagnosed chloracne patients were recruited from the Seveso area who had lived there around the time of the accident, and matched controls were recruited from the same area. In addition, an additional control group was added from the same area. Whereas demographics were investigated, no information was provided to show the comparability of the group. There was an age difference between exposed and non-exposed (age at the time of the accident 8 vs 21 years).

Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	This is in part a case control study and in part a cross sectional study. Of the individuals enrolled, there is information on loss of subjects or missing data and how this was dealt with.
Selective reporting	Were all measured outcomes reported?	+	There is no specific information on the research questions a priori, but it may be assumed the authors did what they set out to do.
Saberi-Hosnijeh et al. (2011) **Saberi-Hosnijeh et al. (2012)** **Saberi-Hosnijeh et al. (2013)**		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	- -	Other occupational exposure or residual confounding has not been taken into account
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Measures of exposure were done well, but decades after exposure had taken place, and the exposures were modelled based on kinetic modelling.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Outcome measures were not addressing functionality of the immune system, but could indicate dysregulation.
Selection	Did selection of study participants result in appropriate comparison groups?	-	The subjects in this cross sectional study were tested several decades after the first exposures had started. The three reports are not based on the identical subjects, but the cohorts were overlapping. Whereas there is an indication of relative similarity between exposed and non-exposed at the time of measurements (2007-2008), it cannot be concluded that the history of the subjects have been comparable. Moreover, the non-exposed subjects were not closely matched.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	At the time of exposure measurement and outcome analysis, all outcomes were reported. For an association of exposure with eczema, the only parameter that showed a significant correlation, individuals with chronic disease (not necessarily related to atopic eczema) were excluded.
Selective reporting	Were all measured outcomes reported?	++	After measurement of exposure in serum and outcome measurement, all data were reported.
Nakamoto et al. (2013)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	Age, BMI, diet were all considered. Especially fatty acids in food was tested as confounder but no significant confounding was noted.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Serum analysis of exposure has been described well and data are clear. It should be noted that the development of atopic dermatitis takes place at young age, whereas the exposure levels were measured at adulthood.
Detection	**KQC** - Can we be confident in the outcome assessment?	- -	The outcomes regarding the immune system (rhinitis and atopic dermatitis) were self-reported and not clinically verified. Whereas the subjects would not have been aware of their exposure, it is not possible to draw a conclusion in terms of the true nature of the outcome, which may not be related to allergy. Hence, the outcome measure is too non-specific.
Selection	Did selection of study participants result in	++	Large cross sectional study. Subjects are well characterized, albeit recruited

	appropriate comparison groups?		over a long period (2002–2010).
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	There were very few subjects eventually excluded from the study because of severe anemia, or missing serum analysis of exposure.
Selective reporting	Were all measured outcomes reported?	++	
Croes et al. (2014)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Main confounders were taken into account, although it is not always clear how, there is information on education, breastfeeding, food consumption, (passive) smoking, and asthma in family.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Exposure (PCDD/Fs, DL-PCBs) was assessed in blood of all individuals recruited, and according state to the art approaches.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	Asthma, animal allergy and hay fever were doctor diagnosed.
Selection	Did selection of study participants result in appropriate comparison groups?	++	Cross-sectional study in two periods (2008-2009 and 2010). The characteristics of subjects are described in supplementary information. Subjects were all adolescents.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	It is a cross sectional study, and there is no indication that subjects were excluded after the eventual selection.
Selective reporting	Were all measured outcomes reported?	++	All measures foreseen were carried out.
Dinse et al. (2016)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	There was some information on possible confounding, nulli- or multiparous, age, but not smoking, breast feeding.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	There is no detailed information on the approach used to assess exposure. Yet, as a part of NHANES, it is likely adequate.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	There is little information on how the ANA determinations were done, although being di=one in the context of NHANES I am inclined to think it has been done adequately.
Selection	Did selection of study participants result in appropriate comparison groups?	+	7,106 subjects in the NHANES study were included in a multi-stage strategy to ensure representativeness. Of these, 4,754 had both chemical and ANA measurements.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	All subjects included were assessed
Selective reporting	Were all measured outcomes reported?	++	All measures aimed for were performed.
STUDIES ON EXPOSURE DURING DEVELOPMENT			
Nagayama et al. (1998)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	There is no information on possible confounding.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	The assessment of exposure is adequate done with good methodology in breast milk.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	The outcome (lymphocyte cell distribution) was done adequately, albeit that the plots of the analysis were not provided.

Selection	Did selection of study participants result in appropriate comparison groups?	-	There is no information on how the subjects were selected.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	There is no indication that subjects were lost.
Selective reporting	Were all measured outcomes reported?	++	All measures aimed for were performed.
Weisglas-Kuperus et al. (2000)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	The data were corrected for sex, early feeding type (breast-fed or formula-fed), duration of breast-feeding, parity (firstborn or second born), maternal and parental occupation, tobacco smoking by one or both parents, family history of atopy in one or more and day care or nursery school attendance.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	References to papers describing the methods for measurement of TEQ in mothers or cord blood were presented.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	The immunological outcomes were assessed in a paediatric clinic and well described.
Selection	Did selection of study participants result in appropriate comparison groups?	+	There is information on the study subjects, 207 children were recruited. In 206 antibody responses to vaccination were measured. Complete health questionnaires were returned by 175 of the parents. Of these, 85 were tested immunologically. Breast fed and formula fed children were present in this cohort; breast fed children were under represented, but these conditions were corrected for.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	All values on individuals tested were presented. A small number of individuals were excluded because they did not respond to vaccination.
Selective reporting	Were all measured outcomes reported?	++	
Van den Heuvel et al. (2002)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	There was an extensive description of potentially relevant confounders and correction.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	There is not much information on the exposure assessment, other than mentioning the CALUX assay. The institute however is well equipped to do this appropriately.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	Measures of outcome parameters were well described and in accord to common practice.
Selection	Did selection of study participants result in appropriate comparison groups?	++	355 subjects (adolescents, born 1980–1983) from two suburbs of Antwerp were invited to participate, 207 responded. 7 were excluded (just moved, unable to participate, illness). Samples were all taken in 1999.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	Of all 200 recruited subjects samples were taken.
Selective reporting	Were all measured outcomes reported?	++	It seems that all the outcomes have been reported.
Kaneko et al. (2006)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**

Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Children were sampled at 1 year of age. There will be no occupational exposure, nor are main differences in body weight and diet to be expected.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Exposure measure well described. For the methodology used to calculate the TEQs they referred to the WHO methodology.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	The outcome measures (lymphocyte distribution and immunoglobulin levels) were determined by well described methodologies.
Selection	Did selection of study participants result in appropriate comparison groups?	++	Recruited within a period of 5 years, residing in the same area for more than 5 years.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	It is not clear why of 415 mothers only 281 breast fed children were sampled. Yet, all of these individuals recruited seem to be included in the analysis
Selective reporting	Were all measured outcomes reported?	++	It seems that all planned measures were reported.
Nagayama et al. (2007b)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Children were sampled at around 10 months of age. There will be no occupational exposure, nor are main differences in body weight and diet to be expected.
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Methodology to measure the exposure was well described and adequate.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	Methodology for assessing lymphocyte subpopulations was well described and adequate.
Selection	Did selection of study participants result in appropriate comparison groups?	+	108 mother children pairs were selected between June-August 1994 and 1995 living in Fukuoka and suburbs.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	Of 108 mother children pairs, blood samples were obtained from 101 infants, of these 92 were used to measure immune parameters. The difference is not big, but there is no explanation for this.
Selective reporting	Were all measured outcomes reported?	+	All outcomes planned seem to be reported; although it is not clear why only 92 of 101 samples were analysed for lymphocyte distribution.
Leijs et al. (2009)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	There was no mention of any confounder or adjustment.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	There is no information in this paper on the methods for exposure assessment, but it is performed at a renowned laboratory.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	There is little information on the assays to measure the outcomes. However, these are clinical measures performed at clinical chemical laboratories.
Selection	Did selection of study participants result in appropriate comparison groups?	+	In the current paper no characteristics are given of the subjects, but there are references on the same cohort (Pluim et al., 1994; Ilsen et al., 1996; Ten Tuscher et al., 2003).
Attrition/ exclusion	Were outcome data completely reported without attrition or	-	Of 60 subjects in the cohort, eventually inly 30 remained to be tested. Whereas the reason for

	exclusion from analysis?		the reduced number of subjects is given, the authors themselves mark this as a weakness of the study.
Selective reporting	Were all measured outcomes reported?	++	
Miyashita et al. (2011)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Confounders (breast feeding, parental smoking, vaccination, Infant weight were taken into consideration. These characteristics were described in a paper by Kishi et al., in press).
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Exposure parameters were according accepted methods (referred to Tokada et al., 2003).
Detection	**KQC** - Can we be confident in the outcome assessment?	++	Identification of infections and asthma followed doctors' diagnosis; for asthma in addition questionnaire based determination according ATS-DLD data were included.
Selection	Did selection of study participants result in appropriate comparison groups?	+	The subjects of this study were all recruited though medical examination between 2002 and 2005 at Sapporo Toho Hospital. Of 7,796 subjects contacted, 514 agreed. The subjects were well characterized. The participation rate was relatively low. However, it is not clear that this would have influenced assessment of exposure related effects. The study was performed in one hospital only.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	After delivery, 23 mother/children pairs were excluded (miscarriage, still birth, relocation, infant mortality). Of 491 remaining mothers, 390 responded and remained in the study.
Selective reporting	Were all measured outcomes reported?	++	All measures foreseen seem to have been performed.
Stolevik et al. (2011)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	There is insufficient information on the study subjects and possible confounding has not been considered.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Exposure was assessed by food frequency questionnaires and no real exposure measurements were done.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Wheeze was assessed with questionnaires. Discrimination between asthma and respiratory tract infections is not easy, but at the younger age wheeze is associated with respiratory tract infections. Exanthema subitum is easier concluded, although also other reasons for rashes may be evident.
Selection	Did selection of study participants result in appropriate comparison groups?	-	There seems to be a selection bias as there was only a 38.5% participation rate in MoBa cohort.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	There is insufficient information provided about numbers of subjects lost to follow-up.
Selective reporting	Were all measured outcomes reported?	++	All measures aimed for were performed.
Stolevik et al. (2013)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	There is insufficient information on the study subjects and possible confounding has not been considered.

Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Exposure was assessed by food frequency questionnaires (FFQ) and no real exposure measurements were done.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Wheeze was assessed with questionnaires. Discrimination between asthma and respiratory tract infections is not easy, but at the younger age wheeze is associated with respiratory tract infections. Antibody titres were assessed using accepted methodologies.
Selection	Did selection of study participants result in appropriate comparison groups?	-	There seems to be a selection bias as there was only a 38.5% participation rate in MoBa cohort.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	There is insufficient information provided about numbers of subjects lost to follow-up.
Selective reporting	Were all measured outcomes reported?	++	All measures aimed for were performed.

A.9.9. Studies on effects on the nervous system

Table 84. Risk of bias appraisal of studies on effects on the nervous system (scores corresponding to one appraisal). Note: appraisal of individual studies focused only on risk of bias; additional quality aspects were considered when evaluating the overall confidence in the body of evidence (see Section 2.2.1.2 of the opinion).

NEURODEVELOPMENT IN CHILDREN			
Lanting et al. (1998)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Unclear TEF scheme used.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Assessors were blinded to exposure and feeding practice.
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	94% of the children assessed at 42 months.
Selective reporting	Were all measured outcomes reported?	++	
Patandin et al. (1999)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/	Were outcome data completely	+	

exclusion	reported without attrition or exclusion from analysis?		
Selective reporting	Were all measured outcomes reported?	+	
Vreugdenhil et al. (2002)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Several confounders considered, including HOME score.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Parent reported. Validated questionnaire.
Selection	Did selection of study participants result in appropriate comparison groups?	++	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Nakajima et al. (2006)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Adjusted for important confounders, co-exposure not known
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Bayley scale of infant Development not standardized in Japan, but justified that outcome is still interpretable
Selection	Did selection of study participants result in appropriate comparison groups?	++	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	Fulfilling outcome test and providing samples was part of inclusion criteria, so no loss
Selective reporting	Were all measured outcomes reported?	++	
Wilhelm et al. (2008)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Adjusted for several confounders, method for selection not given.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Blinding of examiner was not described. Examiner effect observed at two weeks, adjusted for.
Selection	Did selection of study participants result in appropriate comparison groups?	++	Prospective cohort.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Halldorson et al. (2009)		**Risk of bias tier: 2**	

Bias domain	Question	Score	Judgement
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Socioeconomic status not adjusted for
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	CALUX may be confounded by PAH, since increased with meat consumption and decreased with fish (opposite of expected).
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Although self-reported.
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Sioen et al. (2013)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Low volume and fat% in cord blood lead to high LOD.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Parent reported, probably blinded.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Some differences between participants (maternal age and education) and non-participants adjusted for.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Adjusted for as described above.
Selective reporting	Were all measured outcomes reported?	++	
Winneke et al. (2014)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Well addressed, but insufficient information about co-exposure as in all cohorts. High education overrepresented, may affect generalizability
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	both blood and milk data, with high correlation
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Parent - reported. Parents knew exposure but could not interpret it since no Reference values for blood or milk exist.
Selection	Did selection of study participants result in appropriate comparison groups?	++	Recruited in similar way, all exposed to some extent
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	All reported
Nowack et al. (2015)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Important confounders addressed
Detection	**KQB** - Can we be confident in the	++	Well documented in previous papers

	exposure characterisation?		
Detection	**KQC** - Can we be confident in the outcome assessment?	+	SRS good reliability and validity EQ-SQ not validated in children
Selection	Did selection of study participants result in appropriate comparison groups?	-	Insufficient information about invitations at follow up.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	Significant differences between participants and non-participants may influence generalizability of exposure-outcome associations.
Selective reporting	Were all measured outcomes reported?	+	
Neugebauer et al. (2015)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Adjusted for a number of confounders/covariates, including lead
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	Levels in maternal blood and milk
Detection	**KQC** - Can we be confident in the outcome assessment?	-	KITAP is not validated. FBB-ADHS is validated but parent-reported and not blinded to exposure
Selection	Did selection of study participants result in appropriate comparison groups?	+	Predictive cohort, 50% loss to follow up. Exposure similar in participants and non-participants
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	All outcome data reported, but low participation rate at follow up (50%)
Selective reporting	Were all measured outcomes reported?	++	All outcomes reported
Caspersen et al. (2016a)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	All the relevant confounders are counted for (age, BMI, breast feeding, smoking and others). Occupational exposures are not relevant here.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Dietary intake: indirect measure compared to blood levels.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	The outcome is self-reported and parental report of their children's own progress is always subject to some bias.
Selection	Did selection of study participants result in appropriate comparison groups?	++	This is a cohort study and subjects are recruited form the same target population (and they should be blinded towards their own exposure).
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	Loss of subjects was accurately described and I see no clear cause for concern as 85% of those eligible ended up in the final analyses.
Selective reporting	Were all measured outcomes reported?	++	Reporting was detailed and no important information was lacking.
Caspersen et al. (2016b)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	Appropriate covariates were included in their analyses and use of statistical models was appropriate. The only important covariate not measured was maternal or parental IQ but this is rarely measured and it is unlikely that maternal/parental IQ would be related to maternal intake of dioxins.
Detection	**KQB** - Can we be confident in the	-	Dietary intake: indirect measure compared to

	exposure characterisation?		blood levels
Detection	**KQC** - Can we be confident in the outcome assessment?	++	Clinical assessment by a trained health professional
Selection	Did selection of study participants result in appropriate comparison groups?	+	The comparison group is randomly selected and children with ADHD symptoms are selected based on initial screening. When invited to participate both groups had modest participation rate. Still the design in appropriate.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	The outcome data was completely reported. There was a modest response rate among potential ADHD candidates that were invited to participate (37.5%) which on its own is not so problematic as this is an association study but not a case controls study. Exclusion of subjects from the study was minor and should not have influenced the results.
Selective reporting	Were all measured outcomes reported?	++	No indications on selective reporting.
Nakajima et al. (2017)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Breast feeding duration was not taken into consideration, possible confounding by postnatal exposure. Maternal intellectual performance not considered at 6 months.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Ikeno et al. (2018)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	OK since they assess prenatal exposure in relation to endpoint. However, postnatal exposure (and effects) may be relevant and exposure from breastfeeding is not taken into consideration.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Hui et al. (2016)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important	+	

	confounding and modifying variables?		
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Assessed in relation to maternal BEQ, but postnatal exposure may be of importance for the outcome.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
OCCUPATIONAL STUDIES			
Michalek et al. (2001b)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Known confounders adjusted for
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Back calculated from samples in 1987-1997, long time after exposure (1962-1971).
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Neuropathy in 1997 could not be confirmed by nerve measurements of nerve conduction (only performed in 1982)
Selection	Did selection of study participants result in appropriate comparison groups?	+	Matched Reference population, but recruited at a later stage
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	All reported
Selective reporting	Were all measured outcomes reported?	++	All reported
Barret et al. (2001)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	High uncertainty in the back-calculation of exposure.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Pelclova et al. (2001)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Confounders could not be assessed with such low n.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the	+	Blinding not described, but known that all

	outcome assessment?		were highly exposed workers, would probably not lead to bias.
Selection	Did selection of study participants result in appropriate comparison groups?	-	Originally 80 intoxicated workers. Only 12 participated at follow up, no information about non-participants.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	Insufficient information
Selective reporting	Were all measured outcomes reported?	-	Only main variables reported.
Pelclova et al. (2002)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Too low N to account for confounders
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Originally 80 intoxicated workers. Only 11 participated at follow up, no information about non-participants.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	Few participants
Selective reporting	Were all measured outcomes reported?	+	More variables reported also from 1996 examination.
Michalek et al. (2003)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Back calculated many years back in time of high exposure using linear model.
Detection	**KQC** - Can we be confident in the outcome assessment?	-	Self-reported. Aware of own exposure. Anxiety to TCDD exposure from Agent Orange.
Selection	Did selection of study participants result in appropriate comparison groups?	+	Matched comparisons
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Urban et al. (2007)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Too low number of participants to adjust for confounders
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Basis for selection of participants unclear
Attrition/ exclusion	Were outcome data completely reported without attrition or	-	Reasons for loss to follow up not described

	exclusion from analysis?		
Selective reporting	Were all measured outcomes reported?	+	
Pelclova et al. (2009)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Too low N to account for confounders
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Analysis not described, refers to levels in 2008.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Low participation rate (8-11 out of 80), no information about non-participants
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	Reason for loss to follow up not described
Selective reporting	Were all measured outcomes reported?	+	

A.9.10. Studies on effects on teeth and bone

Table 85. Risk of bias appraisal of studies on effects on teeth and bone (scores corresponding to one appraisal). Note: appraisal of individual studies focused only on risk of bias; additional quality aspects were considered when evaluating the overall confidence in the body of evidence (see Section 2.2.1.2 of the opinion).

DEVELOPMENT OF TEETH			
Alaluusua et al. (2002)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	++	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Wang et al. (2003)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	Definitely low risk related to dentist evaluations. But dental developmental history is parent reported, may be associated with recall bias

Selection	Did selection of study participants result in appropriate comparison groups?	++	Matched controls
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Alaluusua et al. (2004)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Age, smoking, sex and education similar between ABR and non-ABR participants. Higher education independent explanator for lower risk of enamel defects, no interaction between TCDD and education level.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	TCDD measured shortly after the accident, but no information on non-ABR participants except two pools from children from the same area, not participating in the non-ABR Group.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	All investigated by the same dentist, high intra-examiner reproducibility, examiner blinded to exposures and participants. unaware of the research hypotheses
Selection	Did selection of study participants result in appropriate comparison groups?	+	Participation rate in ABR 74%, non-ABR 58%
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	All reported
BONE			
Eskenazi et al. (2014)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Variation in background exposure to other PCDD/Fs- and DL-PCBs is unknown.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	++	High participation rate (82%).
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Fukushi et al. (2016)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Limited information, smoking not known.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Sampled 36-39 y after the accident
Detection	**KQC** - Can we be confident in the outcome assessment?	+	DXA Method, different places

Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	

A.8.11. Studies on cancer

Table 86. Risk of bias appraisal of studies on cancer (scores corresponding to one appraisal sal). Note: appraisal of individual studies focused only on risk of bias; additional quality aspects were considered when evaluating the overall confidence in the body of evidence (see Section 2.2.1.2 of the opinion).

INDUSTRIAL ACCIDENTS OR CONTAMINATION INCIDENTS			
Bertazzi et al. (2001)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Smoking status not known
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Warner et al. (2002)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	Only 80% participation
Selective reporting	Were all measured outcomes reported?	- -	Only selected cases reported
Pesatori et al. (2008)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying	NR	Confounding or modifying variables not recorded

	variables?		
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	TCDD measurements not recorded
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	++	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	-	AIP loss of function mutations not recorded
Consonni et al. (2008)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No data on confounding factors such as smoking
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	TCDD measured in soil and only a small number of serum samples collected
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	++	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Pesatori et al. (2009)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No confounding or modifying agents mentioned
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Environmental contamination serum measurements taken much later resident in area not necessarily present at time of accident measured
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	++	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	++	
Warner et al. (2011)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	++	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	

Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
OCCUPATIONAL STUDIES			
Heederik et al. (1998)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Becher et al. (1998)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Collins et al. (2009a)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Small numbers described
Attrition/ exclusion	Were outcome data completely reported without attrition or	+	

	exclusion from analysis?		
Selective reporting	Were all measured outcomes reported?	+	
Collins et al. (2009b)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	No estimated from historical data
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Flesh-Janys et al. (1998)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Confounding factors were not addressed.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Measurements were only available for some workers.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Study was in males but measurements from females also included.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Steenland et al. (2001b)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	-	All participants exposed
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Ketchum et al. (1999)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important	+	

	confounding and modifying variables?		
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Aerial spraying so cannot be confident of exposure
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Akhtar et al. (2004)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Aerial spraying so cannot be confident of exposure
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Pavuk et al. (2005)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Aerial spraying so cannot be confident of exposure
Detection	**KQC** - Can we be confident in the outcome assessment?	++	
Selection	Did selection of study participants result in appropriate comparison groups?	++	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	-	Multiple cancer cases not reported
Ketchum and Michalek (2005)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Smoking and other confounders were not assessed on individual level but were available for a subgroup indicating minor differences.
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Considerable non-differential misclassification, since individual data were available only in part of the subjects.
Detection	**KQC** - Can we be confident in the outcome assessment?	++	

Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Kang et al. (2006)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	Smoking and some other confounders could be adjusted for. Telephone interviews only
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Aerial spraying so cannot be confident of exposure
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Pavuk et al. (2006)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No confounding or modifying factors mentioned
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Aerial spraying so cannot be confident of exposure
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Michalek and Pavuk (2008)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	

Li et al. (2013)		Risk of bias tier: 2	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Confounding or modifying agents not mentioned
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Aerial spraying so cannot be confident of exposure
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Selection bias only patients undergoing g RP
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Landgreen et al. (2015)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Aerial spraying so cannot be confident of exposure
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Hooiveld et al. (1998)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No confounding or modifying agents mentioned
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	-	Only measured TCDD in 47 samples
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	
Boers et al. (2012)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No confounding or modifying agents mentioned
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	

Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	All female workers excluded
Selective reporting	Were all measured outcomes reported?	+	
OTHER STUDIES			
Steenland et al. (1999)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No confounding or modifying agents mentioned
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	No individual TCDD data, only estimates by JEM. Another paper supports the ranking and gives serum TCDD levels for part of the individuals.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Unequal numbers in selected groups
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	+	
De Roos et al. (2005)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No confounding or modifying agents mentioned
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	-	Limited number of samples where detection was found
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	Computer assisted interview
Selective reporting	Were all measured outcomes reported?	+	
McBride et al. (2009)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Mixed exposure
Detection	**KQC** - Can we be confident in the outcome assessment?	-	Small numbers cannot exclude by chance
Selection	Did selection of study participants result in appropriate comparison	+	

	groups?		
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	21% loss to follow up
Selective reporting	Were all measured outcomes reported?	+	
Viel et al. (2011)		**Risk of bias tier: 3**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No confounding or modifying agents mentioned
Detection	**KQB** - Can we be confident in the exposure characterisation?	-	Mixed exposure from incinerator
Detection	**KQC** - Can we be confident in the outcome assessment?	-	Only 34 cases examined some undergoing chemotherapy
Selection	Did selection of study participants result in appropriate comparison groups?	+	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	-	8 cases excluded
Selective reporting	Were all measured outcomes reported?	-	Cumulative sum of congeners reported rather than individuals
Manuwald et al. (2012)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No confounding or modifying agents mentioned
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Exposed only
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	+	
Cheng et al. (2006)		**Risk of bias tier: 2**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	No confounding or modifying agents mentioned
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Unequal numbers in selected groups
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	++	
Selective reporting	Were all measured outcomes reported?	+	
Boers et al. (2010)		**Risk of bias tier: 2**	

Bias domain	Question	Score	Judgement
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	-	Lack of data on potential confounders, but smoking prevalence was considered similar to referents.
Detection	**KQB** - Can we be confident in the exposure characterisation?	+	Individual TCDD data only for a subgroup, but the difference between "exposed" and non-exposed is valid. However non-differential misclassification is likely to be large in the ER analyses.
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	-	Participation based on complete company registers. External reference group with likely some 'healthy worker selection'.
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	++	
Lin et al. (2012b)		**Risk of bias tier: 1**	
Bias domain	**Question**	**Score**	**Judgement**
Confounding	**KQA** - Did the study design or analysis account for important confounding and modifying variables?	+	
Detection	**KQB** - Can we be confident in the exposure characterisation?	++	
Detection	**KQC** - Can we be confident in the outcome assessment?	+	
Selection	Did selection of study participants result in appropriate comparison groups?	++	
Attrition/ exclusion	Were outcome data completely reported without attrition or exclusion from analysis?	+	
Selective reporting	Were all measured outcomes reported?	+	

ANNEX A.10. EFFECTS OF PCDD/Fs AND DL-PCBs ON SERUM LEVELS OF SEX HORMONES AND RELATED PROTEINS

Reported changes in serum levels of sex hormones and related proteins following associations with postnatal or pre/postnatal PCDD/F and DL-PCB exposures are summarised in Table 87. These studies are described or mentioned in Sections 3.1.4.3.1, 3.1.4.3.2, 3.1.4.4–3.1.4.6, 3.1.4.8 and 3.1.4.12.

Table 87. Direction of changes in serum concentrations of sex hormones and related proteins/peptides associated with PCDD/F and DL-PCB exposure. [↑]: increase. [↓]: decrease. [-]: no change

	Sex **Exposure measure** **Age at sampling (years)**	**ASD**	**Testosterone**	**DHT**	**DHEA**	**SHBG**	**Inhibin-B**	**FSH**	**LH**	**E1**	**E2**	**Progesterone**	**Ratio**
STUDIES IN MALES (newborns, infants, boys, men)													
Industrial accidents or contamination incidents													
Mocarelli et al. (2008)	Men Serum 1976/77 40-47 y		-				-	-	-		-		
	Men Serum 1976/77 22–31 y		-				-	↑	-		↓		
	Men Serum 1976/77 32–39 y		-				-	↑	↓		↓		
Mocarelli et al. (2011)	Boys/Breast-fed Maternal serum 1976 18-26 y		-				↓	↑	-		-		
	Boys/Formula fed Maternal serum 1976 18-26 y		-				-	-	-		-		
Sun et al. (2014)	Men Serum 56-81 y	-	-	-	-					-	-	-	
Occupational exposure													
Michalek et al. (1999a)	Men Serum 50-55 y					-							
Gupta et al. (2006)	Men Serum 49 y		↓										
Pelclova et al. (2009)	Men Serum, 64.4 y		-										
Johnson et al. (2001)	Men Serum 29-76 y		↓					-	-		-	-	
Background exposure													
Dhooge et al. (2006)	Men Serum 20-40 y		↓			-	-	-	-		-		
Den Hond et al. (2002)	Boys Serum 17 y		-			-	-	-	-		-		
Croes et al. (2014)	Boys Serum 14–15 y		-			-			-		-		

Virtanen et al. (2012)	Boys Placenta 3 months			-			-	-	-	↑				
Su et al. (2012)	Boys[(b)] Placenta 8 y			(c)					-	-		↓		
Cao et al. (2008)	Boys[(b)] Cord blood Newborn			↓								↓		
Rennert et al. (2012)[(a)]	Boys[(b)] Maternal blood/milk 6/8 y			(c)		↑						(c)		
STUDIES IN FEMALES (newborns, girls, women)														
Industrial accidents or contamination incidents														
Warner et al. (2007)	Women Serum 1976/77 20–40 y											-	-	
Wang et al. (2006)	Women/Pregnant Placenta 28–30 y	-	-	-							-	↓	-	↓
Background exposure														
Su et al. (2012)	Girls[(b)] Placenta 8 y			(c)					-	-		↓		
Cao et al. (2008)	Girls[(b)] Cord blood Newborn			↓								↓		
Rennert et al. (2012)[(a)]	Girls[(b)] Maternal blood/milk 6/8 y			(c)		↑						(c)		

ASD: Androstendione; DHT: Dihydrotestosterone; DHEA: Dehydroepiandrosterone; SHBG: Steroidhormonebinding globuline; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; E1: Estrone; E2: Estradiol; Ratio: 4-OH-E2/2-OH-E2.

(a): 17-OHP=17-hydroxyprogesterone was analysed by Rennert et al. (2012) to preclude an early onset of the adrenogenital syndrome. All samples were below cut-off level.

(b): No difference between boys and girls.

(c): Serum concentrations were below the level of detection.

ANNEX A.11. STUDIES ON THE ADVERSE EFFECTS OF PCDD/Fs and DL-PCBs IN FARM AND COMPANION ANIMALS

A.11.1. Studies in ruminants

Table 88. Studies on the adverse effects of PCDD/Fs and/or DL-PCBs in **ruminants (cow, sheep and goats)**

Reference	Compounds and dose regime	Endpoint	Comments
COWS AND BUFFALOES			
Lavrusenko et al. (1996). Effect of dioxine on the immune system of farm animals.	Not clear but probably TCDD 5, 10 µg/kg (for 15 days) 30 µg/kg (for 10 days) 5, 10 and 30 µg/kg (for 30 days) Oral admin	Immunotoxicity	Dosing seems very high but reporting is not clear. Effects are not clearly presented. Most of the controls seem to be missing. Apparently high mortality; due to treatment? *Study not suitable for the risk assessment*.
Cigliano et al. (2016). Evaluation of serum markers of blood redox homeostasis and inflammation in PCB naturally contaminated heifers undergoing decontamination.	17 PCDD/Fs + 12 DL-PCBs *Field exposure*	Oxidative stress Liver weight	Young cows exposed due to nearby decontamination plant; animals transferred to clean area; TEQ levels around 25 pg TEQ/g fat, primarily due to DL-PCBs; also NDL-PCBs around 165 ng/g; levels decreased in 6 months follow-up; also strong growth. Parameters related to oxidative stress, showing decrease; endpoint not suitable for RA. *Study not suitable for the risk assessment*
Genualdo et al. (2012). Chromosome fragility in river buffalo cows exposed to dioxins.	17 PCDD/Fs + 12 DL-PCBs *Field exposure* *Case study*	Chromosome fragility	Cows (buffalo) from Campania region; milk levels 22 pg TEQ/g fat (primarily PCDD/Fs; possibly CALUX), not detected in milk from control farm; chromosome abberrations and SCEs in lymphocytes. Probably mixed exposure. *Study not useful for RA*
Iannuzzi et al. (2009). Chromosome analyses in dairy cows exposed to dioxins and dioxin-like PCBs using the SCE test.	17 PCDD/Fs + 12 DL-PCBs *Field exposure* *Case study*	SCE	Cows (dairy); Susa valley; steel plant. Field exposure with 2 herds, one showing elevated TEQ in milk (19 vs 2 pg TEQ/g fat, primarily DL-PCBs); possibly mixed exposure; end-point not suitable for RA. *Study not suitable for the risk assessment*
Spagnuolo et al. (2012). Analysis of plasma indices of redox homeostasis in dairy cows reared in polluted areas of Piedmont (northern Italy).	17 PCDD/Fs + 12 DL-PCBs *Field exposure*	Retinol, ascorbate, N-tyr, blood parameters	Cows (dairy); Susa valley; steel plant. Field exposure with 3 herds, two showing elevated TEQ in milk (9, 19.1 vs 2 pg TEQ/g fat; primarily DL-PCBs); possibly mixed exposure; end-points not suitable for RA.

Reference	Compounds and dose regime	Endpoint	Comments
		redox status	*Study not suitable for the risk assessment*
Chamberland et al. (1994). Clinical-chemistry, growth and PCB levels in beef-cattle exposed to a PCB fire.	PCB-118 *Field exposure*	Growth, clinical chemistry	Incident with PCB; levels in body fat. Study concerns a field study with cows (heifers) exposed to a mixture of PCBs, no data on TEQs. *Study not suitable for the risk assessment*
Lloyd et al. (1991). Toxicity from ragwort and fat cow syndrome, or from industrial-chemicals - the value of epidemiologic analysis for interpreting clinicopathological findings.	(dioxins) *Field exposure*	Other	Case report of two farms likely to be affected by nearby waste incinerators. No levels in tissues; possibly coexposure to other contaminants. *Study not suitable for the risk assessment*
Spagnuolo et al. (2011). Effect of dioxin exposure on several indices of blood redox status in lactating buffalo cows.	TEQs *Field exposure*	Plasma proteins, blood redox status	Cows (buffalo) from Campania region; milk levels 22 pg TEQ/g fat (primarily PCDD/Fs; possibly CALUX), not detected in milk from control farm; only parameters related to oxidative stress. Probably mixed exposure. *Study not useful for the risk assessment*
Davies et al. (1985). Possible dioxin poisoning in cattle.	(TCDD) *Field exposure*	Other	Case report Cow (zebu); dead calves (63%), severe clinical jaundice; spraying nearby paddock with 2,4,5-T; route of exposure unclear; no measurements. *Study not suitable for the risk assessment*
SHEEP			
Lavrusenko et al. (1996). Effect of dioxine on the immune system of farm animals.	Probably TCDD but unclear Unclear dose regime	Immunotoxicity	Dosing seems very high but is not very clear, and also the effects are not clearly presented. Most of the controls seem to be missing. Apparently high mortality; due to treatment? *Study not suitable for the risk assessment*
Gutleb et al. (2011). Effects of pre- and postnatal polychlorinated biphenyl exposure on emotional reactivity observed in lambs before weaning.	PCB-118 49 µg/kg bw/day Oral gavage (corn oil) 3 times/week for 6 months (from mating until delivery)	Behavioural effects	*In utero* exposure via the dams. Cross contamination/co-admin with PCB-153. Levels in tissues of lambs reported in Berg et al. (2010), but summarized in this paper. PCB 118 levels 6-7 fold lower in PCB 153 than in 118 group. Some differences in behavioural effects observed. Impurities (no-PCBs, PCDFs) not reported. *Study not suitable for the risk assessment*
Zimmer et al. (2013). Fetal Adrenal Development: Comparing Effects of Combined Exposures to PCB 118 and PCB 153 in a Sheep Model.	PCB-118 49 µg/kg bw/day Oral gavage (corn oil)	Reproductive effects Effects on other	Strong decrease in cortisol levels both in PCB 118 and 153 group. Effect may be due to PCB 153 rather than 118. Impurities not reported.

Reference	Compounds and dose regime	Endpoint	Comments
	3 times/week for 6 months (from mating until delivery)	hormone levels	*Study not suitable for the risk assessment*
Krogenaes et al. (2014). In Utero Exposure to Environmentally Relevant Concentrations of PCB 153 and PCB 118 Disrupts Fetal Testis Development in Sheep.	PCB-118 49 µg/kg bw/day Oral gavage (corn oil) 3 times/week for 6 months From mating until delivery)	Reproductive effects (testis develop)	Same study as Gutleb et al. (2011); cross contamination with PCB 153; no check on impurities. PCB 118 level 200 pg TEQ/g fat, 60 in controls. No effects on testis morphology and weight. Sperm counts/viability not studied. Effects on proteome observed. *Study not suitable for the risk assessment*
Brambilla et al. (2011b). Polychlorodibenzodioxin and -furan (PCDD and PCDF) and Dioxin-like Polychlorobiphenyl (DL-PCB) Congener Levels in Milk of Grazing Sheep as Indicators of the Environmental Quality of Rural Areas.	17 PCDD/Fs + 12 DL-PCBs *Field exposure*	Reproductive effects Milk quality	No clear effects observed on fertility. Only low levels in milk and small range (0.6-2 pg WHO_{1998}-TEQ/g fat). *Study not suitable for the risk assessment*
Iannuzzi et al. (2004). Chromosome fragility in two sheep flocks exposed to dioxins during pasturage.	17 PCDD/Fs *Field exposure*	Reproductive effects Clastogenicity aneugenicity	Levels in milk, soil and grass but low. No clear data on exposure of affected group and nothing on the controls. Effects on chromosome aberrations and SCEs. Potentially other contaminants. *Study not suitable for the risk assessment*
Perucatti et al. (2006). Increased frequencies of both chromosome abnormalities and SCEs in two sheep flocks exposed to high dioxin levels during pasturage.	17 PCDD/Fs *Field exposure*	Reproductive effects Chromosome abnormalities, SCE, mortality	Levels in milk, soil and grass, but not for the controls. Effects on SCEs and chromosome abnormalities. Potentially other contaminants involved. *Study not suitable for the risk assessment*
Lind et al. (2009). Exposure to pastures fertilised with sewage sludge disrupts bone tissue homeostasis in sheep.	Many contaminants, including PCBs. Only DL-PCB 118 reported *Field exposure*	Musculoskeletal, bone	Effect of sewage sludge treatment pasture on bone density. However, no TEQ levels determined and also mixture of contaminants. *Study not suitable for the risk assessment.*
GOATS			
Azza et al. (2014). Toxicological impact of exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) on some hormonal profiles and hematological parameters in goats.	TCDD 0.23 µg/kg bw (equivalent to 1/3 of TCDD LD_{50} ref to rat) Oral admin, 3 doses, 2-day interval	Reproductive effects Effects on hormone levels (estradiol, progesterone,	Goat (Baladi); unclear if 0.23 µg/kg bw is sum of doses or per dose; just one dose applied, being LOAEL. *Study not suitable for the risk assessment.*

Reference	Compounds and dose regime	Endpoint	Comments
		prolactin and cortisol) Hematological parameters	
Fouzy et al. (2008). Effect of dioxins on properties of Egyptian goats' milk and blood profile with relation to mastitis.	17 PCDD/Fs Mixture of native and ^{13}C, equal composition, so may calibration mixture 0.037, 0.077, 0.11, 0.23 µg/kg bw (equal to 1/27, 1/13, 1/6 and 1/3 of LD50 guinea pig = 0.06µg/kg bw) (doses seem not correct: based on stock and LD_{50} guinea pig: 23, 11.6, 7.7, 3.9 ng/kg bw) Oral admin but different number of doses, either 1 or 3 (in 6 days): unclear when milk was collected, during or after dosing follow-up for 16 days	Immunotox Milk and blood profile	Goat (Baladi); exposure poorly described with unlikely low levels in milk, not very different from controls. *Study not suitable for the risk assessment*
Lundberg et al. (2006). Perinatal exposure to PCB 153, but not PCB 126, alters bone tissue composition in female goat offspring.	PCB-126 49 ng/kg bw/day Oral admin (corn oil) From GD60 until delivery (about GD150)	Musculoskeletal, bone	Goat (Norwegian breed); Levels in adipose tissue, plasma and liver
Lyche et al. (2004b). Effects of perinatal exposure to low doses of PCB 153 and PCB 126 on lymphocyte proliferation and hematology in goat kids.	PCB-126 49 ng/kg bw/day Oral admin (corn oil) From GD60 until delivery (about GD150)	Immunotox Blood cell counts	Goat (Norwegian breed); Levels in adipose tissue, plasma and liver
Lyche et al. (2004c). Effects of gestational and lactational exposure to low doses of PCBs 126 and 153 on anterior pituitary and gonadal hormones and on puberty in female goats.	PCB-126 49 ng/kg bw/day Oral admin (corn oil) From GD60 until delivery (about GD150)	Effects on hormone levels (hypothalamic-pitutitary-gonadal axis)	Goat (Norwegian breed); Levels in adipose tissue, plasma and liver

Reference	Compounds and dose regime	Endpoint	Comments
Oskam et al. (2005). Effects of long-term maternal exposure to low doses of PCB126 and PCB153 on the reproductive system and related hormones of young male goat.	PCB-126 49 ng/kg bw/day Oral admin (corn oil) From GD60 until delivery (about GD150)	Reproductive effects (including organs) Effects on other hormone levels	Goat (Norwegian breed); Levels in adipose tissue, plasma and liver
Zimmer et al. (2009). Altered Stress-Induced Cortisol Levels in Goats Exposed to Polychlorinated Biphenyls (PCB 126 and PCB 153) During Fetal and Postnatal Development.	PCB-126 49 ng/kg bw/day Oral admin (corn oil) From GD60 until delivery (about GD150)	Effects on other hormone levels Stress, cortisol, organ weight	Goat (Norwegian breed); Levels in adipose tissue, plasma and liver
Lyche et al. (2006). Perinatal exposure to low doses of PCB 153 and PCB 126 affects maternal and neonatal immunity in goat kids.	PCB-126 49 ng/kg bw/day Oral admin (corn oil) From GD60 until delivery (about GD150)	Immunotoxicity	Goat (Norwegian breed); Levels in adipose tissue, plasma and liver

A.11.2. Studies in pigs

Table 89. Studies on the adverse effects of PCDD/Fs and/or DL-PCBs in **pigs**

Reference	Compounds and dose regime	Endpoint(s)	Comments
Ryan (1983). Higher chlorinated dioxins implicated in the mortality of young-pigs kept on a pentachlorophenol-treated wooden floor.	PCDDs *Field exposure*	Mortality	*Case report.* Levels of dioxins (tetra, hex, hepta and octa) in milk and tissues from two piglets (brain, liver, skin, serum) Exposure route unclear and probably mixed exposure. *Study not suitable for the risk assessment.*
Lavrusenko et al. (1996). Effect of dioxine on the immune system of farm animals.	Unclear, but probably TCDD 10 µg/kg (10 or 30 times) 50 µg/kg (10 or 30 times) 70 µg/kg (10 times) Oral admin	Immunotox	*Same study as before with other species.* Dosing seems very high but is not very clear, and also the effects are not clearly presented. Most of the controls seem to be missing. Apparently high mortality; due to treatment? *Study not suitable for the risk assessment.*

A.11.3. Studies in rabbits

Table 90. Studies identified on the adverse effects of PCDD/Fs and/or DL-PCBs in **rabbits**

Reference	Compounds Dose regime	Endpoint(s)	Comments
Schwetz et al. (1973). Toxicology of chlorinated dibenzo-*p*-dioxins. Rabbit – New Zealand albino (mixed gender)	TCDD HxCDD, OCDD for eye irritation and acnegenic activity Oral, *i.p.* or skin absorption: 0, 31.6, 63, 126, 252, 500 µg/kg bw Single administration	**Lethality (LD_{50})**: Similar for *i.p.*, oral or skin administration. Oral: 115 µg/kg Skin: 275 µg/kg **Acnegenic activity**: certain rabbits treated *i.p.* developed skin lesions typical of those associated with acnegens.	LD_{50} calculated by Litchfield and Wilcoxon method. NOEL *i.p.* was 32 µg/kg bw There is insufficient information to be useful in the risk assessment. *Study not suitable for the risk assesment*
Fanelli et al. (1980). 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin toxic effects and tissue levels in animals from the contaminated area of Seveso, Italy.	TCDD *Field exposure*	Mortality, hepatic lesions	Levels in rabbit liver correspond fairly well to soil contamination. *Study not suitable for the risk assessment*
Kimbrough et al. (1977). Epidemiology and pathology of a tetrachlorodibenzodioxin poisoning episode.	TCDD *Field exposure*	Hepatotoxicity, skin lesions	Pathology: Microscopic hyperkeratosis was found in ear lobe (rabbit bioassay) and microscopic necrosis in liver. *Study not suitable for the risk assessment*

A.11.4. Studies in horses

Table 91. Studies identified on the adverse effects of PCDD/Fs and/or DL-PCBs in **horses**

Reference	Compounds	Endpoint(s)	Comments
Kerkvliet et al. (1992). Dioxin intoxication from chronic exposure of horses to pentachlorophenol-contaminated wood shavings.	Mixture of PCDD/Fs in PCP treated wood savings *Field exposure*	Numerous effects, including death	Case report. Dioxin present as impurity and measured in fat (n=1) and liver (n=2). Study not suitable to derive a NOAEL.
Kimbrough et al. (1977). Epidemiology and pathology of a tetrachlorodibenzodioxin poisoning episode.	Individual PCDD/Fs *Field exposure*	Hepatotoxicity/gastrointestinal effects, and Other	Same study as Carter et al. (1975). No additional information that can lead to NOAEL.
Carter et al. (1975). Tetrachlorodibenzodioxin: an accidental poisoning episode in horse arenas.	TCDD (TCP) *Field exposure*	Numerous effects	Various adverse effects described including death of many horses. Levels in contaminated soil provided but level and route of exposure cannot be established; i.e. no NOAEL can be derived.

A.11.5. Studies in poultry

Table 92. Studies on the adverse effects of PCDD/DFs and/or DL-PCBs in poultry (adult birds), including chicken, quail, duck, pheasant and turkey

Reference	Compounds and dose regime	Results	NOAEL (or LOAEL)
Chicken			
Greig et al. (1973). Toxic effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. White leghorn chicken (4-6 weeks old)	TCDD 25-50 µg/kg Single oral dose	**Mortality:** a dose of 25-50 µg/kg killed the animals 12-21 days later. **Weight gain:** the weight gain was less rapid than in controls. **General condition:** prior to death some animals were in poor condition (laboured breathing, beak agape, feathers ruffled). Accumulation of serous fluid in the pericardial sac (post-mortem finding).	
El-Sabeawy et al. (2001). Biochemical and toxic effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in immature male and female chickens. Chicken	TCDD 0, 10, 100 µg/kg Single *i.p.* dose	**Body weight/wasting syndrome**: significant decrease in bw in immature M and F chickens 10 days after treatment with 10 and 100 µg /kg. Bw gain decrease associated with hepatomegaly in M and F. At 10 µg/kg, significant increase in liver/bw ratio (48%) only in F, and at 100 µg/kg in M. **Lipoprotein lipase (LPL) and GT activity**: levels of GT significantly decreased in F and M at both dose levels.	LOAEL= 10 µg/kg 10 µgTEQ/kg
Sawyer et al. (1986). The biologic and toxic effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in chickens. White leghorn cockerels	TCDD 0, 0.01, 0.1, 1.0, 10, 100, 1,000 µg/kg *i.p.* administered for 3 consecutive days. Animals sacrificed on day 5.	**Bursa of Fabricius**: significant involution at 10 µg/kg for 3 days compared to corn-oil treated controls.	NOAEL= 1 µg/kg 1 µg TEQ/kg
Peden-Adams et al. (1998). Effects of environmentally relevant concentrations of 2,3,7,8-TCDD on domestic chicken immune function and CYP450 activity: F1 generation and egg injection studies. White leghorn chicken	TCDD 0, 8.6, 1,700 ng per day, plus 1,700 ng per day for one month *i.m.* dosing twice weekly during 6 weeks. (These doses were estimates of	**Lymphocyte proliferation**: adult T-cell proliferation significantly suppressed for all dose groups (including controls) when compared to baseline levels. Adult B-cell proliferation was suppressed from baseline for all dose groups. **Egg production**: loss of egg production at the highest dose group after 12 days of treatment.	

Reference	Compounds and dose regime	Results	NOAEL (or LOAEL)
	potential exposure from remediated and contaminated soils at a Superfund site)		
Alonso et al. (1998). Effects of *in ovo* exposure to 2,3,7,8-TCDD on F1 generation adult chickens (*Gallus gallus*). White leghorn chickens	TCDD 0, 8.6, 1,700 ng/day *i.m.* dosing twice weekly during for 6 weeks	**Egg production**: loss of egg production at the highest dose group after 12 days of treatment **Estradiol, testosterone and estrogen receptor levels in F1**: no statistically different from controls. **Body weight in F1**: at both dose groups F bw lower than those of M. Control had lower bw than low dose (8.6) by sex. Low dose M bw were statistically different from control M.	
McKinney et al. (1976). Toxicological assessment of hexachlorobiphenyl isomers and 2,3,7,8 tetrachlorodibenzofuran in chicks. I. Relationship of chemical parameters.	TCDF 0, 1, 5 µg/kg/day Oral (gastric intubation)	**Mortality**: animals at the highest dose died at an average of 11.5 days. **Food consumption and body weight**: both reduced at the highest dose group during the 7- to 14-day observation period, and also reduced at the 1 µg/kg/day group during the 14- to 21-day period. **Liver weight**: no significant effect at any dose group. **Spleen weight**: significant reduction in spleen weight at 1 µg/kg. **Histopathology**: Mild changes only at the high dose group: accumulation of clear fluid (sc edema), ascites, and hydropericardium, with the severity of fluid accumulation greater at the 5 µg/kg dose. The thymus was markedly involuted at 1 µg/kg. Histologically, there was marked depletion of lymphocytic cell types in the spleen and thymus.	LOAEL= 1 µg/kg 0.1 µg TEQ/kg/day
Goldstein et al. (1976). Toxicological assessment of hexachlorobiphenyl isomers and 2,3,7,8,-tetrachlorodibenzofuran in chicks. II. Effects on drug metabolism and porphyrin accumulation. White leghorn cockerels	TCDF 0, 1, 5 µg/kg/day PCB-169 100, 300 mg/kg in diet Oral (gastric intubation)	**Mortality**: animals at the highest dose died before sacrifice. **Liver weight**: not significantly increased at any dose level. Incidence of hepatic porphyrin elevation.	LOAEL = 1 µg/kg 0.1 TEQ µg/kg/day LOAEL= 100 mg/kg
Schwetz et al. (1973). Toxicology of chlorinated dibenzo-*p*-dioxins. White leghorn, single-comb cockerels	TCDD, HxCDDs, OCDD Birds given TCDD at 1 and 10 µg/kg or the HxCDD at 10 and 100 µg/kg	Chick bioassay for chick edema factor. High incidence of mortality by 21 days (no survival at the highest doses), exhibiting pericardial, peritoneal, subcutaneous and pulmonary oedema as well as liver hypertrophy	

Reference	Compounds and dose regime	Results	NOAEL (or LOAEL)
	Oral (gavage) 20 or 21 days of treatment		
Metcalfe (1972). Proposed source of chick edema factor.	PCDDs Animals were fed contaminated fat that was then analysed	Chick edema factor	
Flick et al. (1972). Studies of the chick edema disease part 9 response of chicks fed or singly administered synthetic edema producing compounds.	17 PCDD/Fs (uncertain doses of individuals congeners) Several experiments with 1 day chicks fed or administered single oral or *i.p.* doses of mixtures	Cardiovascular effects, edema after 3 weeks, weight gain	
De Vos et al. (2005). Digestibility, retention and incorporation of low-level dietary PCB contents in laying hens.	PCB-118 (PCBs added to diets as a mixture of 7 (PCB-28, -52, -101, -118, -138, -153, -180) 0, 1.5 and 6 ng/g diet 41 weeks	Performance, egg quality. Levels in fat fraction of egg yolk, abdominal adipose tissue, thigh and breast muscle. Feed conversion and percentage of egg production were determined weekly	Seven indicator PCBs. Congener specific data provided. Only DL-PCB is PCB-118 and TEF 0.00003.
Summer et al. (1996a). Effects induced by feeding organochlorine-contaminated carp from Saginaw Bay, Lake Huron, to laying White Leghorn hens. I. Effects on health of adult hens, egg production, and fertility.	Feeding diets for 18 week chicken that contained 31–35% ocean fish and/or carp which provided concentrations analogous to 3.3 (control), 26 (low-dose) or 59 (high-dose) pg TEQs/g diet ww Control diet contained PCDDs. The diets also contained high levels of NDL-PCBs and potentially other contaminants were not	Reproductive effects, Hepatotoxicity Feed consumption, bw, organ weight haematocrit values	TEQs determined by H4IIE bioassay and calculated (different values)

Reference	Compounds and dose regime	Results	NOAEL (or LOAEL)
	analysed. 8 weeks		
Summer et al. (1996b). Effects induced by feeding organochlorine-contaminated carp from Saginaw Bay, Lake Huron, to laying White Leghorn hens. II. Embryotoxic and teratogenic effects.	TEQs	Reproductive effects	
Stanton et al. (2002). Effect of estrogen and 2,3,7,8-tetrachlorodibenzo-rho-dioxin (TCDD) on plasma fatty acids of immature male chickens (*Gallus domesticus*).	TCDD G1: Vehicle G2: Estrogen G3: TCDD: 50 µg/kg bw/day G4: Estrogen + TCDD: 50 µg/kg bw/day *i.p.*	Plasma lipids and fatty acid changes	Single dose study
Spear and Moon (1986). Thyroid-vitamin A interactions in 3 week chicks exposed to 3,4,3',4'-tetrachlorobiphenyl: influence of low dietary vitamin A and iodine.	PCB-77 10 µg/g bw On days 2 and 6 *i.m.* Animals maintained on experimental diets with (i) low Vit A (ii) low Vit A and low iodine and (iii) control	Metabolic rate, food intake, serum T3 and T4 decreased. Thyroid size increased.	Single dose study
Ax and Hansen (1975). Effects of purified polychlorinated biphenyl analogs on chicken reproduction.	PCB-118 and Aroclors (possible presence of PCDDs) 20 ppm Oral (diet) 10 weeks + 2 weeks elimination period	Reproductive effects, fertility, embryo mortality	Single dose study
Fanelli et al. (1980). 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin toxic effects and tissue levels in animals from the contaminated area of Seveso, Italy.	TCDD ***Field exposure***	Mortality, pathology Hepatic lesions and hydrpericardia	Seveso area Levels in tissues

Reference	Compounds and dose regime	Results	NOAEL (or LOAEL)
Chicken			
Newsome et al. (1984). Chlorinated compounds in tissues raised on pentachlorophenol-contaminated litter.	OCDD (Exposure to commercial wood shavings containing PCP) ***Field exposure***	Gross pathology	Levels in tissues (liver, fat, muscle)
Bernard et al. (2002). The Belgian PCB/dioxin incident: Analysis of the food chain contamination and health risk evaluation.	PCB-118, 17 PCDD/Fs ***Field exposure***	Chick edema	Report Belgian incident
Quail			
Boily et al. (2003a). Retinoids, LRAT and REH activities in eggs of Japanese quail following maternal and *in ovo* exposures to 3,3 ',4,4 '-tetrachlorobiphenyl. Japanese quail	PCB-77 5 µg/g bw *i.p.*	Embryo mortality, retinol levels, maternal toxicity	Single dose study Also *In ovo*
Elliott et al. (1997). Comparative toxicity of polychlorinated biphenyls to Japanese quail (*Coturnix c-japonica*) and American kestrels (*Falco sparverius*). Japanese Quail	PCB-77 PCB-126 Acute - Single oral doses. PCB-77: 250 mg/kg PCB-126: 25 mg/kg Sacrificed after 5 days.	Hepatic and renal porphyrin levels	Single dose study
Miranda et al. (1987). Effects of polychlorinated biphenyls on porphyrin synthesis and cytochrome P-450-dependent monooxygenases in small intestine and liver of Japanese quail. Japanese Quail	PCB-77 300 µmol/kg (87.6 mg/kg) Oral admin Sacrificed at 48 h	Porphyrin synthesis	Single dose study
Pheasants			
Hornung et al. (1998). Lack of	PCB-105	**Egg production**: not significantly different between treatment groups,	None

Reference	Compounds and dose regime	Results	NOAEL (or LOAEL)
developmental and reproductive toxicity of 2,3,3',4,4'-pentachlorobiphenyl (PCB 105) in ring-necked pheasants. Ring-necked pheasant (*Phasianus colchicus*)	0, 0.06, 0.6, 6 mg/kg bw/week For 10 weeks after which hens were bred with untreated roosters once per week for 8 weeks Oral administration in gelatin capsule	except at week 6 of the egg-laying period when cumulative egg production in the 6 mg PCB 105/kg hen group was greater than controls. **Embryo mortality and chick mortality**: no significantly different between treatment groups. **Total body and heart weights**: not different between groups in chicks 1 day posthatch. Liver weights of chicks at the highest dose group were greater than controls at 1 day posthatch. The first chick to hatch from each hen was reared to 21 days posthatch total body, liver, and heart weights were not different between groups. **Malformations:** no dose-related malformations of the beak or limbs. **Cardiac effects**: No signs of sc edema, ascites, or pericardial edema in chicks at 1 or 21 days posthatch.	

Table 93. Studies on the adverse effects of PCDD/Fs and/or DL-PCBs *in ovo* in **poultry** (studies with more than one dose group)

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
CHIKEN						
Peden-Adams et al. (1998). Effects of environmentally relevant concentrations of 2,3,7,8-TCDD on domestic chicken immune function and CYP450 activity: F1 generation and egg injection studies.	TCDD 6 µL of 0, 20, 200 pg/mL and 2, 20, 200 ng/mL F1 generation n=300 eggs, 50 eggs/group Examined at 14-day old post-hatch	Yolk sac	not reported?		Immunotoxicity (lymphocyte proliferation)	Also study in adults (see Table FARM-8)
Ivnitski et al. (2001). 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) inhibition of coronary development is preceded by a decrease in myocyte proliferation and an increase in cardiac apoptosis.	TCDD 0, 0.24, 0.40 pmol/egg Fertile eggs	Yolk sac	Before incubation	0, 1.5, 2.5 pg/g egg	Both doses Immunotoxicity Cardiovascular effects	
Bruggeman et al. (2005). Effects of early prenatal exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) on postnatal reproduction in the laying hen (*Gallus gallus*).	TCDD 0, 10, 20 ng/egg n=1,000 eggs	Yolk sac	Embryonic day 0	0, 200, 400 pg/g egg	Hatchability and body weight gain depressed with 200 pg/g egg. Reproductive effects seen in all TCDD adult hens	
Bruggeman et al. (2003). Embryonic exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in chickens: effects of dose and embryonic stage on hatchability and growth.	TCDD 0, 8, 20, 50 ng/egg n=600 eggs	Yolk sac	Embryonic day 4, 8, 12	0, 160, 400, 1,000 pg/g egg	Metabolic effects Organ weight, glucose, TG depending on dose and time. T3/T4 ratio increased accompanied delayed	

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
					growth	
Henshel et al. (1997a). The relative sensitivity of chicken embryos to yolk- or air-cell-injected 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.	TCDD 0, 10, 100, 300, 1,000 pg/g egg - Embryos sacrificed prior to hatching 0, 10, 30, 60, 100, 300, 1,000 pg/g egg - Embryos allowed to hatch n=204 eggs, fertile	Yolk sac Air sac	Enbryonic day 0	0, 10, 100, 300, 1,000 pg/g egg	Reproductive effects Embryo lethality Mortality, embryo growth	NOAEL= 100 pg/g egg for embryo lethality
Powell et al. (1996). Effects of 3,3',4,4',5-pentachlorobiphenyl (PCB 126) and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) injected into the yolks of chicken (*Gallus domesticus*) eggs prior to incubation.	**TCDD**: 0, 0.04, 0.08, 0.16, 0.32, 0.64 µg/kg egg ww **PCB-126**: 0, 0.1, 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, 12.8 µg/kg egg ww Examined within 24h of hatching	Yolk sac	Prior to incubation	**TCDD**: 0, 40, 80, 160, 320, 640 pg/g egg **PCB-126**: 0, 10, 20, 40, 80, 160, 320, 640, 1,280 pg TEQ/g egg	Musculoskeletal, bone Reproductive effects: hatching success Body weight, lethality, edema	**TCDD**: 40 pg TEQ/g egg **PCB-126**: 160 pg TEQ/g egg
Walker and Catron (2000). Characterization of cardiotoxicity induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and related chemicals during early chick embryo development. Two strains White Leghorn chiken eggs: Babcock variety (WLB) and Plymouth Rock Barred (PRB) variety	**TCDD**: 0, 0.125, 0.25, 0.5, 1.0, 2.0, 3.0 pmol/g egg dosed on day 0 and up to day 12 **PCB-126**: 0, 0.875, 1.75, 3.5, 7.0 pmol/g egg	Yolk sac	Prior to incubation	**TCDD**: 0, 40,80, 160, 320, 640, 960 pg/g egg **PCB-126**: 0, 28, 57, 114, 228 pg TEQ/g egg	Cardiovascular effects including increase in heart weight for TCDD and PCB-126. Other strain Plymouth Rock-Barred more sensitive.	**TCDD**: 40 pg/g egg **PCB-126**: 28 pg TEQ/g egg
Heid et al. (2001). Correlation of cardiotoxicity mediated by halogenated aromatic hydrocarbons to aryl hydrocarbon	**TCDD**: 0, 0.06, 0.12, 0.24, 0.40, 0.8 pmol/g (19-258 pg/g)	Yolk sac	Prior to incubation		Cardiovascular effects	

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
receptor activation.	**PeCDD**: 0, 0.1, 0.2, 0.4, 0.8 pmol/g (36-285 pg/g) **TCDF**: 0, 0.12, 0.24, 0.36, 0.48 pmol/g (37-122 pg/g) **2,3,4,7,8-PeCDF**: 0, 0.75, 1.5, 2.0, 3.0 pmol/g (256-1023 pg/g) **PCB-77**: 0, 2, 4, 6, 8 pmol/g (584-2336 pg/g) Fertile eggs, examined at incubation day 10					
Brunström (1989). Toxicity of coplanar polychlorinated-biphenyls in avian embryos. Chicken (also duck and turkey)	**PCB-118**: 500, 2,000, 8,000 µg/kg **PCB-156**: 100, 500, 2,000 µg/kg Fertile eggs. Examined after 18 days	Yolk sac	Incubation day 5	15, 60, 120 pg TEQ/g egg 3, 15, 60 pg TEQ/g egg	Mortality	NOAEL= PCB-118: 60 pg TEQ/g egg PCB-156: 3 pg TEQ/g egg
Brunström (1988). Sensitivity of embryos from duck, goose, herring gull, and various chicken breeds to 3,3',4,4'-tetrachlorobiphenyl. Chicken (also duck and goose)	PCB-77 (purity 98%) 0, 1 000, 5 000 µg/kg egg Fertile eggs	Yolk sac	Incubation day 5		Mortality	
Brunström and Reutergardh (1986). Differences in sensitivity of some avian species to the embryotoxicity of a PCB, 3,3',4,4'-	PCB-77 (purity ≥98%) 0.004, 0.02 mg/kg	Yolk sac	Incubation day 5	0.4, 2 pg TEQ/g egg	Hatching	

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
tetrachlorobiphenyl, injected into the eggs. Chicken (also pheasant and Mallard)						
Brunström and Lund (1988). Differences between chick and turkey embryos in sensitivity to 3,3',4,4'-tetrachloro-biphenyl and in concentration/affinity of the hepatic receptor for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Chicken (also in turkeys)	PCB-77 (≥98% purity) 0, 2, 10, 50 µg/kg egg Experiment terminated after 18 days of incubation	Yolk sac	Incubation day 5		At 50 µg/kg egg all chick embryos died during incubation (a 20-fold higher dose caused 60% mortality among the turkey embryos). At the highest doses not causing substantial mortality among the embryos, the thymus weight was significantly reduced in the chick embryos (not affected in the turkey embryos)	Levels in avian embryos
Lipsitz et al. (1997). Assessment of cerebral hemispheric symmetry in hatchling chickens exposed *in ovo* to polychlorinated biphenyl congeners.	**PCB- 77**: 3.0, 9.0 µg/kg egg **PCB-126**: 0.3, 0.9 µg/kg egg **PCB-77+PCB-126**: 0.09 µg/kg egg + 0.8 µg/kg egg	Yolk sac	Incubation day 0	Dosages based on the LD_{50} values of PCB-77 (8.8 µg/kg egg) and PCB-126 (0.6 µg/kg egg) (as in Powell et al., 1996).	Neurotoxicity Cerebral hemispheric symmetry may be affected by a variety of extrinsic and intrinsisc factors	
de Roode et al. (2002a). Effects of furazolidone, PCB77, PCB126, Aroclor 1248, paraquat and p,p '-DDE on transketolase activity in embryonal chicken brain.	**PCB-126**: 0, 0.00115, 0.0115, 0.115 µg/egg **PCB-77**: 0, 0.015, 0.15, 0.3 µg/egg	Yolk sac	Incubation day 0		Thiamine, transketolase activity	

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
	Examined in day 19					
Zhao et al. (1997). Inhibition of 3,3',4,4',5-pentachlorobiphenyl-induced chicken embryotoxicity by 2,2',4,4',5,5'-hexachlorobiphenyl.	PCB-126 0.5, 1.0, 2.0, 3.0, 4.0, 8.0, 12.0 µg/kg Fertilised eggs	Yolk sac	Incubation day 4	0,50, 100, 200, 300, 400, 800, 1200 pg TEQ/g egg	Reproductive effects Hepatotoxicity, gastrointestinal effects, Lethality Dose dependant at all doses	
Gould et al. (1997). Effects of polychlorinated biphenyl mixtures and three specific congeners on growth and circulating growth-related hormones.	PCB-77 (purity >99%) 3, 30, 300 ng/egg (converted to ppm based on the dose administered divided by the weight of the egg yolk, presumed to be 15 g): 0.0002, 0.002, 0.02 ppm Fertile eggs, examined in day 17 of incubation	Yolk sac	Incubation day 0	300 ng/g egg is 0.6 pg TEQ/g egg	Metabolic effects (thyroid function) Effects on other hormone levels Embryonic growth, pituitary GH content, mortality	
Gould et al. (1999). Effects of polychlorinated biphenyls on thyroid hormones and liver type I monodeiodinase in the chick embryo.	PCB-77 3, 30, 300 ng/egg (converted to ppm based on the dose administered divided by the weight of the egg yolk (14.9 ±0.5 g): 0.0002, 0.002, 0.02 ppm Fertile eggs , examined on incubation day 21	Yolk sac	Incubation day 0	300 ng/g egg is 0.6 pg TEQ/g egg	Metabolic effects (thyroid function) Growth	
de Roode et al. (2002b).	Bioassay	Yolk sac	Before		Morphological	

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
Embryotoxic potential of persistent organic pollutants extracted from tissues of guillemots (Uria aalge) from the Baltic Sea and the Atlantic Ocean.	0.03, 0.3, 3 *bird egg equivalents* of contaminants/egg. Fertilised eggs		onset of the incubation		alterations bursa of Fabricius, mortality, malformations, hepatic porphyrin levels.	
Carro et al. (2013). Effects of an environmentally relevant polychlorinated biphenyl (PCB) mixture on embryonic survival and cardiac development in the domestic chicken.	Bioassay 0, 0.03, 0.08, 0.3, 0.5, 0.7, 2.06 mg PCBs/g egg weight. Fertile eggs, allowed to hatch at embryonic day 20	Albumin	Embryonic day 0	0, 0.004, 0.010, 0.039, 0.064, 0.090, 0.266 ng TEQ_{1998}/g egg	Cardiovascular effects Embryo survival	
Sechman et al. (2011). Effect of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) on steroid concentrations in blood and gonads of chicken embryo.	TCDD Experiment 1: n=400 eggs 0, 2.5, 5, 10 ng/egg At Embryonic day 7 Experiment 2: n=500 eggs 0, 2.5, 5, 10 ng/egg	Across the chorioallantoic membrane into the albumen	Embryonic day 7 and 6	50, 100, 200 pg/g egg	Hormonal activity in ovary and testis, hatchability Variable effects depending on endpoint and not simple dose response	
Henshel et al. (1997b). Brain asymmetry as a potential biomarker for developmental TCDD intoxication: A dose-response study.	TCDD 0, 10, 100, 300, 1,000 pg/g egg Embryos sacrificed prior to hatching 0, 10, 30, 60, 100, 300, 1,000 pg/g egg. Embryos allowed to hatch.	Injection through a hole in the shell above the air sac	Before incubation	0, 10, 100, 300, 1,000 pg/g egg	Brain asymmetry Observable at all doses depending on timing, brain region and doses	

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
	Fertilised eggs					
Cheung et al. (1981). Cardiovascular teratogenicity of 2,3,7,8-tetrachlorodibenzo-para-dioxin in the chick-embryo.	TCDD Control plus 9 dose levels of TCDD ranging from 0.009 to 77.5 pmol/egg Fertile eggs, examined at day 14 n=374 eggs	Injection into the egg white through a hole at the pointed end of the shell	Embryonic day 0		Cardiovascular effects in control at 28% and 60% in highest dose. Teratogenicity, lethality	No NOAEL
Fan et al. (2000). Ventricular preexcitation sensitive to flecainide in late stage chick embryo ECGs: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin impairs inotropic but not chronotropic or dromotropic responses to isoproterenol and confers resistance to flecainide.	TCDD 1, 2 nmol/egg Fertilised eggs	Fluids surrounding the embryo	At incubation day 16 to 18 (close to hatching at 21 days)	6,400, 13,000 pg/g egg	Cardiovascular ECCG effects Neurotoxicity	Not useful. No real dose response.
Canga et al. (1993). 2,3,7,8-tetrachlorodibenzo-*p*-dioxin increases cardiac myocyte intracellular calcium and progressively impairs ventricular contractile responses to isoproterenol and to calcium in chick-embryo hearts.	TCDD 0, 1, 5 nmol Fertilised eggs, examined at 18- to 20-day old	Fluids surrounding the embryos	Not reported	0, 6360, 3,180 pg/g egg	Cardiovascular effects	
Nikolaidis et al. (1988). Effects of TCDD and its congeners 3,3',4,4'-tetrachloroazoxybenzene and 3,3',4,4'-tetrachlorobiphenyl on lymphoid development in the thymus of avian embryos.	PCB-77 100-300 µg/kg egg Examined at day 19	Injection via a hole in the shell outside the air chamber at the blunt end of the	Incubation day 13	10, 30 pg TEQ/g	Immunotoxicity of bursa cells Dose response decrease in bursa size	LOAEL=10 pg TEQ/g

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
		egg				
Sommer et al. (2005). Early developmental 2,3,7,8-tetrachlorodibenzo-*p*-dioxin exposure decreases chick embryo heart chronotropic response to isoproterenol but not to agents affecting signals downstream of the beta-adrenergic receptor.	TCDD 0, 0.24, 0.3 pmol/egg Incubation day 0 0, 0.3 pmol/egg Incubation day 5	Air sac	Incubation day 0 and 5	0, 1.5, 1.9 pg/g egg on day	Cardiovascular effects	
Wikenheiser et al. (2013). Altering HIF-1 alpha Through 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) exposure affects coronary vessel development.	TCDD 0, 1.0, 3.0 pmol/g	Air sac	At HH30 (6.5-7 days) and HH35 (8.5-9 days) of incubation	0, 320, 960 pg/g egg	Immunotoxicity Cardiovascular effects Mortality	NOAEL= 320 pg/g egg
Allred and Strange (1977). Effects of 2,4,5-trichlorophenoxyacetic acid and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on developing chicken embryos.	TCDD 6.65 10^{-4}, 6.65 10^{-5}, 6.65 10^{-6}, 6.65 10^{-7} mg/kg egg Fertile eggs, examined on embryonic day 18	Air sac			Liver weight, embryo viability, LD50	
Ivnitski-Steele et al. (2005). 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) inhibition of coronary vasculogenesis is mediated, in part, by reduced responsiveness to endogenous angiogenic stimuli, including vascular endothelial growth factor A (VEGF-A).	TCDD 0, 0.075, 0.15, 0.24, 0.3 pmol/g egg Fertile eggs	Air sac	Incubation day 5	0, 24, 48, 76, 95 pg/g egg	Cardiovascular effects All doses decreased VEGF-A secretion	
Yaeger et al. (2006a). Embryonic growth and hatching implications of developmental 670-nm phototherapy and dioxin co-exposure.	TCDD 0, 20, 200 ppt Fertile eggs injected	Air sac	Prior to the start of incubation		Reproductive effects Embryonic growth, hatching	670 nm light cotreatment.

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
Yeager et al. (2006b). Survivorship and mortality implications of developmental 670-nm phototherapy: Dioxin co-exposure.	TCDD 0, 20, 200 ppt Fertile eggs	Air sac	Prior to the start of incubation		Survival and hatching success	670 nm light cotreatment
Yeager et al. (2006b). Brief report: embryonic growth and hatching implications of developmental 670-nm phototherapy and dioxin co-exposure.	TCDD 0, 20, 200 ppt Fertile eggs	Air sac	Prior to the start of incubation		Reproductive effects Musculoskeletal, bone Liver weight/length	670 nm light cotreatment
Lim et al. (2008). Attenuation of TCDD-induced oxidative stress by 670 nm photobiomodulation in developmental chicken kidney.	TCDD 0, 2, 200 pg/g egg (dose range that reflects environmental background concentrations up through approximately the LD_{50} for chick embryo)	Air sac (assumed as next paper)	Embryonic day 0	0, 2, 200 pg/g egg	Renal toxicity, weight	
Lim et al. (2007). Suppression of endogenous antioxidant enzymes by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-induced oxidative stress in chicken liver during development.	TCDD 0, 2, 20, 200 pg/g egg (dose range that reflects environmental background concentrations up through approximately the LD_{50} for chick embryo)	Air sac	Embryonic day 0	0, 2, 20, 200 pg/g egg	Organ's weights	
Henshel (1998). Developmental neurotoxic effects of dioxin and dioxin-like compounds on domestic and wild avian species.	TCDD 0, 10, 100, 300, 1,000 pg/g egg Embryos sacrificed prior to hatching 0, 30, 60 pg/g egg Embryos allowed to hatch	not reported?		0, 10, 100, 300, 1,000 pg/g egg	Immunotoxicity, Brain asymmetry	

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
Fox and Grasman (1999). Effects of PCB 126 on primary immune organ development in chicken embryos. White leghorn eggs	PCB-126 0.051, 0.13, 0.32, 0.80 ng/g egg Examined from day 0 until day 20	Air sac	Prior to incubation	51, 130, 320, 800 pg/g egg 5, 13, 32, 80 pg TEQ/g egg	Immunotoxicity (lymphoid cell numbers and viability)	NOAEL= 5 pg/g egg
Goff et al. (2005). Effects of PCB 126 on primary immune organs and thymocyte apoptosis in chicken embryos.	PCB-126 0.05, 0.13, 0.32, 0.64, 0.80 ng/g egg	Air sac	Incubation day 0	50, 130, 320, 640, 800 pg/g egg 5, 13, 32, 64, 80 pg TEQ/g egg	Immunotoxicity	NOAEL 5pg TEQ/g egg
Grasman and Whitacre (2001). Effects of PCB 126 on thymocyte surface marker expression and immune organ development in chicken embryos. White leghorn eggs	PCB-126 0, 0.051, 0.13, 0.32, 0.8 ng/g egg Examined on day 20	Air sac	Before incubation	51, 130, 320, 800 pg/g egg 5, 13, 32, 80 pg TEQ/g egg	Immunotoxicity (masses and cellularity of lymphoid organs, thymocyte phenotypes) Mortality	NOAEL= 5 pg/g egg
McNabb et al. (2001). Thyroid function in PCB-Exposed avian embryos and chicks.	PCB-126 Doses up to 0.8 ng/g Sampled on day 20 of the 21 incubation period	Air sac	Prior to incubation	Up to 80 pg TEQ/g egg	Metabolic effects (yhyroid function)	
Jin et al. (2001). Role of oxidative stress and antioxidant defense in 3,3 ',4,4 ',5-pentachlorobiphenyl-induced toxicity and species-differential sensitivity in chicken and duck embryos.	PCB-126 0, 0.4, 0.8, 1.2, 1.6 µg/kg egg	Air sac	Prior to incubation	0, 40, 80, 120, 160 pg TEQ/g egg	Hepatotoxicity, gastrointestinal effects. Mortality, edema, malformations	LOAEL= 40 pg TEQ/g egg

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
Chiken and duck eggs						
Lavoie et al. (2007). Effect of *In ovo* exposure to an organochlorine mixture extracted from double crested cormorant eggs (Phalacrocorax auritus) and PCB 126 on immune function of juvenile chickens.	PCB-126 0, 0.55, 0.96, 1.38, 1.79 ng WHO_{1998}-TEQ/egg (55 g/egg) (TEF=0.1) Fertile eggs	Air sac	Prior to incubation	0, 0.1, 0.175, 00.25, 0.325 ng/g (0.01, 0.0175, 0.025, 0.0325 ng WHO-TEQ_{98}/g)	Immunotox Decreased antibody titres at all doses in resulting 28 day chicks. Decreased thymus and bursa weights with highest dose dpending on age of chick	
McKernan et al. (2007). Egg incubation position affects toxicity of air cell administered polychlorinated biphenyl 126 (3,3 ',4,4 ',5-pentachlorobiphenyl) in chicken (*Gallus gallus*) embryos.	PCB-126 0, 500, 1 000, 2 000 pg/g egg Fertile eggs	Air sac	Day 4 of developme nt	0, 50, 100, 200 pg TEQ/g egg	Embryonic survival, pipping, and hatching success Depending on dose, position of egg affects results	
Hoffman et al. (1998). Comparative developmental toxicity of planar polychlorinated biphenyl congeners in chickens, American kestrels, and common terns. White Leghorn eggs	**PCB-126**: 0, 0.3, 0.5, 1.0, 3.2 ng/g **PCB-77**: 0, 0.12, 1.2, 6, 12 ng/g Concentrations selected on the basis of initial range finders and studies of others	Air sac	Incubation day 4	PCB 126 0, 30,50,100 320 pg TEQ/g egg	Reproductive effects Embryonic development	
Brunström (1992). Embryolethality and induction of 7-ethoxyresorufin O-deethylase in chick embryos by polychlorinated biphenyls and polycyclic aromatic hydrocarbons having Ah receptor affinity.	**PCB-77** **PCB-126** **PCB-169** Dosing unclear Examined 72 h later	Air sac	Incubation day 7		Mortality	
Rifkind et al. (1984). Coordinate induction of	PCB-77	Injected through a	Incubation day 17		Histopathology No plasma enzyme	NOAEL 5nmol/egg

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
cytochrome P-448 mediated mixed function oxidases and histopathologic changes produced acutely in chick embryo liver by polychlorinated biphenyl congeners.	0, 0.5, 5, 50, 500 nmol/egg	hole made in the-shell			changes	
Cohen-Barnhouse et al. (2011a). Developmental and posthatch effects of *in ovo* exposure to 2,3,7,8-TCDD, 2,3,4,7,8-PECDF, and 2,3,7,8-TCDF in japanese quail (*Coturnix japonica*), common pheasant (*Phasianus colchicus*), and white leghorn chicken (*Gallus gallus domesticus*) embryos. Chicken (also quail and pheasant)	**TCDD**: 0, 0.049, 0.096, 0.19, 0.42, 0.77, 1.6, 3.1 pmol/g egg **PeCDF**: 0.044, 0.087, 0.14, 0.33, 0.69, 1.4, 2.5 pmol/g egg **TCDF**: 0.074, 0.15, 0.25, 0.52, 1.1, 1.8, 4 pmol/g egg	Air sac	Prior to incubation		Reproductive effects Deformities, changes in body and relative organ masses, organ pathology of hatchlings, embryo mortality	
Cohen-Barnhouse et al. (2011b). Sensitivity of Japanese Quail (*Coturnix japonica*), Common Pheasant (*Phasianus colchicus*), and White Leghorn Chicken (*Gallus gallus domesticus*) Embryos to *In Ovo* Exposure to TCDD, PeCDF, and TCDF. Chicken (also quail and pheasant)	**TCDD**: 0, 0.049, 0.096, 0.19, 0.42, 0.77, 1.6, 3.1 pmol/g egg **PeCDF**: 0.044, 0.087, 0.14, 0.33, 0.69, 1.4, 2.5 pmol/g egg **TCDF**: 0.074, 0.15, 0.25, 0.52, 1.1, 1.8, 4 pmol/g egg	Air sac	Prior to incubation		Hatchability, embryo lethality	NOAEL= 61 pg/g egg
1802 - **Somers et al. (1978).** Influence of hen dietary calcium and phosphorus on integrity of	TCDD Eggs sprayed with 2,4,5-T				Eggs shell strength	2,4,5-T measuremen ts, but no

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
egg-shell as it would influence hatching success and consequences of pre-incubation 2,4,5-T spraying with and without a high TCDD level.	alone or 2,4,5-T + 2 ppm TCDD.					TCDD determinatio n. Not useful for the risk assessment
QUAIL						
Boily et al. (2003a). Retinoids, LRAT and REH activities in eggs of Japanese quail following maternal and *in ovo* exposures to 3,3 ',4,4 '-tetrachlorobiphenyl. Japanese quail	PCB-77 0.2, 1, 2 µg/g egg (10 g eggs)	Yolk sac	Incubation day 3	20, 100, 200 pg TEQ/g	Embryo mortality, retinol levels and metabolism, maternal toxicity	
Boily et al. (2003b). Retinoid metabolism (LRAT, REH) in the yolk-sac membrane of Japanese quail eggs and effects of mono-ortho-PCBs. Japanese quail	PCB-105 2, 10, 20 µg/egg, or 40, 200 400 ng/g	Yolk sac	Incubation day 3	1.2, 6, 12 pg TEQ/g egg	Retinoid metabolism	
McMurry and Dickerson (2001). Effects of binary mixtures of six xenobiotics on hormone concentrations and morphometric endpoints of northern bobwhite quail (*Colinus virginianus*). Northern bobwhite quail	TCDD 0, 0.003, 0.01, 0.03, 0.1, 0.3 µg/kg	Below the air sac		3, 10, 30, 100, 300 pg/g egg	Effects on other hormone levels Survival,	NOAEL= 100 pg/g egg survival
Cohen-Barnhouse et al. (2011a). Developmental and posthatch effects of *in ovo* exposure to 2,3,7,8-TCDD, 2,3,4,7,8-PECDF, and 2,3,7,8-TCDF in japanese quail (*Coturnix japonica*), common pheasant	**TCDD**: 0, 022, 0.50, 0.75, 1.2, 2.9, 5.7, 11, 28, 37 pmol/g egg **PeCDF**: 0.42, 0.92, 1.8, 2.6, 5.3, 11.2, 11.3, 21, 22 pmol/g egg	Below the air sac	Prior to incubation	**TCDD**: 0, 7, 160, 240, 384, 928, 1,824, 3,520, 8,960, 11,840 pg/g egg **PeCDF**: TEF 0.03	Reproductive effects Deformities, changes in body and relative organ masses, organ pathology of hatchlings, embryo mortality	-

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
(*Phasianus colchicus*), and white leghorn chicken (*Gallus gallus domesticus*) embryos. Japanese quail (also pheasant and chicken)	**TCDF**: 0.42, 0.63, 1.6, 2.9, 4.8, 7.9, 8.6, 15, 24, 31 pmol/g egg			**TCDF:** TEF 0.1		
Cohen-Barnhouse et al. (2011b). Sensitivity of Japanese Quail (*Coturnix japonica*), Common Pheasant (*Phasianus colchicus*), and White Leghorn Chicken (*Gallus gallus domesticus*) Embryos to *In Ovo* Exposure to TCDD, PeCDF, and TCDF. Japanese quail (also pheasant and chicken)	**TCDD**: 0, 022, 0.50, 0.75, 1.2, 2.9, 5.7, 11, 28, 37 pmol/g egg **PeCDF**: 0.42, 0.92, 1.8, 2.6, 5.3, 11.2, 11.3, 21, 22 pmol/g egg **TCDF**: 0.42, 0.63, 1.6, 2.9, 4.8, 7.9, 8.6, 15, 24, 31 pmol/g egg	Below the air sac	Prior to incubation	**TCDD**: 0, 7, 160, 240, 384, 928, 1,824, 3,520, 8,960, 11,840 pg/g egg	Hatchability, embryo lethality	NOAEL TCDD: 1,824 pg/g egg
DUCKS						
Brunström (1989). Toxicity of coplanar polychlorinated-biphenyls in avian embryos. Duck (also chicken and turkeys)	No clear reporting of the dosing	Yolk sac	Incubation day 5		Mortality	
Brunström (1988). Sensitivity of embryos from duck, goose, herring gull, and various chicken breeds to 3,3',4,4'-tetrachlorobiphenyl. Duck (local duck suppliers) (also chicken and goose)	PCB-77 (purity 98%) 0, 1,000, 5,000 µg/kg egg	Yolk sac	Incubation day 5	0, 1,000, 5,000 ng/g egg	No embryo mortality or pericardial toxicity at highest dose for duck or goose. Diiffcult to assess useful true NOAEL without dose relationship	NOAEL= 5,000 ng/g egg 500 pg TEQ/g egg

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
Brunström and Reutergardh (1986). Differences in sensitivity of some avian species to the embryotoxicity of a PCB, 3,3',4,4'-tetrachlorobiphenyl, injected into the eggs. Mallard (also pheasant and chicken)	PCB-77 (purity ≥98%) 0.1 mg/kg egg	Yolk sac	Incubation day 4 or 5	100 ng/g egg Mallard	Mallard single dose 100 ng/g no effect	NOAEL= 100 ng/g egg 10 pg TEQ/g egg
TURKEY						
Brunström (1989). Toxicity of coplanar polychlorinated-biphenyls in avian embryos. Turkey (also chicken and duck)	PCB-126 0, 20, 60 µg/kg egg	Yolk sac	Incubation day 5	0, 20, 60 ng/g egg	Significant mortality at lower dose	LOEL= 20 ng/g egg
Brunström and Lund (1988). Differences between chick and turkey embryos in sensitivity to 3,3',4,4'-tetrachloro-biphenyl and in concentration/affinity of the hepatic receptor for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Turkey (also chicken)	PCB-77 (purity ≥98%) 0, 40, 200, 1,000 µg/kg egg Experiment terminated after 24 days of incubation	Yolk sac	Incubation day 5	0, 40, 200, 1000 ng/g egg	At 50 µg/kg egg all chick embryos died during incubation, while a 20-fold higher dose caused 60% mortality among the turkey embryos. *At the highest doses not causing substantial mortality among the embryos, the thymus weight was significantly reduced in the chick embryos, while it was not affected in the turkey embryos*	NOAEL= 200 ng/g egg Levels in avian embryos
PHEASANT						
Cohen-Barnhouse et al. (2011a). Developmental and	**TCDD**: 0, 0.075, 0.1, 0.22, 0.31, 0.82, 3.2, 6.7 pmol/g	Air cell	Prior to		Reproductive effects	Concentrations available in

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
posthatch effects of *in ovo* exposure to 2,3,7,8-TCDD, 2,3,4,7,8-PeCDF, and 2,3,7,8-TCDF in japanese quail (*Coturnix japonica*), common pheasant (*Phasianus colchicus*), and white leghorn chicken (*Gallus gallus domesticus*) embryos. Common pheasant	egg **2,3,4,7,8-PeCDF**: 0.14, 0.24, 0.39, 0.6, 1.1, 4.1, 6.8 pmol/g egg **TCDF**: 0.13, .017, 029, 065, 1.1, 4.8, 14 pmol/g egg 80 eggs/dose group		incubation		Deformities, changes in body and relative organ masses, organ pathology of hatchlings, embryo mortality Less sensitive than chicken	ng/g egg
Cohen-Barnhouse et al. (2011b). Sensitivity of Japanese Quail (*Coturnix japonica*), Common Pheasant (*Phasianus colchicus*), and White Leghorn Chicken (*Gallus gallus domesticus*) Embryos to *In Ovo* Exposure to TCDD, PeCDF, and TCDF. Common pheasant	**TCDD**: 0, 0.075, 0.1, 0.22, 0.31, 0.82, 3.2, 6.7 pmol/g egg **2,3,4,7,8-PeCDF**: 0.14, 0.24, 0.39, 0.6, 1.1, 4.1, 6.8 pmol/g egg **TCDF**: 0.13, .017, 029, 065, 1.1, 4.8, 14 pmol/g egg 80 eggs/dose group	Air cell	Prior to incubation	**TCDD**: 0, 0.075, 0.1, 0.22, 0.31, 0.82, 3.2, 6.7 pmol/g egg **PeCDF**: 0.14, 0.24, 0.39, 0.6, 1.1, 4.1, 6.8 pmol/g egg **TCDF**: 0.13, 0.017, 0.029, 0.065, 1.1, 4.8, 14 pmol/g egg	Hatchability, embryo lethality TCDD less potent in quail and pheasant than PCDF and TCDF	
Nosek et al. (1993). Embryotoxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the ring-necked pheasant. Ring-necked pheasant	TCDD 0, 0.01, 0.1, 1, 10, 100, 1,000, 10,000, 100,000 pg/g egg	Albumin Yolk sac	Embryonic day 0	0, 0.01, 0.1, 1, 10, 100, 1,000, 10,000, 100,000 pg/g egg	LD_{50} injected into the albumin: 1,354 pg TCDD/g egg LD_{50} injected into the yolk: 2,182 pg TCDD/g egg, Doses up to and 1,000 pg/g egg had no effect in body growth, organ weights, carcass	NOAEL estimated as 100 pg/g egg

Reference	Compounds and dose regime	Site of injection	Time of injection	Conversion of dose Assuming 50 g egg	Results	NOAEL (or LOAEL)
					morphometrics, incidence of edema, incidence of histological alterations in the liver, spleen, heart, Bursa of Fabricius, or thymus. At 1,000 pg/g egg, no effect on cardiac morphometrics, cardiac malformations (1-d-old hatchlings), or on antibody-mediated immunity (28-day old chicks)	
Brunström and Reutergardh (1986). Differences in sensitivity of some avian species to the embryotoxicity of a PCB, 3,3',4,4'-tetrachlorobiphenyl, injected into the eggs. Phaesant (also maillard and chicken)	PCB-77 (purity ≥98%) Highest dose: 1.0 mg/kg egg Dosing unclear Fertilised eggs	Yolk sac	After 4 days of incubation	10o and 100o pg/g egg	Zero hatching at high dose in pheasant	
GOOSE						
Brunström (1988). Sensitivity of embryos from duck, goose, herring gull, and various chicken breeds to 3,3',4,4'-tetrachlorobiphenyl. Goose (also chicken and duck)	PCB-77 0, 100, 1,000 µg/kg egg	Yolk sac	Incubation day 5	0, 100, 1,000 ng/g egg	No mortality or gross abnormalities at highest dose	

A.11.6. Studies in fish

Table 94. Studies on the adverse effects of PCDD/Fs and/or DL-PCBs in trout

Reference	Compounds Dosed regime	Parameters measured and measure of effect	NOAEL (or LOAEL)
Giesy et al. (2002). Effects of chronic dietary exposure to environmentally relevant concentrations to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on survival, growth, reproduction and biochemical responses of female rainbow trout (*Oncorhynchus mykiss*). Rainbow trout (*Oncorhynchus mykiss)* Juveniles and adults (F) (Other results from this study are published in Walter et al. (2000))	TCDD Average daily concentrations: 0, 1.8, 18, 90 ng/kg ww feed 320 days Oral (via feed)	**Reproductive outcomes**: All fish in the control group died due to pump failure so there were no outcomes for this group. - Survival of eggs to hatching: significantly reduced in all TCDD-exposed groups compared to the surrogate control group. - Survival of fry: significantly lower in the 18 and 90 ng TCDD/kg groups compared to the 18 ng TCDD/kg and control group. No treatment-related effects on egg quality, size or number **Clinical- and gross pathology, histopathological examinations:** No significant changes in gross pathology, in serum chemistry, or in erythrocyte parameters at any exposure level or duration. Dose-related hepatocellular changes seen in all TCDD-exposed groups but not in the control fish. **Adult mortality**: 14.3, 25.7 and 40% in the 1.8, 18 and 90 ng TCDD/kg exposure groups, respectively.	NOAEL not established (lack of suitable control group and limited statistics)
Hawkes and Norris (1977). Chronic oral toxicity of 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) to rainbow-trout. Rainbow trout (*Oncorhynchus mykiss)* Juveniles	TCDD 0.0023 µg/kg, 2.3 µg/kg or 2,300 µg/kg diet (reported to correspond to doses of 0.0000096, 0.0108 or 6.3 µg TCDD/kg bw/day) 105 days Oral (feed)	**Chronic oral toxicity**: - Growth: no effects - Mortality: highest treatment group had 88% mortality following 71 days of exposure **Mortality, food consumption, growth, fin erosion**: no effects in the lowest or middle TCDD groups. In the highest TCDD group, average mortality of 50% and 88% after 61 and 71 days, respectively. Feeding activity and growth reduced, and fin erosion and liver pathology increased.	NOAEL=0.0108 µg TCDD/kg bw LOAEL=6.3 µg TCDD/kg bw
Spitsbergen et al. (1988a). Morphologic lesions and acute toxicity in rainbow trout (*Salmo gairdneri*) treated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin	TCDD Acute toxicity experiment:	**Mortality**: no mortality after 80 days in the control or 1 µg/kg. Mortality was 20, 90 and 95% in the 5, 25 and 125 µg/kg bw groups, respectively. 80 day LD_{50}=10 µg/kg.	NOAEL not established (limited statistics)

Reference	Compounds Dosed regime	Parameters measured and measure of effect	NOAEL (or LOAEL)
Rainbow trout (*Oncorhynchus mykiss*) Juveniles	0, 1, 5, 25, 125 µg TCDD/kg bw Experiments for histopathology and haematology: 0, 0.1, 1, 10 µg TCDD/kg bw *i.p.* single	**Histopathology:** reduced density of leucocytes and thrombocytes in fish treated with 1 or 10 µg/kg, results not given for 0.1 µg/kg bw group. Gross and microscopic lesions in fish treated with 10 µg/kg, not in fish treated with 0.1 or 1 µg/kg	
Spitsbergen et al. (1988b). Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) or aroclor-1254 on the resistance of rainbow-trout, salmo-gairdneri richardson, to infectious hematopoietic necrosis virus. Rainbow trout (*Oncorhynchus mykiss*) Juveniles	TCDD 0, 0.1, 1, 10 µg TCDD/kg *i.p.* single	**Growth, mortality, morphologic lesions**: No mortality observed five weeks after treatment. Reduced feed intake and activity, and fin necrosis (which was not observed in any of the other groups) at the highest dose. After challenge with infectious haematopoietic necrosis virus (IHNV): mortality in TCDD-exposed fish not significantly different from the control group (although more severe and diffuse lesions of IHNV disease in fish in the exposed groups versus controls).	NOAEL (fin necrosis)=0.1 µg TCDD/kg bw
Van der Weiden et al. (1992). Concurrence of p450-1a1 induction and toxic effects after administration of a low-dose of 2,3,7,8 (TCDD) in the rainbow trout (*Oncorhynchus mykiss*) Rainbow trout (*Oncorhynchus mykiss*) Juveniles	TCDD 0.006, 0.03, 0.06, 0.30, 0.60 3.06 µg TCDD/kg bw *i.p.* single Killed after 3, 6 or 12 weeks	**Growth:** reduced at the highest dose group 6 weeks after exposure. **Mortality**: 20% mortality in the highest dose group after 12 weeks. **Haemorrhages**: in 3 highest dose groups (0.30, 0.60, 3.06 µg/kg bw) after 6 weeks of treatment. **Organ weight**: no pronounced changes in relative liver weight. Relative spleen weight increased after 3 and 6 weeks of treatment. **Histopathology**: inflammation, single cell necrosis, sinusoidal dilatation of the liver. **Immunotoxicity:** Lymphocyte depletion and congestion observed from 0.30 ug/kg dose levels.	NOAEL (growth)=0.6 µg TCDD/kg bw
Walter et al. (2000). Pathologic alterations in adult rainbow trout, Oncorhynchus mykiss, exposed to dietary 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Rainbow trout (*Oncorhynchus mykiss*) Adults (F)	TCDD 0, 1.8, 18, 90 ng/kg diet Oral (feed) 50, 100, 150, 200, 250+ days	**Reproductive effects**: The proportion of primary to secondary oocytes varied among fish but was not associated with any dose group, time interval or other histopathological alteration. **Hepatotoxicity**: dose-related hepatocellular changes in all TCDD treated groups but not in control fish. **Clinical pathology**: No TCDD-related alterations in any serum chemistry parameters or in erythrocyte parameters at any exposure time. Total number of leukocytes decreased in the	NOAEL not established (limited statistics)

Reference	Compounds Dosed regime	Parameters measured and measure of effect	NOAEL (or LOAEL)
(Part of the study by Giesy et al., (2002))		highest dose compared to controls (no clear dose-response). **Gross pathology**: necrosis of the caudal and occasionally anal fins. Incidence of fin lesions slightly greater in treated groups than in the controls at the same time intervals (not dose dependent). **Histopathology**: inflammation, fibroblasts and neovascularization increased. Changes not dose-related and occurred with similar frequency among all treatment groups. **Growth**: no statistically significant differences in growth among treatment groups after 200 days of exposure.	
Brown et al. (2002). Dietary accumulation and biochemical responses of juvenile rainbow trout (*Oncorhynchus mykiss*) to 3,3 ',4,4 ',5-pentachlorobiphenyl (PCB 126). Rainbow trout (*Oncorhynchus mykiss*) Juveniles	PCB-126 0, 12.4, 126 µg/kg ww Oral (feed) For 30 days, plus 160 days of clean food	**Liver and thyroid histology:** not affected after 30 days of exposure. Significantly lower didehydroretinol, didehydroretinyl palmitate and tocopherol levels in fish exposed to 126 ng/g than in control fish. Significantly lower muscle T3 and T4 levels in both exposed groups compared to control fish. **Growth:** not affected after 30 days of exposure.	NOAEL=126 µg PCB-126/kg feed (highest level tested)
Bellehumeur et al. (2016). Exposure to sublethal levels of PCB-126 impacts fuel metabolism and swimming performance in rainbow trout. Rainbow trout (*Oncorhynchus mykiss*) Adult (F)	PCB-126 0, 100, 400 µg/kg bw *i.p.* single	**Swimming performance**: Assessed after 1, 3, 5, 7 or 9 days following *i.p.* injection. Highest for fish in the high dose group, although their initial condition factor was also higher, largely due to their greater body mass. Trout in the high and low dose groups showed impaired recovery following intense exercise as they swam comparatively poorly when provided a second challenge. **Spleen somatic indices**: reduced in all groups. **Muscle glucose, glycogen contents**: reduced in all groups. **Plasma cortisol, glucose levels**: elevated in all groups (indicating higher metabolic costs during recovery and muscle restoration).	NOAEL not established (difference in fish size in groups at the start of the study)
Kleeman et al. (1988). Species differences in 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxicity and biotransformation in fish. Rainbow trout (*Oncorhyncus mykiss*)	TCDD 0, 1, 5, 25, 125 µg/kg bw *i.p.*	**Lethality**: 80-day LD_{50} (median, 95 CI)=10 (7-15) µg/kg **Body weight gain**: significant decrease at all doses greater than 1 µg/kg. **Fin necrosis:** observed at the two highest dose groups.	Based on growth in rainbow trout, NOAEL=1 µg TCDD/kg bw

Reference	Compounds Dosed regime	Parameters measured and measure of effect	NOAEL (or LOAEL)
Quabius et al. (2000). Influence of dietary exposure to polychlorinated biphenyl 126 and nutritional state on stress response in tilapia (*Oreochromis mossambicus*) and rainbow trout (*Oncorhynchus mykiss*). Trout (*Oncorhynchus mykiss*) Tilapia (*Oreochromis mossambicus*)	PCB-126 0, 25, 2,500 µg/kg food/day (approximately 0, 0.5, 50 mg/kg bw per day) Oral (feed) Examination after 5 days exposure or after 3 weeks of starvation.	**Mortality**: no mortality. **Behavior**: no changes observed. **Food consumption**: no changes observed. **Resting plasma ACTH and cortisol levels**: not affected by treatment. **Resting plasma glucose**: affected only in fish sampled at the end of the starvation period (both doses in trout).	NOAEL=50 mg/kg bw (highest dose tested)
Belpaeme (1996). Cytogenetic studies of PCB77 on brown trout (*Salmo trutta fario*) using the micronucleus test and the alkaline comet assay. Brown trout (*Salmo trutta*) Juveniles			Waterborne exposure
Helder (1981). Effects of 2,3,7,8-tetrachlorodibenzo-dioxin (TCDD) on early life stages of rainbow trout (*Salmo gairdneri*, Richardson). Rainbow trout (*Oncorhyncus mykiss*) Juveniles			Waterborne exposure
Mehrle et al. (1988). Toxicity and bioconcentration of 2,3,7,8-tetrachlorodibenzodioxin and 2,3,7,8-tetrachlorodibenzofuran in rainbow-trout. Rainbow trout (*Oncorhyncus mykiss*)			Waterborne exposure
Delistraty and Stone (2007). Dioxins, metals, and fish toxicity in ash residue from space heaters burning used motor oil. Rainbow trout (*Oncorhyncus mykiss*)			Study not eligible. Mixed exposure
Helder et al. (1982). The toxicity and toxic potential of fly-ash from municipal incinerators assessed by means of a fish early life stage test. Rainbow trout (*Oncorhyncus mykiss*)			Study not eligible. Mixed exposure
Brinkmann et al. (2015). Towards science-based sediment quality standards-Effects of field-collected sediments in rainbow trout (*Oncorhynchus mykiss*).			Study not eligible. Mixed exposure

Reference	Compounds Dosed regime	Parameters measured and measure of effect	NOAEL (or LOAEL)
Rainbow trout (*Oncorhynchus mykiss*)			
Fitzsimons et al. (1995). Occurrence of a swim-up syndrome in Lake Ontario lake trout in relation to contaminants and cultural practices. Lake trout (*Salvelinus namaycush)*			Study not eligible. Mixed exposure
Cook et al. (2003). Effects of aryl hydrocarbon receptor-mediated early life stage toxicity on lake trout populations in Lake Ontario during the 20th century. Lake trout (*Salvelinus namaycush*)			Study not eligible. Mixed exposure
Whittle et al. Foodchain accumulation of PCDD and PCDF isomers in the great-lakes aquatic community. Lake trout (*Salvelinus namaycush*)			Study not eligible. Mixed exposure
Maier et al. 2015. Biological plausibility as a tool to associate analytical data for micropollutants and effect potentials in wastewater, surface water, and sediments with effects in fishes. Rainbow trout (*Oncorhyncus mykiss*) Brown trout (*Salmo trutta*)			Study not eligible. Mixed exposure
Buckman et al. (2007b). PCBs can diminish the influence of temperature on thyroid indices in rainbow trout (*Oncorhynchus mykiss*). Rainbow trout (*Oncorhynchus mykiss*) Juveniles			Study not eligible. Mixed exposure
Miranda et al. (1992). Differential effects of 3,4,5,3',4',5'-hexachlorobiphenyl (HCB) on interrenal steroidogenesis in male and female rainbow trout *Oncorhynchus mykiss*. Rainbow trout (*Oncorhyncus mykiss*) Adults (M and F)			Not a relevant endpoint
Palace et al. (1996). Mixed-function oxidase enzyme activity and oxidative stress in lake trout (*Salvelinus namaycush*) exposed to 3,3',4,4',5-pentachlorobiphenyl (PCB-126).			Not a relevant endpoint

Reference	Compounds Dosed regime	Parameters measured and measure of effect	NOAEL (or LOAEL)
Lake trout (*Salvelinus namaycush*) Juveniles			
Ait-Aissa et al. (2003). Biomarker responses in juvenile rainbow trout (*Oncorhynchus mykiss*) after single and combined exposure to low doses of cadmium, zinc, PCB77 and 17beta-oestradiol. Rainbow trout (*Oncorhynchus mykiss*) Juveniles			Single dose study. Endpoints not relevant.
Palace et al. (1997). Metabolism of H-3-retinol by lake trout (*Salvelinus namaycush*) pre-exposed to 3,3',4,4',5-pentachlorobiphenyl (PCB 126). Lake trout (*Salvelinus namaycush*)			Study not relevant.
Foster and Curtis (1999). 2,2',4,4',5,5'- and 3,3',4,4',5,5'-Hexachlorobiphenyl pretreatments alter the biliary excretion of a challenge dose of 7,12-(3H)dimethylbenz(a)anthracene in rainbow trout (*Oncorhyncus mykiss*). Rainbow trout (*Oncorhyncus mykiss*)			Co-adminsitration of PAHs. Study not eligible
Brown et al. (1998). Biochemical and histological responses in rainbow trout (*Oncorhynchus mykiss*) exposed to 2,3,4,7,8-pentachlorodibenzofuran. Rainbow trout (*Oncorhynchus mykiss*)			One dose group
Nault et al. (2102). Effects of polychlorinated biphenyls on whole animal energy mobilization and hepatic cellular respiration in rainbow trout, *Oncorhynchus mykiss.* Rainbow trout (*Oncorhynchus mykiss*)			One dose group
Vijayan et al. (1997). 3,3',4,4'-Tetrachlorobiphenyl affects cortisol dynamics and hepatic function in rainbow trout. Rainbow trout (*Oncorhynchus mykiss*)			One dose group
Gilbert et al. (1995). Retinoic acid hydroxylation in rainbow trout (*Oncorhynchus mykiss*) and the effect of a coplanar PCB, 3,3',4,4'-tetrachlorobiphenyl. Correction of title from Retinoic acid hydroxylation in rainbow trout (*Oncorhynchus mykiss*) and the effect of a coplanar PCP, 3,3',4,4'-tetrachlorobiphenyl.			One dose group. Not eligible parameters.

Reference	Compounds Dosed regime	Parameters measured and measure of effect	NOAEL (or LOAEL)
Rainbow trout (*Oncorhynchus mykiss*)			
Otto et al. (1997). Role of exogenous glutathione in teleost fish and its effects on antioxidant defense responses in rainbow trout exposed to 3,3 ',4,4 '-tetrachlorobiphenyl. Rainbow trout (*Oncorhyncus mykiss*)			One dose group. Endpoint not relevant.

Table 95. Studies on the adverse effects of PCDD/Fs and/or DL-PCBs in salmon

Reference	Comments
Miller et al. (1979). Response of coho salmon and guppies to 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) in water.	Waterborne exposure
Servizi et al. (1993). Effects of biotreated bleached kraft mill effluent on fingerling chinook salmon (*oncorhynchus-tshawytscha*).	Not relevant. Exposure to effluent (mixed exposure).
Asplund et al. (1999). Organohalogen substances in muscle, egg and blood from healthy Baltic salmon (*Salmo salar*) and Baltic salmon that produced offspring with the M74 syndrome.	Study not eligible. Mixed exposure
Stehr et al. (2000). Exposure of juvenile chinook and chum salmon to chemical contaminants in the Hylebos Waterway of Commencement Bay, Tacoma, Washington.	Study not eligible. Mixed exposure
Williams and Giesy (1992). Relationships among concentrations of individual polychlorinated biphenyl (PCB) congeners, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin equivalents (TCDD-EQ), and rearing mortality of chinook salmon (*Oncorhynchus-tshawytscha*) eggs from lake-michigan.	Study not eligible. Mixed exposure
Vuorinen et al. (2002). PCDD, PCDF, PCB and thiamine in Baltic herring (*Clupea harengus* L.) and sprat *Sprattus sprattus* (L.) as a background to the M74 syndrome of Baltic salmon (*Salmo salar* L.).	Study not eligible. Mixed exposure
Zitko and Choi (1973). Oral toxicity of chlorinated dibenzofurans to juvenile Atlantic salmon.	Study not eligible. Mixed exposure
Vuorinen et al. (1997). The M74 syndrome of Baltic salmon (*Salmo salar*) and organochlorine concentrations in the muscle of female salmon.	Study not eligible. Mixed exposure
Arukwe et al. (2001). *In vivo* modulation of nonylphenol-induced zonagenesis and vitellogenesis by the antiestrogen, 3,3 ' 4,4 '-tetrachlorobiphenyl (PCB-77) in juvenile fish.	One dose group

Table 96. Studies on the effects of PCDD/Fs and/or DL-PCBs in feeding trials with Atlantic salmon

Reference	Feeds and experimental design	Dose and effects	NOAEL (or LOAEL)
Berntssen et al. (2010b). Reducing persistent organic pollutants while maintaining long chain omega-3 fatty acid in farmed Atlantic salmon using decontaminated fish oils for an entire production cycle. **Lock et al. (2011)**. Dietary decontaminated fish oil has no negative impact on fish performance, flesh quality or production-related diseases in Atlantic salmon (*Salmo salar*).	Control diet (uncleaned fish oil, mixture of POPs), diet with clean oil Feed concentrations: Control: 0.29 ng/kg feed (1.5 ng PCDD/F/kg feed and 2.7 ng sum PCDD/F+DL-PCB/kg feed Clean: 0.064 ng TCDD/kg feed (0.4 ng PCDD/F/kg feed and 0.6 ng sum PCDD/F+DL-PCB/kg feed Feeding rate 0.076% bw/day. Four replicates of 200 fish/dietary treatment. Approx. 18 months exposure.	**Dose:** Control feed: 0.02 ng PCDD/F + DL-PCB_{2005} TEQ/kg bw/day Clean oil feed: 0.004 ng PCDD/F + DL-PCB_{2005} TEQ/kg bw/day Fish grew from 81 g to 4.9 kg Growth: no effects Feed conversion: no effects Mortality: none No significant changes were observed in production-related diseases (fin/skin erosion, bone deformity, cataracts) between treatments.	NOAEL=0.02 ng PCDD/F + DL-PCB_{2005} TEQ/kg bw/day (highest dose tested)
Berntssen et al. (2010a). Chemical contaminants in aquafeeds and Atlantic salmon (Salmo salar) following the use of traditional- versus alternative feed ingredients. **Torstensen et al. (2008)**. Novel production of Atlantic salmon (*Salmo salar*) protein based on combined replacement of fish meal and fish oil with plant meal and vegetable oil blends.	Control diet (fish meal and fish oil; mixture of POPs), diet with mainly plant oil and meal. Feed concentrations: Control: 0.27 ng/kg feed (2.2 ng PCDD/F/kg feed and 8.1 ng sum PCDD/F+DL-PCB/kg feed Clean: 0.04 ng TCDD/kg feed (0.25 ng PCDD/F/kg feed and 0.98 ng sum PCDD/F+DL-PCB/kg feed Feeding rate: overfeeding Triplicates of 500 fish/dietary treatment Approx. 12 months exposure	**Dose:** for calculation of dose the feeding rate used by Berntssen et al. (2010) was applied to this study: Control feed: 0.06 ng PCDD/F + DL-PCB_{2005} TEQ/kg bw/day Plant-based feed: 0.007 ng PCDD/F + DL-PCB_{2005} TEQ/kg bw/day Fish grew from 350 g to 3.9 kg (control fish) and to 3.3 kg (plant-fed fish) Growth: Significantly lower in plant-fed fish Mortality: negligible (<1% in both groups)	NOAEL=0.06 ng PCDD/F + DL-PCB_{2005} TEQ/kg bw/day (highest dose tested)
Olli et al. (2010). Removal of persistent organic pollutants from Atlantic salmon (*Salmo salar* L.) diets: Influence on growth, feed utilization efficiency and product quality.	Control diet (uncleaned fish oil), diet with clean oil. Mean feed concentrations: Control: 1.4 ng PCDD/F/kg feed and 2.8 ng sum PCDD/F+DL-PCB/kg feed Clean: 0.2 ng PCDD/F/kg feed and 0.5 ng sum PCDD/F+DL-PCB/kg feed.	**Dose:** for calculation of dose, the feeding rate used by Berntssen et al. (2010a) was applied to this study: Control feed: 0.02 ng PCDD/F + DL-PCB_{2005} TEQ/kg bw/day Clean oil feed: 0.004 ng PCDD/F + DL-PCB_{2005} TEQ/kg bw/day Fish grew from 65 g to 4.4 kg.	NOAEL=0.02 ng PCDD/F + DL-PCB_{2005} TEQ/kg bw/day (highest dose tested)

Reference	Feeds and experimental design	Dose and effects	NOAEL (or LOAEL)
	Feeding rate: 10% overfeeding. Four replicates of 300 fish/dietary treatment. Approx. 18 months exposure.	Growth: significantly increased in clean oil group in one of five time periods, not in the other four periods. No significant differences in nutrient digestibility or condition factor between treatments Mortality: none	

Table 97. Studies on the adverse effects of PCDD/Fs and/or DL-PCBs in sea bream, bass and sole

Reference	Compounds Dose regime	Parameters measured and measure of effect	NOAEL (or LOAEL)
Kleeman et al. (1998). Species differences in 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxicity and biotransformation in fish. Largemouth bass (*Micropterus salmoide*)	TCDD 0, 1, 5, 25, 125 µg/kg *i.p.*	**Lethality**: 80-day LD_{50} (median, 95 CI)=11 (9-14) µg/kg **Body weight gain**: no significant decrease compared to controls. **Fin necrosis:** observed at the two highest dose groups. Cutaneous hyperpigmentation observed.	NOAEL (fin necrosis): 5 µg/kg
Arellano et al. (2001). Histopathological alterations and induction of cytochrome P-450 1A in the liver and gills of the gilthead seabream (Sparus aurata) exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Gilthead sea bream (*Sparus aurata*)			Waterborne exposure
Calo et al. (2010). Estrogenic followed by anti-estrogenic effects of PCBs exposure in juvenil fish (*Spaurus aurata*). *Spaurus aurata*			Waterborne exposure. One dose group
Torre et al. (2015). Influence of titanium dioxide nanoparticles on 2,3,7,8-tetrachlorodibenzo-*p*-dioxin bioconcentration and toxicity in the marine fish European sea bass (Dicentrarchus labrax). Sea bass (*Dicentrarchus labrax*)			Waterborne exposure. Not a relevant study
Cannas et al. (2013). PCBs contamination does not alter aerobic metabolism and tolerance to hypoxia of juvenile sole (Solea solea L. 1758). Sole (*Solea solea*)			Mixed exposure, not relevant (Mix of 4 congeners (PCB-153, -149, 105, 118)
Houtman et al. (2007). Biomonitoring of estrogenic exposure and identification of responsible compounds in bream from Dutch surface waters. Bream (*Abramis brama*)			Mixed exposure, not relevant
Navas et al. (2005). Organochlorine compounds in liver and concentrations of vitellogenin and 17beta-estradiol in plasma of sea bass fed with a commercial or with a natural diet.			Mixed exposure, not relevant

Reference	Compounds Dose regime	Parameters measured and measure of effect	NOAEL (or LOAEL)
Sea bass (*Dicentrarchus labrax*)			
Greco et al. (2010). Bioaccumulation markers and biochemical responses in European sea bass (Dicentrarchus labrax) raised under different environmental conditions. Sea bass (*Dicentrarchus labrax*)			Mixed exposure, not relevant
Schnitzler (2008). Effects of persistent organic pollutants on the thyroid function of the European sea bass (*Dicentrarchus labrax*) from the Aegean sea, is it an endocrine disruption?. Sea bass (*Dicentrarchus labrax*)			Mixed exposure, not relevant
Schnitzler et al. (2012). Environmental factors affecting thyroid function of wild sea bass (Dicentrarchus labrax) from European coasts. Wild sea bass (*Dicentrarchus labrax*)			Mixed exposure, not relevant
Hinck et al. 2007. Chemical contaminants, health indicators, and reproductive biomarker responses in fish from the Colorado River and its tributaries. Largemouth bass (*Micropterus salmoides*)			Mixed exposure, not relevant
Hinck et al. 2008. Chemical contaminants, health indicators, and reproductive biomarker responses in fish from rivers in the Southeastern United States. *Sci Total Environ.* 2008. 390:538-57 Largemouth bass (*Micropterus salmoides*) Common carp (*Cyprinus carpio*)			Mixed exposure, not relevant
Hodson et al. 1992. Effects of bleached kraft mill effluent on fish in the St-Maurice river, Quebec. White suckers (*Cutostomus commersoni*)			Mixed exposure, not relevant
Martyniuk et al. (2009). Aquatic contaminants alter genes involved in neurotransmitter synthesis and gonadotropin release in largemouth bass. Largemouth bass (*Micropterus salmoides*)			Not a relevant endpoint
Vaccaro et al. (2005). Effects of 17 beta-estradiol, 4-nonylphenol and PCB 126			Not a relevant endpoint

Reference	Compounds Dose regime	Parameters measured and measure of effect	NOAEL (or LOAEL)
on the estrogenic activity and phase 1 and 2 biotransformation enzymes in male sea bass (Dicentrarchus labrax). Sea bass (*Dicentrarchus labrax*)			
Rankouhi et al. (2004). Effects of natural and synthetic estrogens and various environmental contaminants on vitellogenesis in fish primary hepatocytes: comparison of bream (*Abramis brama*) and carp (*Cyprinus carpio*). Sea bream (*Abramis brama*)			*In vitro* study only one dose; not a relevant study
Lauriano et al. (2012). Mast cells in the intestine and gills of the sea bream, *Sparus aurata*, exposed to a polychlorinated biphenyl, PCB 126. Sea bream (*Sparus aurata*)			*In vitro* exposure, only one dose; not a relevant study
Ábalos et al. (2008). Effects on growth and biochemical responses in juvenile gilthead seabream 'Sparus aurata' after long-term dietary exposure to low levels of dioxins. Gilthead sea bream (*Sparus aurata*)			Exposure to a mixture of PCDD/Fs at one dose, not relevant endpoints – only EROD induction was significant

Table 98. Studies on the adverse effects of PCDD/Fs and/or DL-PCBs in eel

Reference	Comments
Foekema et al. (2016). Maternally transferred dioxin-like compounds can affect the reproductive success of european eel.	Field exposure. TK modelling. Not relevant
Couderc et al. (2016). Thyroid endocrine status of wild European eels (*Anguilla anguilla*) in the Loire (France). Relationships with organic contaminant body burdens.	Field exposure
Geeraerts et al. (2011). Reproduction of European eel jeopardised by high levels of dioxins and dioxin-like PCBs?	Field exposure
Burroni et al. (2009). Persistent organic pollutants and enzyme activities in European eel (*Anguilla anguilla*) from Orbetello lagoon.	Field exposure
Oliver et al. (2015). Lipid increases in European eel (Anguilla anguilla) in Scotland 1986-2008: an assessment of physical parameters and the influence of organic pollutants.	Field exposure
Palstra et al. (2006). Are dioxin-like contaminants responsible for the eel (Anguilla anguilla) drama?	Field exposure
Nigro et al. (2002). Induction of DNA strand breakage and apoptosis in the eel *Anguilla anguilla*.	Not a relevant endpoint
Otto et al. (1997). Role of exogenous glutathione in teleost fish and its effects on antioxidant defense responses in rainbow trout exposed to 3,3 ',4,4 '-tetrachlorobiphenyl.	Single dose, and endpoints not relevant
Sures et al. (2006). Effects of infection with *Anguillicola crassus* and simultaneous exposure with Cd and 3,3',4,4',5-pentachlorobiphenyl (PCB 126) on the levels of cortisol and glucose in European eel (*Anguilla anguilla*).	One dose group only
Sures and Knopf (2004). Individual and combined effects of cadmium and 3,3',4,4',5-pentachlorobiphenyl (PCB 126) on the humoral immune response in European eel (*Anguilla anguilla*) experimentally infected with larvae of *Anguillicola crassus* (Nematoda).	One dose group only
van Ginneken et al. (2009). PCBs and the energy cost of migration in the European eel (*Anguilla anguilla* L.).	One dose group only

Table 99. Studies on the adverse effects of PCDD/Fs and/or DL-PCBs in sturgeon

Reference	Comments
Ndayibagira et al. (1995). Effects of 3,3',4,4'-tetrachlorobiphenyl on the dynamics of vitamin-a in brook trout (*Salvelinus-fontinalis*) and intestinal retinoid concentrations in lake sturgeon (*Acipenser-fulvescens*). Sturgeon (*Acipenser fulvescens*)	One dose group
Foster et al. (2001). Plasma androgen correlation, EROD induction, reduced, condition factor, and the occurrence of organochlorine pollutants in reproductively immature white sturgeon (*Acipenser transmontanus*) from the Columbia River, USA. White sturgeon (*Acipenser transmontanus*)	Field exposure
Koch et al. (2006). Elevated organochlorines in the brain-hypothalamic-pituitary complex of intersexual shovelnose sturgeon. Shovelnose sturgeon (*Scaphirhynchus platorynchus*)	Field exposure

Table 100. Studies on the adverse effects of PCDD/Fs and/or DL-PCBs in carp

Reference	Compounds Dose regime	Parameters measured and measures od effect	NOAEL (or LOAEL)
Van der weiden et al. (1994). Concurrence of P450-1A induction and toxic effects in the mirror carp (*Cyprinus-carpio*), after administration of a low-dose of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Carp (*Cyprinus carpio*) Juveniles	TCDD 0, 0.01, 0.03, 0.05, 0.27, 0.57, 2.93 µg/kg bw *i.p.* single Sampling 1, 3, 6 and 12 weeks after treatment	**Mortality**: 60 % between 6-12 weeks after administration of the highest dose. **Growth:** statistical decrease in body weight after 12 weeks in the highest dose group. **Pathology:** Cutaneous haemorrhages, apathetical behaviour, swollen gills, sunken eyes at doses of 0.27 µg/kg bw and higher after 3 weeks. Histopathological effects in spleen (increased number of erythrocytes and melano-macrophage centres) at 0.05 µg/kg and higher; data not statistically analysed. Significant decreases in haemoglobin and haematocrit at the highest dose, and significant increase in spleen and kidney weight at this dose after 12 weeks.	NOAEL=0.57 µg/kg bw (growth, organ weight, Hb, Ht)
Kleeman et al. (1998). Species differences in 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxicity and biotransformation in fish. Carp (*Cyprinus carpio*)	TCDD 0, 1, 5, 25, 125 µg/kg *i.p.*	**Lethality**: 80-day LD_{50} (median, 95 CI) = 3 (2-4) µg/kg **Body weight gain**: non significant decrease. **Fin necrosis:** observed at the two highest dose groups. Cutaneous hyperpigmentation evident at the lowest dose (1 µg/kg) and further graded increases in pigmentation with increasing dose.	NOAEL (fin necrosis)= 5 µg/kg bw
Van der weiden et al. (1989). Bioavailability of PCDDs and PCDFs from bottom sediments and some associated biological effects in the carp (*cyprinus-carpio*).			Mixed exposure, not relevant.
Bervoets (2009). Bioaccumulation of micropollutants and biomarker responses in caged carp (*Cyprinus carpio*).			Field exposure
Svobodova et al. (1996). Ontogenetic characterization of young carp (*Cyprinus carpio*) obtained by artificial reproduction of parental fishes loaded with PCB residues.			Field exposure
Xu et al. (2002). Endocrine effects of sublethal exposure to persistent organic pollutants (POPS) on silver carp (*Hypophthalmichthys molitrix*).			Field exposure
Van der weiden et al. (1993). Cytochrome-P450-1A induction in the common carp (*cyprinus-carpio*) following exposure to contaminated sediments with halogenated polyaromatics.			Sediment from the field, mixed exposure

Reference	Compounds Dose regime	Parameters measured and measures od effect	NOAEL (or LOAEL)
Hinck et al. 2007. Chemical contaminants, health indicators, and reproductive biomarker responses in fish from the Colorado River and its tributaries.			Field exposure
Hinck et al. 2008. Chemical contaminants, health indicators, and reproductive biomarker responses in fish from rivers in the Southeastern United States.			Field exposure
Rankouhi et al. (2004). Effects of natural and synthetic estrogens and various environmental contaminants on vitellogenesis in fish primary hepatocytes: comparison of bream (*Abramis brama*) and carp (*Cyprinus carpio*).			*in vitro* study, not relevant

Table 101. Studies on the adverse effects of PCDD/Fs and/or DL-PCBs in tilapia

Reference	Compounds Dose regime	Endpoint health category	NOAEL (or LOAEL)
Hart et al. (1999). Leukocyte hypocellularity in the spleen and pronephros of tilapia (*Oreochromis niloticus*) exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) may result from antiproliferative effects and enhanced apoptosis.	TCDD 0, 1, 5 µg/kg/day *i.p.* For 5 days	**Splenic and Pronephric Cellularity:** Significant reductionin splenic and pronephric cellularity at 5 µg/kg. **Histopathology**: lymphoid depletion observed at the highest dose group	NOAEL=1 µg/kg/day
Quabius et al. (2000). Influence of dietary exposure to polychlorinated biphenyl 126 and nutritional state on stress response in tilapia (*Oreochromis mossambicus*) and rainbow trout (*Oncorhynchus mykiss*).	PCB-126 Low dose: 25 mg/kg food/day (equal to 0.5 mg/kg fish/day) High dose: 2,500 mg/kg food/day (equal to 50 mg/kg fish/day) Control food Oral (feed)	**Mortality**: no mortality. **Behavior**: no changes observed. **Food consumption**: no changes observed. **Resting plasma ACTH and cortisol levels**: not affected by treatment. **Resting plasma glucose**: affected only in fish sampled at the end of the starvation period (high-dose only). Confinement in fish sampled either before or after starvation led to significant increases in all parameters investigated. **Morphometric analysis**: reduced nuclear area of starved fish sampled at rest, and only at the highest dose.	
Adeogun et al. (2016). Intersex and alterations in reproductive development of a cichlid, Tilapia guineensis, from a municipal domestic water supply lake (Eleyele) in Southwestern Nigeria.			Field exposure
Quabius et al. (1997). Interrenal stress responsiveness of tilapia (Oreochromis mossambicus) is impaired by dietary exposure to PCB 126.			One dose group

Table 102. Studies on the adverse effects of PCDD/Fs and/or DL-PCBs in other fish species

Reference	Compounds Dose regime	Endpoint(s)	NOAEL (or LOAEL)
Regala et al. (2001). The effects of tributyltin (TBT) and 3,3',4,4',5-pentachlorobiphenyl (PCB-126) mixtures on antibody responses and phagocyte oxidative burst activity in channel catfish, Ictalurus punctatus. Catfish (*Ictalurus punctatus*)	PCB-126 Acute: *i.p.* single 0, 0.01, 1 mg/kg Repeated: 0, 1.7, 170 µg/kg. Every 3 days over 16 days to yield a cumulative dose of 0.01 or 1 mg/kg.	**Antibody response**: Acute: the highest dose resulted in lower antibody response. Repeated: no effect.	
Kleeman et al. (1998). Species differences in 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxicity and biotransformation in fish. Yellow perch (*Perca fluvialis*) Bullhead (*Ictalurus melas*)	TCDD 0, 1, 5, 25, 125 µg/kg *i.p.*	**Lethality**: 80-day LD_{50} (median, 95 CI) for: Yellow perch: 3 (2-4) µg/kg Bullhead: 5 (4-8) µg/kg **Body weight gain**: Yellow perch: significant decrease at 5 µg/kg. Bullhead: non significant decrease. **Fin necrosis:** Yellow perch: observed at the two highest dose groups. Cutenous homorrhages. Bullhead: observed at the two highest dose groups. No cutaneous homorrhages.	NOAEL: Yellow perch: 1 µg/kg (growth) Bullhead: 5 µg/kg (fin necrosis)
Hutchinson et al. (1999). Evaluation of immune function in juvenile turbot *Scophthalmus maximus* (L.) exposed to sediments contaminated with polychlorinated biphenyls. Turbot (*Scophthalmus maximus*)			Field exposure
Bussolaro et al. (2012). Bioaccumulation and related effects of PCBs and organochlorinated pesticides in freshwater fish *Hypostomus commersoni*. Catfish (*Hypostomus commersoni)*			Field exposure
Hinck et al. 2007. Chemical contaminants, health indicators, and reproductive biomarker responses in fish from the Colorado River and its tributaries.			Field exposure

Reference	Compounds Dose regime	Endpoint(s)	NOAEL (or LOAEL)
Channel catfish (*Ictalurus punctatus*)			
Maisano et al. (2016). PCB and OCP accumulation and evidence of hepatic alteration in the Atlantic bluefin tuna, T. thynnus, from the Mediterranean Sea. Atlantic bluefin tuna (*Thunnus thynnus*)			Field exposure
4503 - **Whittle et al. (1992).** Foodchain accumulation of PCDD and PCDF isomers in the great-lakes aquatic community. Alewife, Asmelt, Aculpin			Field exposure
Maier et al. (2015). Biological plausibility as a tool to associate analytical data for micropollutants and effect potentials in wastewater, surface water, and sediments with effects in fishes. Chub (*Leuciscus cephalus*)			Mixed exposure

Table 103. Studies on the adverse effects of PCDD/Fs and/or DL-PCBs in several fish species administered *in ovo* (more than one dose group studies)

Reference	Compounds Dose regime	Endpoint(s)	Comments
Carvalho and Tillitt (2004). 2,3,7,8-TCDD effects on visual structure and function in swim-up rainbow trout. Rainbow trout	TCDD 0, 38, 113, 300 pg/g egg	Visual/motor function	
Carvalho et al. (2004). Intra-strain dioxin sensitivity and morphometric effects in swim-up rainbow trout (*Oncorhynchus mykiss*). Rainbow trout (*Oncorhynchus mykiss*)	TCDD 0, 38, 113, 200, 300, 500, 1,000 pg/g egg	Mortality, yolk-sac edema, morphometric measures.	
Hornung et al. (1999). 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin alters cardiovascular and craniofacial development and function in sac fry of rainbow trout (*Oncorhynchus mykiss*). Rainbow trout (*Oncorhynchus mykiss*)	TCDD 0, 385, 640 pg/g egg	Reproductive effects, cardiovascular effects, musculoskeletal, bone, mortality, craniofacial development	
Zabel et al. (1995a). Toxic equivalency factors of polychlorinated dibenzo-*p*-dioxin, dibenzofuran and biphenyl congeners based on early-life stage mortality in rainbow-trout (*Oncorhynchus mykiss*). Rainbow trout (*Oncorhynchus mykiss*)	TCDD, 12378-PeCDD, 123478-HxCDD, 1234678-HpCDD TCDF, 23478-PeCDF PCB-77, -126, -105, -118 Exact dosing not clear to me Injection	Reproductive effects, fry sac mortality	Acute toxicity
Zabel et al. (1995b). Interactions of polychlorinated dibenzo-*p*-dioxin, dibenzofuran, and biphenyl congeners for producing rainbow trout early life stage mortality. Rainbow trout	Individual PCDD/Fs and DL-PCBs Combined exposure to pairs of congeners Injection	Reproductive effects, early life stage mortality	Acute toxicity
Walker et al. (1992). An egg injection method for assessing early life stage mortality of polychlorinated dibenzo-para-dioxins, dibenzofurans, and biphenyls in rainbow-trout (*Oncorhynchus mykiss*).	TCDD Injection: 0, 194, 291, 437, 656, 983 pg/g egg	Reproductive effects, mortality, LD50	

Reference	Compounds Dose regime	Endpoint(s)	Comments
Rainbow trout (*Oncorhynchus mykiss*)			
Helder (1981). Effects of 2,3,7,8-tetrachlorodibenzo-dioxin (TCDD) on early life stages of rainbow trout (*Salmo gairdneri*, Richardson). Rainbow trout	TCDD Different experiments: (i) eggs (ii) newly hatch fry Aquatic exposure	Growth retardation, mortality	Aquatic exposure
Akerman et al. (1998). Studies with oxythiamine to mimic reproduction disorders among fish early life stages. Sea trout (*Salmo trutta*), rainbow trout (*Oncorhynchus mykiss*)	PCB-77 0, 0.5, 5.0, 50 µg/kgcontrolled exposure	Reproductive effects, deformities	Mixed exposure – not relevant
Ishaq et al (1999). Organic pollutant characterization and toxicity testing of settling particulate matter by nanoinjection in sea trout (*Salmo trutta*) eggs. Trout (*Salmo trutta*)	Individual PCDD/Fs and DL-PCBs, TEQs by bioassay Extract of settling particulate matter – exposure to the fraction containing PCDDs, PCDFS, and other planar compounds.	Reproductive effects, deformities at hatching, larval stages and on the basis of larvae mortality	Mixed exposure – not relevant
Wright and Tillitt (1999). Embryotoxicity of Great Lakes lake trout extracts to developing rainbow trout. Trout	TEQs (bioassay) Exposure to lake trout extracts Lake Michigan lake trout extract: 0, 0.02, 0.10, 0.20, 1.0, 2.0, 4.0, 10.0, 20.0 eggEQ/g egg Lake Superior lake trout extract: 0, 0.02, 2.0, 20.0 eggEQ/g egg	Reproductive effects, mortality, gross pathological lesions	Mixed exposure – not relevant
Mac and Edsall (1991). Environmental contaminants and the reproductive success of lake trout in the Great Lakes: an epidemiological approach. Lake trout	PCB-77 Field exposure	Reproductive effects, swim-up mortality	Exposure route not relevant
Guiney et al. (2000). Hemodynamic dysfunction and	TCDD	Mortality, yolk-sac edema	Aquatic

Reference	Compounds Dose regime	Endpoint(s)	Comments
cytochrome P4501A mRNA expression induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin during embryonic stages of lake trout development. Lake trout	Nominal water concentration of [^{3}H]TCDD ranged from 3 to 100 ppt (ng/L water): 0, 60, 110, 170 ppt Waterborne exposure		exposure
Zabel et al. (1995c). Potency of 3,3',4,4',5-pentachlorobiphenyl (PCB-126), alone and in combination witH 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), to produce lake trout early life-stage mortality. Lake trout	TCDD, PCB-126 TCDD: 0, 10, 17, 22, 43, 72, 110, 425 pg/g] PCB-126: 141, 13200, 27200, 34600, 39000, 102000 pg/g Waterborne exposure	Reproductive effects, cardiovascular effects, musculoskeletal, bone, mortality	Aquatic exposure
Guiney et al. (1996). Assessment of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin induced sac fry mortality in lake trout (*Salvelinus namaycush*) from different regions of the Great Lakes. Lake trout (*Salvelinus namaycush*)	Lake Ontario eggs: [^{3}H]TCDD: 0, 2, 4, 6, 8, 10, 15, 20, 30, 40, 60, 80, 100, 120, 150 ng/L water Lake Superior eggs: [^{3}H]TCDD: 10, 20, 40, 62, 100 ng/L water Aquatic exposure	Reproductive effects, sac fry mortality	Aquatic exposure
Walker et al. (1994). Translocation of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin from adult female lake trout (*Salvelinus namaycush*) to oocytes - effects on early-life stage development and sac fry survival. Lake trout (*Salvelinus namaycush*)	TCDD Total amounts (11 weeks) provided for the duration of the study: - Tank A: 25.1 µg (4.6 µg from feed, 20.5 µg from minnows) - Tank B: 22.8 µg (15.3 µg from feed, 7.5 µg from minnows) - Tank C: 62.2 µg (46.2 µg from	Reproductive effects	Aquatic exposure

Reference	Compounds Dose regime	Endpoint(s)	Comments
	feed, 16.0 µg from minnows) Waterborne exposure		
Iida et al. (2014). Transient suppression of AHR activity in early red seabream embryos does not prevent the disruption of peripheral nerve projection by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Sea bream	TCDD 0.1, 1.7, 12 g/L [0.3, 5.3, 37 n] Waterborne exposure	Reproductive effects, neurotoxicity, hatchability, mortality	Aquatic exposure
Ortiz-Delgado and Sarasquete (2004). Toxicity, histopathological alterations and immunohistochemical CYP1A induction in the early life stages of the seabream, *Sparus aurata*, following waterborne exposure to B(a)P and TCDD. Sea bream (*Sparus aurata*)	TCDD 0.025, 0.05, 0.1, 1.5, 5 pg/L Waterborne exposure	Histopathological analysis, hatching	Aquatic exposure
Yamauchi et al. (2006). Toxic effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in developing red seabream (*Pagrus major*) embryo: An association of morphological deformities with AHR1, AHR2 and CYP1A expressions. Red seabream (*Pagrus major*)	TCDD 3.1, 6.2, 12.5, 25, 50, 100 g/L Waterborne exposure	Mortality, yolk sac edema, body growth, others	Aquatic exposure
Arukwe et al. (2014). Effects on Development, Growth Responses and Thyroid-Hormone Systems in Eyed-Eggs and Yolk-Sac Larvae of Atlantic Salmon (*Salmo salar*) Continuously Exposed to 3,3 ',4,4 '-Tetrachlorobiphenyl (PCB-77). Atlantic salmon (*Salmo salar*)	PCB-77 0, 1, 10 ng/L Waterborne exposure	Metabolic effects (thyroid function), development, growth,	Aquatic exposure
Olufsen and Arukwe (2011). Developmental effects related to angiogenesis and osteogenic differentiation in Salmon larvae continuously exposed to dioxin-like 3,3',4,4'-tetrachlorobiphenyl (congener 77). Salmon	PCB-77 0, 1, 10 ng/L Waterborne exposure	Cardiovascular effects, musculoskeletal, bone, growth, survival	Aquatic exposure

Reference	Compounds Dose regime	Endpoint(s)	Comments
Foekema et al. (2014). Internal effect concentrations of organic substances for early life development of egg-exposed fish. Sole	PCB-126 0.003, 0.01, 0.03 µg/L	Reproductive effects, mortality and disrupted development	Aquatic exposure
Buckler et al. (2015). Sensitivity of shovelnose sturgeon (*Scaphirhynchus platorynchus*) and pallid sturgeon (*S. albus*) early life stages to 3,3',4,4',5-pentachlorobiphenyl and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin exposure. Sturgeon	TCDD PCB-126 Pallid sturgeon: 0, 60, 194, 383, 671 ng/g egg Shovelnose sturgeon: 2, 87, 213, 1145, 1711 ng/g egg Waterborne exposure	Reproductive effects, develop and morphological effects, mortality	Aquatic exposure

Table 104. Studies on the adverse effects of PCDD/Fs and/or DL-PCBs in poultry *in ovo* (one dose group studies).

Reference	Compounds	Dosing
Fujisawa et al. (2014). TCDD-induced chick cardiotoxicity is abolished by a selective cyclooxygenase-2 (COX-2) inhibitor NS398.	TCDD	50 pmol TCDD / egg
Ivnitski-Steele et al. (2004). 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin reduces myocardial hypoxia and vascular endothelial growth factor expression during chick embryo development.	TCDD	0, 0.24 pmol/g egg on GD0
Ivnitski-Steele and Walker (2003). Vascular endothelial growth factor rescues 2,3,7,8-tetrachlorodibenzo-*p*-dioxin inhibition of coronary vasculogenesis.	TCDD	0, 0.3 pmol/g on GD0
Janz and Bellward (1996a). *In ovo* 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure in three avian species .1. Effects on thyroid hormones and growth during the perinatal period.	TCDD	0, 0.1 µg/kg on E4.5
Janz and Bellward (1996b). *In ovo* 2,3,7,8-tetrachlorodibenzo-*p*-dioxin exposure in three avian species .2. Effects on estrogen receptor and plasma sex steroid hormones during the perinatal period.	TCDD	0, 0.1 µg/kg on E4.5
Walker et al. (1997). Expression of the aryl hydrocarbon receptor (AhR) and AhR nuclear translocator during chick cardiogenesis is consistent with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-induced heart defects.	TCDD	0, 1.0 pmol/g egg prior to incubation
Yeager et al. (2006d). 670 nanometer light treatment attenuates dioxin toxicity in the developing chick embryo.	TCDD	0, 200 ppt on E0
Blankenship et al. (2003). Mechanisms of TCDD-induced abnormalities and embryo lethality in white leghorn chickens.	TCDD	0, 150 pg/g egg
Bruggeman et al. (2006). Effect of a single *in ovo* injection of 2,3,7,8-tetra-chlorodibenzo-*p*-dioxin on protein expression in liver and ovary of the one-day-old chick analyzed by fluorescent two-dimensional difference gel electrophoresis and mass spectrometry.	TCDD	0, 20 ng/egg on ED0
Kanzawa et al. (2004). Biochemical and molecular biological analysis of different responses to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in chick embryo heart and liver. *Archives of Biochemistry and Biophysics.* 2004. 427:58-67	TCDD	0, 1.0 pmol/g egg
Hilscherova et al. (2003). Oxidative stress in liver and brain of the hatchling chicken (*Gallus domesticus*) following *in ovo* injection with TCDD.	TCDD	0, 150 pg/g egg
Stanton et al. (2003). Fatty acid metabolism in neonatal chickens (*Gallus domesticus*) treated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) or 3,3 ',4,4 ',5-pentachlorobiphenyl (PCB-126) *in ovo*.	TCDD PCB-126	TCDD: 0, 0.2 mg/kg egg PCB-126: 0, 1.0 mg/kg egg
Katynski et al. (2004). 3,3 ',4,4 ',5-Pentachlorobiphenyl (PCB 126) impacts hepatic lipid peroxidation, membrane fluidity and beta-adrenoceptor kinetics in chick embryos.	PCB-126	0, 1.6 µg/kg
Roelens et al. (2005). The dioxin-like PCB 77 but not the ortho-substituted PCB 153 interferes with chicken embryo thyroid hormone homeostasis and delays hatching.	PCB-77	Experiment 1: 1 µg + PCB153 Experiment 2: 0, 1 µg
Beck et al. (2006). Exposure to PCB 77 induces tissue-dependent changes in iodothyronine deiodinase activity patterns in the embryonic chicken.	PCB-77	1 µg on day 4 of incubation

A.11.7. Studies in cats and dogs

Table 105. Studies identified on the adverse effects of PCDD/Fs and/or DL-PCBs in cats and/or dogs

Reference	Compounds	Endpoint(s)	Comments
Schwetz et al. (1973). Toxicology of chlorinated dibenzo-*p*-dioxins. Dog (Beagle) (M and F, two of each)	TCDD 0.3, 3 mg/kg Oral	**Lethality**: (n death/n treated) M: At 0.3 mg/kg: 0/2 At 3 mg/kg: 2/2 F: At 0.03 mg/kg: 0/2 At 0.33 mg/kg: 0/2	NOEL = 0.3 mg/kg/bw There is insufficient information provided to be used in the risk assessment. *Study not useful for the risk assessment*
Kimbrough et al. (1977). Epidemiology and pathology of a tetrachlorodibenzodioxin poisoning episode. Cats	PCDD/Fs? *Case report*	Autopsies of 2 cats: Severe emaciation, skin lesions, alopecia, edema, ascites. Adipose tissue was absent. Liver: degeneration of liver cells. Fibrosis in the periphery of the lobules, proliferation of bile ducts, enlarged Kupffer cells, pleomorphic hepatocytes. Atrophic spleen. Degenerative changes in the kidneys. Interstitial fibrosis and acute focal interstitial nephritis (in one cat).	*Study not suitable for the risk assessment*

A.11.8. Studies in fur animals

Table 106. Studies on the effects of the target compounds in mink: studies with animal feed supplemented with pre-designed concentrations of PCDD/Fs and/or DL-PCBs

Reference	Compounds Dose Regime	Results	NOAEL (or LOAEL)
Aulerich et al. (1985). Toxicological manifestations of 2,4,5,-2′,4′,5'-, 2,3,6,2′,3′,6'-, and 3,4,5,3′,4′,5'-hexachlorobiphenyl and Aroclor 1254 in mink.	PCB-169 *Reproductive study* Mink (n=90, F) were fed diets that contained PCB-169 at 0, 0.1 or 0.5 mg/kg feed from 1 month prior to breeding through parturition	All mink fed 0.5 mg/kg feed PCB-169 died within 60 days, while those fed 0.1 mg/kg feed (300 ng WHO_{2005}TEQ/kg bw/day) showed 50% mortality after 3 months of exposure (control: 0%)	Based on mortality, LOAEL=300 ng WHO_{2005}-TEQ/kg bw/day
Aulerich et al. (1987). Toxicity of 3,4,5,3' ,4' ,5'-Hexachlorobiphenyl to mink.	PCB-169 *Sub-chronic study* Mink (n=50, F) were fed diets supplemented with PCB-169 at 0.05 or 0.01 mg/kg feed	In the 0.05 mg/kg feed group, 50% (5/10) of the minks died (in pair-fed and ad-libitum controls, 20% and in 0.01 mg/kg feed, 0%). At 0.01 mg/kg feed, liver, kidney and adrenal weights were increased and serum concentrations of T3 and free T3 decreased.	Based on changes in organ weights and thyroid hormone levels, LOAEL=0.01 mg/kg feed, corresponding to 30 ng WHO_{2005}-TEQ/kg bw per day
Aulerich et al. (1988). Biological Effects of Epidermal Growth Factor and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on developmental parameters of neonatal mink.	TCDD *Post-natal developmental study* Newborn mink (n=82, M, F) were administered TCDD at 0.1 or 1 µg/kg bw/day by *i.p.* injection for 12 consecutive days	The higher dose of TCDD caused mortality (>50%) while the lower one reduced body weight gain	Based on retarded growth, LOAEL=100 ng TCDD/kg bw/day
Hochstein et al. (1988). Acute toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin to mink.	TCDD *Acute study* Mink (n=16, M) were administered TCDD once *p.o.* at 0, 2.5, 5.0, or 7.5 µg/kg bw. Minks were observed for 28 days	Body weight decreased significantly vs. control already at the lowest dose.	Based on decreased body weight, LOAEL=2.5 µg TCDD/kg bw
Hochstein et al. (1998). Effects of Dietary Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Adult Female Mink	TCDD *Sub-chronic study* Adult mink (n=56, F) distributed among six dietary concentrations of TCDD (8 mink/group) at 0, 1, 10,	Band (immature) neutrophils significantly greater (without a clear dose-response) in all TCDD treatment groups relative to controls, suggesting low-grade inflammation. However, no change in mature (segmented) or total neutrophils.	Based on mortality and body weight loss: NOAEL=100 ng/kg feed, corresponding to 5.5 ng

Reference	Compounds Dose Regime	Results	NOAEL (or LOAEL)
(*Mustela vison*).	100, 1,000, 10,000 and 100,000 ng/kg feed. Mink fed the diets for up to 125 days.	Mink in all groups, including control, lost body weight during 18 week exposure period, with some surviving animals losing more than 30% of initial weight (final body weight was significantly decreased in survivors of the 1,000 ng/kg group). Significant mortality in the 1,000, 10,000 and 100,000 ng/kg groups (62.5, 100 and 100%, respectively, by day 125). Cortisol and thyroid hormone concentrations altered in treated mink at dose levels of 10 and 100 ng/kg surviving to study termination, but not in a statistically significantly manner. However, a general dose-dependent upward tendency in plasma T4, free T4 and free T3 and a downward tendency in plasma cortisol.	TCDD/kg bw per day
159 - **Hochstein et al. (2001)**. Chronic toxicity of dietary 2,3,7,8-TCDD to mink.	TCDD *Reproductive study* Adult mink (n=60, F) administered diets containing TCDD at 0.6 (control), 16, 53, 180, or 1,400 ng/kg feed for 131-132 days. Exposed F mink mated with unexposed M on days 35-64 following start of TCDD treatment.	Mating and reproduction: no F mink in 16 or 1,400 ng/kg feed groups whelped. Also control whelping rate poor (5/12). At euthanasia, evidence of resorbed foetuses in uteri of two F mink from highest dose group (1,400 ng/kg feed). In groups where kits were whelped, a decrease in kit body weights at 180 ng/kg feed at birth, but not at 3 or 6 weeks. Three-week survival rates for control, 53 and 180 ng/kg feed groups were 83%, 47% and 11%, respectively. Kits that survived to 6 weeks of age appeared normal. Statistically significant dose-dependent decrease in F1 serum total solids and white blood cell count identified in 180 and 1,400 ng/kg feed groups, relative to controls. In serum, iron concentration decreased and total carbon dioxide level increased in all groups.	Based on clinical chemistry findings, LOAEL=16 ng/kg feed, corresponding to 1.6 ng TCDD/kg bw per day
Beckett et al. (2008). The effects of PCB 126 on mink (*Mustela vison*) reproduction and kit survivability and growth.	PCB-126 WHO_{2005}-TEQs *Reproductive study* Mink (n=28, F) administered 0, 0.24, 2.4, and 24 µg PCB-126/kg feed from 21 days prior to breeding until weaning of kits at six weeks of age, corresponding to 0, 24, 240, 2,400 ng WHO_{2005}-TEQ/kg feed.	No significant differences in number of F mink that whelped or average litter size between control group and 24 ng WHO_{2005}-TEQ/kg feed group. F mink at two highest dose groups (240 and 2,400 ng WHO_{2005}-TEQ/kg feed) that had confirmed matings, failed to whelp and fetal implantation sites or placental scars, indicating partial fetal development, were identified by histological examination of their uterine horns.	Based on fertility outcome, NOAEL=24 ng WHO_{2005}-TEQ/kg feed, corresponding to 2.4 ng WHO_{2005}-TEQ/kg bw per day

Reference	Compounds Dose Regime	Results	NOAEL (or LOAEL)
Moore et al. (2009). Hepatic P450 Enzyme Activity, Tissue Morphology and Histology of Mink (*Mustela vison*) Exposed to Polychlorinated Dibenzofurans.	TCDF, 2,3,4,5,7,8-PeCDF WHO_{2005}-TEQs *Sub-chronic study* Mink (n=50, F) were distributed among 8 treatments groups (6 mink in each of the 7 dosed groups, and 8 mink in the control group) being exposed (in feed) to: TCDF: 0.98, 3.8, 20 ng WHO_{2005}-TEQ/kg bw/day PeCDF: 0.62, 2.2, 9.5 ng WHO_{2005}-TEQ/kg bw/day TCDF/PeCDF mixture: 4.1 ng WHO_{2005}-TEQ/kg bw/day (TCDF) 2.8 ng WHO_{2005}-TEQ/kg bw/day (PeCDF)	No statistically significant treatment related changes in gross morphology or histology (jaws, liver, kidney, spleen), although fatty liver was only detected in (a few) exposed mink). Hepatic EROD activity increased at all PeCDF doses, at two highest TCDF doses, and by mixture. No morphological changes could be linked to exposures.	Based on morphological changes, NOAEL for TCDF=20 ng WHO_{2005}-TEQ/kg bw per day NOAEL for PeCDF=9.5 ng WHO_{2005}-TEQ/kg bw per day
Moore et al. (2012). Effects of dietary exposure of mink (*Mustela vison*) to 2,3,7,8-TCDD, 2,3,4,7,8-PeCDF, and 2,3,7,8-TCDF on reproduction and offspring viability and growth.	TCDD, TCDF, 2,3,4,7,8-PeCDF WHO_{2005}-TEQs *Reproductive study* Mink (n=117, F) received targeted dietary concentrations of TCDD, PeCDF and TCDF in feed (9 mink/group) corresponding to (ng WHO_{2005}-TEQ/kg feed): TCDD: 23, 53, 77, 101 TCDF: 68, 146, 240, 287 PeCDF: 50, 86, 109, 186 (ng WHO_{2005}-TEQ/kg bw per day): TCDD: 2.1, 4.6, 6.0, 8.4 TCDF: 5.2, 12, 21, 25 PeCDF: 4.0, 7.6, 9.0, 15 Adult F mink exposed for 5-6 months. Kits exposed *in utero* and via lactation until weaning; some kits additionally through the age of 27 weeks via lactation and diet.	No significant effects on reproductive performance. In 27-week-old male mink, relative liver size increased at the highest doses of PeCDF and TCDF while relative spleen and adrenal weights increased at the highest dose of TCDD (but were not accompanied by histopathological changes). Liver, heart and thyroid mineralization increased at 25 ng WHO_{2005}-TEQ/kg bw/day of TCDF.	Based on tissue morphology in mink treated with TCDF, NOAEL=240 ng WHO_{2005}-TEQ/kg feed, corresponding to 21 ng WHO_{2005}-TEQ/kg bw per day
Bursian et al. (2012). Incidence of jaw lesions and activity and gene expression of hepatic	TCDD, TCDF, 2,3,4,7,8-PeCDF WHO_{2005}-TEQs *Reproductive study*	Histopathological assessment of the mandible and maxilla of 27-week-old juvenile mink indicated the presence of jaw lesions (gingival epithelial proliferation and cysts) in mink exposed to TCDD, TCDF, or PeCDF.	Based on jaw lesions in mink treated with TCDD, NOAEL=2.1 ng TCDD/kg

Reference	Compounds Dose Regime	Results	NOAEL (or LOAEL)
P4501A enzymes in mink (*Mustela vison*) exposed to dietary 2,3,7,8-TCDD, 2,3,7,8-TCDF, and 2,3,4,7,8-PeCDF.	Mink (n=117, F) received targeted dietary concentrations of TCDD, PeCDF or TCDF in feed (9 mink/group) corresponding to (ng WHO_{2005}-TEQ/kg feed): TCDD: 23, 53, 77, 101 TCDF: 68, 146, 240, 287 PeCDF: 50, 86, 109, 186 (ng WHO_{2005}-TEQ/kg bw per day): TCDD: 2.1, 4.6, 6.0, 8.4 TCDF: 5.2, 12, 21, 25 PeCDF: 4.0, 7.6, 9.0, 15 Adult F mink were exposed for 5-6 months. Kits exposed *in utero* and via lactation until weaning. Some kits additionally through the age of the 27 weeks via diet.	Jaw lesion severity was predominantly mild to moderate, expect for one animal at the highest PeCDF dose (15 ng WHO-TEQ/kg bw per day) whose lesion score was severe. Jaw lesions occurred dose-dependently in all other groups except for control and the lowest TCDD treatment group.	bw/day (LOAELs for TCDF and 2,3,4,7,8-PeCDF: 5.2 and 4.0 ng WHO_{2005}-TEQ/kg bw/day, respectively)

F: female; M: male.

Table 107. Studies on the effects of the target compounds in mink: feeding studies with fish contaminated with PCDD/Fs, DL-PCBs and other pollutants

Reference	Compounds Dose Regime	Results	NOAEL (or LOAEL)
Heaton et al. (1995a). Dietary exposure of mink to carp from Saginaw Bay, Michigan. 1. Effects on reproduction and survival, and the potential risks to wild mink populations.	BEQs (bioassay) *Reproductive study* Mink (n=60, M, F) were randomly assigned to five treatment groups (15 animals per group) fed diets containing carp at 0.015 (control), 0.72, 1.53, and 2.56 mg PCBs/kg diet, or 1, 19, 40 and 81 ng BEQ/kg diet. Animals were fed on these diets prior to and throughout the reproductive period (182 days in total). The total BEQs ingested by the mink over the treatment period were 23, 360, 660, and 1,000 ng BEQ/mink, respectively.	Gestation length was shortened in all three treatment groups. The weight of kits was reduced at the highest dose at birth and at all doses at 3 and 6 weeks. F mink fed the highest dose whelped the fewest number of kits, all of which were stillborn or died within 24 hours. A number of relative organ weights were altered in adult and/or kit mink in all treatment groups.	Based on adverse effects on gestation length, kit survival and growth rate as well as relative organ weights, LOAEL=19 ng BEQ/kg diet, corresponding to 3.6 ng BEQ/kg bw/day
Heaton et al. (1995b). Dietary exposure of mink to carp from Saginaw Bay, Michigan: 2. Hematology and liver pathology.	BEQs (bioassay) *Sub-chronic study* Mink (n=60, M, F) were randomly assigned to five treatment groups (15 animals per group) fed diets containing carp at 0.015 (control), 0.72, 1.53, and 2.56 mg PCBs/kg diet, or 0, 1.0, 19, 40 and 81 ng BEQ/kg diet. Animals were fed on these diets prior to and throughout the reproductive period (182 days in total). The total BEQs ingested by the mink over the treatment period were 23, 360, 660, and 1,000 ng BEQ/mink, respectively.	Treated mink showed a general dose-dependent occurrence of listlessness, nervousness when approached, anorexia, and melena. Erythrocyte counts were lower in all mink exposed to the diets compared to controls, while the number of white blood cells was larger than in controls. Significant differences ($p<0.05$) in the concentrations of neutrophils, lymphocytes, monocytes, and eosinophils were observed between the control and carp-fed groups. Haematocrit values for the mink fed the two highest dose groups were significantly lower than in controls and the lowest dose group.	Based on haematological changes, LOAEL was the same as in the previous study
Restum et al. (1998). Multigenerational study of the effects of consumption of PCB-contaminated carp from Saginaw Bay, Lake Huron, on mink. 1. Effects on mink reproduction, kit growth and survival, and	17 PCDD/Fs, 12 DL-PCBs The diet also contained other contaminants (e.g. metals, pesticides, NDL-PCBs with levels reported) *Mutigenerational study* Mink (n=96, M and F) randomly assigned to 4 dietary groups (24 animals per group) (P1) fed diets containing carp at 0 (control), 0.25, 0.5 or 1.0 mg/kg PCBs for 6 months. Mink mated within their	All doses, including the lowest dose reduced vulvar swelling in P1 and F1-1 generations and F1-1 kits' body weight gain at 3 and 6 weeks. The lowest dose also increased spleen weight in F1-1 animals and caused hepatocellular lipidosis in P1 mink.	Carp calculated to contain 120 ng WHO_{2005}-TEQ/kg and 8.4 mg PCBs/kg, so 14.3 ng WHO_{2005}-TEQ/mg PCBs. Thus, 0.25 mg/kg PCBs in feed equals to 3.6 ng WHO_{2005}-TEQ/kg

Reference	Compounds	Dose Regime	Results	NOAEL (or LOAEL)
selected biological parameters.		respective dietary groups. The first year F1 generation (F1-1) kits weaned at 6 weeks of age and half of the P1 mink switched (except controls) to control diet while other half remained on their respective treatment diet and continued on the trial for a 2nd reproductive season. F1-1 mink whelped by P1 females exposed to either 0, 0.25, 0.5 or 1.0 mg/kg feed PCBs for 6 months. Half of the kits switched from their parents' diet to control diet after weaning, while other half remained on their parents' diet throughout study. F1-1 mink continued on trial through reproductive season and whelped F2 generation.		feed [(a)] Based on reduced vulvar swelling and body weight gain, LOAEL=0.25 mg/kg, corresponding to about 0.4 ng WHO_{2005}-TEQ/kg bw per day [(b)]
Bursian et al. (2006a). Dietary exposure of mink (*Mustela vison*) to fish from the Housatonic River, Berkshire County, Massachusetts, USA: Effects on reproduction, kit growth, and survival.	WHO_{1998}-TEQs *Reproductive study* Mink (n=72, F) randomly assigned to 6 treatment groups (12 mink/group), receiving about 1 month prior to mating diets containing goldfish and carp at concentrations equivalent to 1.1 (control diet), 3.5, 5.7, 9.2 16.1, 68.5 ng WHO_{1998}-TEQ/kg. Mink fed on diets for two months before breeding through weaning of kits. Twelve kits from each treatment group maintained on their respective diets for an additional 180 days.		At 6 weeks of age, survival of kits in the highest dose group (68.5 ng WHO_{1998}-TEQ/kg) significantly lower compared with control kits and the 16.1 ng WHO_{1998}-TEQ/kg group (p=0.0391). At birth, kits in the 5.7 ng WHO_{1998}-TEQ/kg group had significantly greater body weights (p=0.0106) when compared with kits in the control group and all other groups from birth to 6 weeks, but this may have been incidental.	Based on kit mortality, NOAEL=16.1 ng WHO_{1998}-TEQ/kg feed for kit survival, corresponding to 1.6 ng WHO_{1998}-TEQ/kg bw per day
Bursian et al. (2006b). Dietary exposure of mink (*Mustela vison*) to fish from the Housatonic River, Berkshire County, Massachusetts, USA: Effects on organ weights and histology and hepatic concentrations of PCBs and 2,3,7,8-TCDD equivalence.	WHO_{1998}-TEQs *Reproductive study* Mink (n=72, F) randomly assigned to 6 treatment groups (12 mink/group), receiving for 1 month prior to mating, diets containing goldfish and carp at concentrations equivalent to 1.1 (control diet), 3.5, 5.7, 9.2 16.1, 68.5 ng WHO_{1998}-TEQ/kg. Mink fed on the diets 8 weeks prior to breeding through weaning of kits. Offspring maintained on their respective diets for an additional 180 days.		Dose-dependent maxillary and/or mandibular squamous cell proliferation: 1/6 juveniles, 2/6 juveniles, and 6/6 juveniles in the 9.2, 16.1, and 68.5 ng WHO_{1998}-TEQ/kg groups, respectively.	Based on jaw lesions, NOAEL=5.7 ng WHO_{1998}-TEQ/kg feed, corresponding to 0.6 ng WHO_{1998}-TEQ/kg bw per day
Bursian et al. (2006c). Assessment of effects in mink caused by consumption of carp collected from the Saginaw River, Michigan, USA.	WHO_{1998}-TEQs *Reproductive study* Mink (n=40, F) randomly assigned to 4 treatment groups (10 mink/group), receiving diets containing contaminated carp equivalent to 2.5 (control diet), 28, 47, 73 ng WHO_{1998}-TEQ/kg. Mink fed on diets for 3 weeks prior to breeding through weaning of		Mandibular and maxillary squamous cell proliferation observed at 48 and 73 ng WHO_{1998}-TEQ/kg, but not at 28 ng WHO_{1998}-TEQ/kg	Based on jaw lesions, NOAEL=28 ng WHO_{1998}-TEQ/kg feed, corresponding to 2.8 ng WHO_{1998}-TEQ/kg bw per day

Reference	Compounds Dose Regime	Results	NOAEL (or LOAEL)
	the resulting offspring at 6 weeks. Eight kits from each group further maintained on diets until 27 weeks of age.		
Martin et al. (2006). Changes in thyroid and vitamin A status in mink fed polyhalogenated-aromatic-hydrocarbon-contaminated carp from the Saginaw River, Michigan, USA.	WHO_{1998}-TEQs *Developmental study* Mink (n=40, F) randomly assigned to 4 treatment groups (10 mink/group) and fed diets that contained 0% (control), 10%, 20% or 30% wild carp (equivalent to 3.4 (control), 27.9, 47.6, and 73.2 ng WHO_{1998}-TEQ/kg feed, respectively. Mink fed 3 weeks prior to breeding through weaning. The weaned kits were continued on diets until 27 weeks of age.	Reductions in plasma retinyl palmitate and total esters (in juvenile females) and in kidney total retinyl esters (in kits and juvenile mink) observed at all dose levels. In 6-week-old kits, T4 and free T4 were increased at the lowest dose only versus control and were thus not deemed dose-related.	Based on thyroid hormones, NOAEL=73.2 ng WHO_{1998}-TEQ/kg feed, corresponding to 7.3 ng WHO_{1998}-TEQ/kg bw per day
Bursian et al. (2013a). Dietary exposure of mink (*Mustela vison*) to fish from the upper Hudson River, New York, USA: Effects on reproduction and offspring growth and mortality.	17 PCDD/Fs, 12 DL-PCBs WHO_{2005}-TEQs *Reproductive study* Minks (n=105, M and F) fed diets containing contaminated fish (carp) at 0, 2.5, 5.0, 10, 15 and 20% of total diet, corresponding to measured concentrations of total PCBs of 0.0074, 0.72, 1.5, 2.8, 4.5 and 6.1 mg/kg feed (corresponding to 0.41, 4.8, 10, 18, 28 and 38 ng WHO_{2005}-TEQ/kg feed). Exposure started about two months prior to breeding and continued up to the age of 7 months for some of the offspring.	Mean number of kits whelped alive per litter reduced in the high dietary group ($p<0.04$). Percentage of F whelping at least one kit was 100% in the control, 4.8 and 10 ng WHO_{2005}-TEQ/kg feed groups, and 90, 87, and 73% for F in the three highest dose groups. Compared to controls, mean number of kits whelped alive per litter was 44% less (CI 17–63%, p=0.0039) in the 28 ng WHO_{2005}-TEQ/kg feed group and 49% less (CI 21–67%, p=0.0023) in the highest dose group. Kit mortality increased over time, ultimately resulting in no kits surviving to end of trial with exception of those in control and in the 4.8 ng WHO_{2005}-TEQ/kg feed group.	Based on kit mortality, NOAEL= 0.72 mg/kg total PCBs, corresponding to 4.8 ng TEQ_{2005}/kg feed. Using the conversion factor of 100 g feed/kg bw, this is equivalent to 0.5 ng WHO_{2005}-TEQ/kg bw per day
Bursian et al. (2013b). Dietary exposure of mink (*Mustela vison*) to fish from the upper Hudson River, New York, USA: Effects on organ mass and pathology.	WHO_{2005}-TEQs *Developmental and sub-chronic study* Mink (n=105, M and F) randomly assigned to 6 treatment groups (between 15-20 mink/group) treated beginning two months before breeding and continuing through gestation, lactation, and early kit growth for 170 days and, for some kits, for a further 170 days, with diets containing carp incorporated into basal mink diet at 0, 2.5, 5.0, 10, 15 and 20% of total diet (equivalent to 0.41, 4.8, 10, 18, 28 and 38 ng WHO_{2005}-TEQ/kg feed).	Mandibular and/or maxillary squamous cell hyperplastic foci occurred dose-dependently in all exposed groups but not in controls.	Based on jaw lesions, LOAEL=4.8 ng WHO_{2005}-TEQ/kg feed, corresponding to 0.5 ng WHO_{2005}-TEQ/kg bw per day

F: female; M: male.
(a): The TEQ content was not provided in the paper but calculated by the CONTAM Panel based on the data shown in Table 1.
(b): Based on the studies of Moore et al. (2012), Bleavins and Auerlich (1981), and Bursian et al. (2013), the average daily feed intake level was estimated at 100 g/kg bw.

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Abbreviations

ADME	Absorption, distribution, metabolism and excretion
AHR	Aryl hydrocarbon receptor
AFHS	Air Force Health Study
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	Bioconcentration factor
BFRs	Brominated Flame Retardants
BIOCONTAM Unit	EFSA Unit on Biological Hazards and Contaminants
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limit
BMI	Body mass index
bw	Body weight
CAT	Critical appraisal tool
Cd	Cadmium
CI	Confidence interval
CONTAM Panel	EFSA Panel on Contaminants in the Food Chain
CYP	Cytochrome P450
DATA Unit	EFSA Evidence Management Unit (former DCM Unit)
DL-PCBs	Dioxin-like PCBs
DM	Dry matter
EFSA	European Food Safety Authority
ELS	Extensive literature search
EPA	Environmental Protection Agency
EROD	Ethoxyresorufin-O-deethylase
EU	European Union
FAO/WHO	Food and Agriculture Organization of the United Nations/World Health Organization
FDA	US Food and Drug Administration (US)
FEDIAF	European Pet Food Industry Federation
FFQ	Food Frequency Questionaire
FLEHS	Flemish Environment and Health Study
FSH	Follicle stimulating hormone
GC	Gas chromatography
GD	Gestation day
GST	Glutathione *S*-transferase
HBGV	Health-based guidance value

HRMS	high-resolution mass spectrometry
IARC	International Agency for Research on Cancer
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
i.m.	intramuscular
i.p.	intraperitoneal
IPCS	International Programme on Chemical Safety
KVHS	Korean Veterans Health Study
LB	Lower bound
LD_{50}	Lethal dose, median
LH	Luteinizing hormone
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
LOD	Limit of detection
LOQ	Limit of quantification
MS	Mass spectrometry
MSWI	Municipal solid waste incinerator
NATO	North Atlantic Treaty Organization
NDL-PCBs	Non dioxin-like PCBs
NHANES	National Health and Nutrition Examination Survey
NK	Natural killer (cells)
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NTP	US National Toxicology Program
OCP	Organochlorine pesticides
OECD	Organisation for Economic Co-operation and Development
OHAT	NTP Office of Health Assessment and Translation
OR	Odds ratio
PBDEs	Polybrominated diphenyl ethers
PB(P)K	Physiologically-based (pharmaco)kinetic (model)
PCBs	Polychlorinated biphenyls
PCDDs	Polychlorinated dibenzo-*p*-dioxins
PCDFs	Polychlorinated dibenzofurans
PND	Post-natal day
POPs	Persistent organic pollutants
RfD	Reference dose
s.c.	Subcutaneous
SCAN	Scientific Committee on Animal Nutrition

SCE	Sister chromatid exchange
SCF	Scientific Committee on Food
SD	Standard deviation
SEM	Standard error of the mean
SGOT	Serum glutamic oxaloacetic transaminase
SOP	Standard operational procedure
SWHS	Seveso Women's Health Study
T3	Triiodothyronine
T4	Thyroxine
TBG	Thyroxin binding globulin
TCDD	2,3,7,8- tetrachlorodibenzo-*p*-dioxin
TDI	Tolerable daily intake
TEF	Toxicity equivalency factor
TEQ	Toxic equivalents
TSH	Thyroid stimulating hormone
TWI	Tolerable Weekly Intake
UB	Upper bound
US EPA	United States Environmental Protection Agency
WHO	World Health Organization
ww	Wet weight