Annex to: Risk Assessment of N-nitrosamines in Food. doi:10.2903/j.efsa.2023.7884

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Annex E – Protocol for an Expert Knowledge Elicitation on the Uncertainty of the Risk Assessment of Nitrosamines in Food – Evidence dossier / Result report

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1. Context

1.1. Terms of Reference relevant for this Evidence dossier

In accordance with Art. 29 (1) (a) of Regulation (EC) No 178/2002, the Commission asks EFSA for a scientific opinion on the risks for human health related to the presence of *N*-nitrosamines (*N*-NAs) in food.

The CONTAM Panel will assess the risk of public health related to the presence of *N*-NAs as contaminants in food matrices prior to consumption.

The CONTAM Panel considered that dietary exposure to *N*-NAs is to be assessed for the general population. For this, 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 to the most detailed level of the Foodex2 classification system. Different food commodities will be grouped as needed and relevant, to better explain their contribution to the total dietary exposure to *N*-NAs. Exposure estimates will be calculated per dietary survey and age class. The mean and the high (95th percentile) dietary exposures will be calculated by combining *N*-NAs mean occurrence values for food samples collected in different countries with the daily consumption of each food at individual level in each dietary survey.

1.2. Working group (WG)

Role	Name
EFSA Scientific officer	Anna CHRISTODOULIDOU
	Francesca RIOLO
	Federico CRUCIANI
WG Chair	Bettina GRASL-KRAUPP
WG Member	Margherita BIGNAMI
	Stephen HECHT
	Marco IAMMARINO
	Jean-Charles LEBLANC
	Aldo BENIGNI
	Cristina FORTES
	Carlo Nebbia
Hearing expert	Andy Hart
Panel members	Ron HOOGENBOOM
	Laurent BODIN
EU observer	Frans VERSTRAETE

1.3. Steering group

Role	Name
EFSA scientific officer	Anna CHRISTODOULIDOU
	Francesca Riolo
WG member	Bettina GRASL-KRAUPP
EKE support	Olaf MOSBACH-SCHULZ
	Andy HART
Elicitor	Olaf MOSBACH-SCHULZ
Administrative support	-

1.4. Elicitation group

The elicitation groups are defined for each session as sub-group of the working group.

1.5. Timeline

Date	Topic	Status
Working group		
11/01.2022	Selection of parameters for EKE	
	Preparation of the evidence dossier(s)	
	Review of the EKE protocol	
03+04/05	Review of the result report(s)	
Steering group		
	Framing of the EKE question(s)	
17/01.2022	Finalisation of the protocol	
	Draft version of the evidence dossier	
24/01.2022	Finalisation of the evidence dossier	
	Review of the technical report	
Elicitation group		
	Decision on elicitation timeline and location	
	Invitation of the experts	na
18/01.2022	Distribution of the draft evidence dossier to the experts	
24/01.2022	Review of the evidence dossier by the experts	
11/01.2022	Training of the experts	
09/03, 25/03, 06/04, 17/08	Elicitation sessions Exposure	
10/03, 07/04	Elicitation session Hazard	
07/04, 03/05, 17/08	Elicitation sessions: Total assessment	
	Technical report on the elicitation	
	Result report	
	Feedback to the experts	
Finalisation		
	Final technical documentation	
	Archived	

1.6. Elicitations

Date	Topic	Status
1st session: Hazard		
10/03.2022, PM	Virtual meeting organized	
07/04.2022, AM	Virtual meeting organized	
2nd session: Exposure		
09/03.2022, PM	Virtual meeting organized	
25/03.2022, AM	Virtual meeting organized	
06/04.2022, PM	Virtual meeting organized	
17/08.2022, AM	Virtual meeting organized	
3rd session: MoE		
07/04.2022, PM	Virtual meeting organized	
03/05.2022, PM	Virtual meeting organized	
17/08.2022, PM	Virtual meeting organized	

2. Evidence dossier

2.1. Definition *N*-nitrosamines (*N*-NAs)

The definition of *N*-NAs can be found in Section "1.3.1 Chemistry" of the opinion:

N-Nitroso compounds are a group of chemical compounds considered to be causally involved in the development of cancer in humans and animals. The identified *N*-NAs have been grouped into two primary classes, acyclic and cyclic, according to their structure. In addition, since volatility of *N*-NAs is a characteristic often reported in the literature, they were further subdivided to volatile and non-volatile based on the threshold of boiling point (BP) = 250° C.

- ACYCLIC *N*-NAs, volatile
- ACYCLIC *N*-NAs, non-volatile
- CYCLIC *N*-NAs, volatile
- CYCLIC *N*-NAs, non-volatile

Other *N*-NAs are aromatic nitrosamines are characterized by aromatic ring(s) directly attached to the *N*-nitroso functional group

For detailed list of *N*-NAs see the draft opinion:

2.2. Definition of contaminated food groups

The discussion of pathways can be found in Section "1.3.3 Sources of *N*-NAs in food" of the opinion:

- Meat, esp. cured meat
- Processed fish
- Beer
- Milk, cheese
- Soy sauce
- Vegetables, esp. leafy vegetables, pickled/salted vegetables, potatoes
- Non-alcoholic beverages, incl. water, fermented beverages
- Alcoholic beverages, excl. beer (see above)
- Human milk

For detailed list of food groups, consumption and occurrence/literature data see Annex C of the scientific opinion.

3. Elicitations

3.1. Session: "Hazard"

3.1.1. Elicitation group

Role	Name
Scientific officer	Anna CHRISTODOULIDOU
Elicitor	Andy HART
Recorder	Anna CHRISTODOULIDOU Olaf MOSBACH-SCHULZ
WG Experts	Bettina GRASL-KRAUPP
	Margherita BIGNAMI
	Stephen HECHT
	Cristina FORTES
	Aldo BENIGNI
Panel Member	Laurent BODIN
Specialists	NA
Observer	Frans VERSTRAETE

3.1.2. Step 1: Total Uncertainty Assessment of Hazard – NDEA only

3.1.2.1. Time and resources appropriate for this elicitation

- One half day total

3.1.2.2. Context 1:

Critical endpoint: Carcinogenicity

Please consider

- all relevant evidence in the draft Opinion
- the BMD modelling for NDEA for different endpoints/organs provided in Annex B
    - Similar results from BMD modelling when using all or subset of dose levels
    - Different results from BMD modelling for different organs – liver and oesophagus
    - Not possible to combine organs in one model
    - **Reference value chosen[1] = BMDL 10 µg/kg bw per day, BMDU 34 µg/kg bw per day based on tumours in liver in rats**
- the full list of hazard uncertainties as identified in the table is provided in Appendix G

3.1.2.3. 1st EKE question

Table 1. Framing of the EKE question no. 1

Topic	Description
Parameter	**Total uncertainty of the reference value**
Strata	NDEA
Question	What would be the relative change of the **reference value** for NDEA if all uncertainties affecting the hazard assessment were to be resolved, e.g. by obtaining perfect information/studies on all aspects of hazard identification and characterisation?
Unit	[-] Changed by a multiplicative factor of x (x<1 for decreasing the reference value, x>1 for increasing it)
Operationalisation	A perfect set of studies is conducted to evaluate the hazard of NDEA and the change in the reference point is observed. The ratio of this changed value to the existing reference value of the assessment is the answer.

[1] The reference point proposed at the time of the first elicitation was 9 µg/kg bw per day and the individual judgements were based on that. The reference point was later changed to 9.9 µg/kg bw per day and then rounded to 10 µg/kg bw per day, and this was taken into account in a subsequent stage of the uncertainty analysis, when assessing overall uncertainty (see later).

3.1.2.4. Meeting notes: 10/03.2022, 14:00-15:30

The current status of the BMDL modelling

- Key study of Brantom (1983) selected: 16 doses
- Fitting with all doses gave no appropriate fitting (AIC criterium used): BMDL: M 0.019, F 0.010 / BMDU M 0.038, F 0.021. However the fitting was sufficient considered the justification provided in section 3.1.7 of the scientific opinion.
- Different endpoints were fitted
- Relative stable BMDL results
- The EFSA guidance document on BMDL to be followed

Proposal: BMDL= 10 to 21 (BMDU) µg/kg BW per day

- The assessment focus oesophagus / liver tumour in rats
- A point of departure in oesophagus would be higher than a point of departure calculated for liver tumours (malignant and benign)
- The uncertainty checklist is reviewed:
  - Uncertainties identified in epidemiological studies: Problems in exposure quantification, which make the epi studies confirmatory but not suitable for risk characterisation.
    - Uncertainty on the target organ in humans (not liver)
  - Uncertainties in animal studies:
    - Evaporation of doses / boiling point is high, thus evaporation is no problem for *N*-NA
    - amount of dose calculated from "ppm feed/water" using default values / for NDEA direct doses were given
    - Dosage via drinking water, not gavage: From kinetic point of view drinking water exposure is more realistic than gavage
    - combined data on different liver tumours
    - endogenous nitrosamines are not relevant for the assessment

Main uncertainty: Dosage via bottled drinking water, not gavage

Reported dose may not be the real dose of the animals, e.g. playing with water / daily water consumption in rats is quite stable

More relevant application of the dose by continuous intake, instead peak dose by gavage, closer to the human intake / gavage could increase carcinogenicity

Toxicokinetic by intake via water may be different from application via feed

Framing of the question

EKE Question: What would be the relative change of the reference value for NDEA if all uncertainties affecting the hazard assessment were to be resolved, e.g. by obtaining perfect information/studies on all aspects of hazard identification and characterisation?

- Reference value = BMDL (as given)
- Change=factor (relative change: <1 decrease, >1 increase of the BMDL)
- Note: This implies that the experts are to consider that the experimental setting is constant, but with perfect dosage system

3.1.2.5. Summary of relevant evidence found in the literature (quantitative & qualitative):

See draft opinion.

3.1.2.6. Discussion of the 1st EKE question:

EKE Question: What would be the relative change of the reference value for NDEA if all uncertainties affecting the hazard assessment were to be resolved, e.g. by obtaining perfect information/studies on all aspects of hazard identification and characterisation?

Uncertainty	Lower reference values	Higher reference values
Dosing via bottled drinking water, so actual intake might differ from measured (less accurate than gavage)	• Large loss of water from bottles	• Little or no loss of water

3.1.2.7. Individual results

Each expert provided a plausible lower and upper bound, a median and lower and upper quartiles for for the relative change required by the EKE question. All of the judgements fell within the range 0.8 to 1.

3.1.2.8. Review and discussion of individual distributions:

Distributions fitted to the experts' individual judgements were displayed and discussed.

Discussion 15:30 –16:30, 10/03.2022

- **Lower bound**
  - No advanced system was used in the experimental setting (ordinary bottle)
  - Reported imprecision of bottle filling by about +/-10%
  - From experience of the experts, unlikely to have more than 10% loss
- **Upper bound**
  - Animals need easy access to water, adjusting water bottles to allow this leads to dripping, which can't be avoided

The discussion of this EKE question was halted at 16:30 on 10 March, to allow brief consideration of the next EKE question before expert B had to leave the meeting.

In view of the limited time and the limited degree of uncertainty affecting the hazard assessment, it was decided not to elicit a consensus distribution. Instead, the judgements provided by the experts were reviewed at the subsequent meeting on 7 April, prior to the assessment of overall uncertainty. The facilitator proposed that the WG agree on a plausible range which covers all the experts' individual judgements. Reviewing the range of judgements expressed previously, the experts agreed that 0.8 would result from extreme water loss that would be seen only for very few individual animals; in view of that, they suggested that the lower bound should be higher than 0.8. In conclusion, the experts agreed take 0.95 – 1 as their consensus plausible range (i.e. 98% probability interval) for the relative change for the reference point for NDEA.

Consensus range for the relative change of the reference value for NDEA if all uncertainties affecting the hazard assessment were to be resolved: 0.95 – 1.

3.1.3. Step 2: Total Uncertainty Assessment of Hazard – NDEA plus additional *N*-NAs

3.1.3.1. Context 2:

Critical endpoint: Carcinogenicity

Please consider

- the judgements made for NDEA alone (from Question 1, above)
- all relevant evidence in the draft Opinion
- the BMD modelling for NDEA for different endpoints/organs
- BMD modelling for other *N*-NAs if available
- the full list of hazard uncertainties as identified in the list of uncertainties presented in Appendix G of the draft opinion

3.1.3.2. 2nd EKE question

Table 2. Framing of the EKE question no. 2

Topic	Description
Parameter	**Total uncertainty of the reference value**
Strata	NDEA plus other *N*-NAs, specifically NDMA, NMEA, NDEA, NDPA, NDBA, NMA, NSAR, NMOR, NPIP, NPYR
Question	What would be the LOWEST reference value considering NDEA AND ALL OTHER *N*-NAs if all uncertainties affecting the hazard assessment were to be resolved, e.g. by obtaining perfect information/studies on all aspects of hazard identification and characterisation?
Unit	[-] Changed by a multiplicative factor of x (x<1 for decreasing the reference value, x>1 for increasing it)
Operationalisation	A perfect set of studies is conducted to evaluate the hazard of NDEA AND THE SPECIFIED ADDITIONAL *N*-NAs and the change is observed. The ratio of changed and existing reference value of the assessment is the answer.

3.1.3.3. Summary of relevant evidence found in the literature (quantitative & qualitative):

See draft opinion.

3.1.3.4. Discussion of the 2nd EKE question:

Due to limited time, the EKE Question was simplified to require a single probability judgement, as follows: *What is your probability that none of the other nitrosamines being considered (NDMA, NMEA, NDPA, NDBA, NMA, NSAR, NMOR, NPIP, NPYR) would have a reference value below 10 µg/kg bw per day (the BMDL of NDEA) if all*

uncertainties affecting the hazard assessment were to be resolved, e.g. by obtaining perfect information/studies on all aspects of hazard identification and characterisation?

*** Individual answers of the experts***

Expert	A	B	C	D	E	F
Probability	99%	99%	99%	99%	95%	Cannot say*

* Expert F later said they could agree with the consensus judgement below.

Discussion notes 16:35 to end of meeting, 10/03.2022

- List of *N*-NAs:
  - Certainty from data, none of the NNAs is more carcinogenic than NDEA
  - Three NNAs have a similar potency: NDEA, NMEA and NDMA
  - TD50: 0.026, 0.05, 0.009; within the experimental variation
- The following table of BMD modelling results was displayed:

(NDMA) female	All in	0.035	0.063	AIC >5
(NDMA) male	Last higher out	0.051	0.078	Only model Hill m5-ab fits with AIC >5
(NDMA) female	Last higher out	0.034	0.057	
(NDMA) male	2 higher out	0.046	0.079	Expon. m5-ab Hill m5-ab AIC >5
(NDMA) female	2 higher out	0.030	0.057	
(NDMA) male	3 higher out	0.044	0.079	Expon. m5-ab Hill m5-ab AIC >5
(NDMA) female	3 higher out	0.031	0.058	

Consensus judgement: The WG is 95-99% certain that the lowest BMDL for carcinogenicity for any nitrosamine detected in food is 10 ug/kg bw per day.

Discussion: above statement agreed by all (after expert B had to leave) as outcome of overall uncertainty assessment for hazard assessment, including both questions (NDEA and other NAs). Expert E agreed that this could be taken as also covering the uncertainty relating to over-estimation of water intake. All agreed that, given the low probability of lower BMDLs and the much larger magnitude of uncertainty for the exposure assessment, it was not worthwhile or necessary to quantify further the magnitude of the possible decrease below 10 ug/kg bw per day. It was noted that dimethyl has TD50 of 0.009 compared to TD50 0.026 for NDEA but these are less reliable estimates compared to the BMDL studies. WG say there is widespread agreement that there are 3 most toxic NAs and they are closely similar.

3.2. Session: "Exposure"

3.2.1. Elicitation group

Role	Name
Scientific officer	Anna CHRISTODOULIDOU
Elicitor	Olaf MOSBACH-SCHULZ
Recorder	Andy HART
Experts	Francesca RIOLO
	Marco IAMMARINO
	Jean-Charles LEBLANC
	Ron HOOGENBOOM
Specialists	NA
Observers	Bettina GRASL-KRAUPP
	Frans VERSTRAETE

3.2.2. Specific definitions

The definition of the age groups can be found in Section "2.1.1.1 Food Consumption Data", Table 3 of the opinion:

The uncertainty analysis focused on NDEA, because it is the *N*-NA inducing tumours at the lowest $BMDL_{10}$ value, and sufficient data are available for this *N*-NA. The analysis focussed mainly on the exposure age group of toddlers, because the estimated P95 MOE for TCNAs was lower for toddlers than other age groups.

Table 3. Definition of "Toddler" and their data sources according to the opinion

Population group	**Age range**	**Countries with food consumption surveys covering more than 1 day**
Toddlers	≥ 12 months to < 36 months old	Belgium, Bulgaria, Cyprus, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Netherlands, Portugal, Slovenia, Spain

The description of the exposure assessment can be found in the opinion:

- Concentration data of *N*-NAs in food in Section 2.1.1.2
- Occurrence data submitted to EFSA in Section 3.2.1
- Occurrence data in the literature in Section 3.2.2
- Dietary exposure assessment in Section 3.3

3.2.3. 1st EKE: NDEA: Influence of left-censored data, limited evidence in literature and influence of missing food categories

3.2.3.1. Context 1 for the first EKE question:

- The **exposure assessment is made with occurrence data of EFSA, literature data and additional information on additional food categories**
- The final conclusion is based on the **high exposed population (P95)**
- Uncertainty assessment is only done **for toddlers** and only **for NDEA**
- For all food in the mean diet of European toddlers survey data with a perfect measurement is assumed, which **allows quantification of all values above zero**.

3.2.3.2. 1st EKE Question

Table 4. Framing of the EKE question no. 1

Topic	Description
Parameter	**Influence of left-censored data, limited evidence in literature and influence of missing food categories**
Strata	Age class: toddlers Compounds: NDEA
Question	What is the **relative change of the exposure assessment** *of high consumer in the European population in the specified age class regarding the specified compound(s)* **after assuming perfect measurements for all food items in comparison to the existing assessment**?[Factor]
Unit	[-] expressed as factor
Operationalisation	The perfect measurements of the complete diet of toddlers in whole Europe are included in the assessment and the change is observed. The ratio of changed and existing exposure assessment is the answer.

3.2.3.3. Evidence for the 1st EKE

The description of the exposure assessment can be found in the opinion:

- Handling of left-censored data in the assessment in Section 3.2
- Occurrence data on food submitted to EFSA in Section 3.2.1
- Occurrence data on food selected from the literature in Section 3.2.2
- Mean LB, MB and UB chronic dietary exposure (ng/kg bw per day) to the individual and total TCNAs in Table 20
- P95 LB, MB and UB chronic dietary exposure (ng/kg bw per day) to the individual and total TCNAs in Table 22
- Contributing food categories in section 3.3.1
- Main contributing category (Meat and meat products is the main contributing category for all considered compounds and age groups.) in Table 10 of the Annex C

The contribution of the food categories in the diets of different surveys are shown on graph 1 of the opinion (Section 3.3.2).

The following table was filled during the meeting on 09th March 2022 and updated on 17th August 2022. Calculations and additional comments are included in the EXCEL file (see above sheet Simple_UA_model)

Simplified exposure model of toddlers intake of NDEA based on Scenario 2 (17th Aug. 2022)												**Please review the evidence and judge on possible lower, upper bound and median (fair) estimates of the concentration of NDEA in the food items of the toddlers diet. (Please completely fill columns W to Y of the simplifyed exposure model (green cellls) to explore the ratio of lower and upper limits. Results are calculated below in cells Z to AE, line 8)**
- The food categories are selected to comprise more than 95% of the "Mean diet of an European toddler"												
- The estimation of the intake uses mean and high consumption (P95) data per FoodEx2_L3 category												

Consumption of toddlers						**Evidence for NDEA concentration**							**Concentration**			**Intake**					
Food category (foodex2 Level 3)	**Mean diet**	**Proportion of the mean diet**	**Proportion in the food category**	**High consumer diet**		**Evidence base**	**Merging level**	**No of samples**	**Percent left censored**	**LB (LC equal 0)**	**MB (LC equal LOQ/2)**	**UB (LC equal LOQ)**	**Lower bound**	**(fair) Median estimate**	**Upper Bound**	**Mean consumption * Lower bound**	**Mean consumption * Median concentration**	**Mean consumption * Upper bound**	**High consumption * Lower bound**	**High consumption * Median estimate**	**High consumption * Higher bound**
	(a)			(b)									**(c)**	**(d)**	**(e)**	(1)=a*c	(2)=a*d	(3)=a*e	(4)=b*c	(5)=b*d	(6)=b*e
cp. FoodEx2 Level 3	g/kg BW	% total	% group	g/kg BW				[-]	% samples	µg/kg	µg/kg	µg/kg	µg/kg	µg/kg	µg/kg	ng/kg BW	ng/kg BW	ng/kg BW	ng/kg BW	ng/kg BW	ng/kg BW
													Uncertainty factors to the reference model:			**1.08**	**12.04**	**26.01**	**1.05**	**10.72**	**22.98**
													Reference model:			1.820	2.788	3.756	6.817	12.273	17.730
													Uncertainty factors in the simplified model:			**0.09**	**X**	**2.16**	**0.10**	**X**	**2.14**
foodex2_L3	Mean amount	Mean relative	within group	P95 amount		litsource	TERM LEVEL	No samples	Percent ND	Lower bound	Middle bound	Upper bound	Intake simplified model:			3.021	33.557	72.518	12.828	131.533	282.037
Total	115.801																				
Water-based beverages	**35.587**	**31%**		**137**		**missing data**							0.007	0.024	0.040	0.238	0.840	1.441	0.914	3.221	5.528
Unbottled water	24.566	21.2%	69.0%	67.676																	
Bottled water	5.678	4.9%	16.0%	35.556																	
Soft drinks	2.345	2.0%	6.6%	13.773																	
Drink mixes	0.143	0.1%	0.4%	0.485																	
Herbal and other non-tea infusions	1.799	1.6%	5.1%	11.538																	
Tea beverages	1.055	0.9%	3.0%	7.500																	
Beer or similar	**0.078**	**0.1%**		**0.000**		**occurrence**	**2**	**73**	**98.6**	**0.005**	**0.144**	**0.283**	0.005	0.144	0.283	0.000	0.011	0.022	0.000	0.000	0.000
Beer and beer-like beverage	0.000	0.0%	0.0%	0.000																	
Beer-like beverages	0.076	0.1%	96.8%	0.000																	
Beer	0.003	0.0%	3.2%	0.000																	

Fruit / Fruit & vege juices	**14.236**	**12.3%**		**67.273**		**missing data**							0.109	0.348	0.587	1.548	4.953	8.358	7.313	23.404	39.496
Fruit juices (100% from named source)	2.928	2.5%	20.6%	14.286																	
Fruit nectars (min. 25-50% fruit as defined in EU legislation)	0.792	0.7%	5.6%	5.769																	
Mixed juices with added ingredients	0.292	0.3%	2.1%	0.000																	
Fruit/vegetable juice concentrate	0.211	0.2%	1.5%	1.488																	
Pome fruits	3.153	2.7%	22.1%	10.750																	
Miscellaneous fruits with inedible peel, large	2.801	2.4%	19.7%	9.350																	
Berries and small fruits	0.888	0.8%	6.2%	4.643																	
Citrus fruits	0.749	0.6%	5.3%	4.629																	
Stone fruits	0.518	0.4%	3.6%	3.381																	
Miscellaneous fruits with inedible peel, small	0.187	0.2%	1.3%	1.316																	
Dried fruit	0.165	0.1%	1.2%	1.034																	
Ready-to-eat fruit-based meal for children	0.650	0.6%	4.6%	5.195																	
Fruit / vegetable spreads and similar	0.646	0.6%	4.5%	4.000																	
Other processed fruit products (excluding beverages)	0.256	0.2%	1.8%	1.433																	
Milk and formulae, incl. dairy products	**33.526**	**29.0%**		**142.411**		**missing data**							0.000	0.004	0.008	0.010	0.144	0.278	0.043	0.612	1.182
Milk	18.349	15.8%	54.7%	52.265																	
Follow-on formulae	3.978	3.4%	11.9%	32.028																	
Infant formulae	2.523	2.2%	7.5%	20.958																	
Fermented milk products	5.889	5.1%	17.6%	20.604																	
Buttermilk	0.211	0.2%	0.6%	0.920																	
Cream and cream products	0.153	0.1%	0.5%	0.810																	
Butter	0.238	0.2%	0.7%	1.008																	
Dairy desserts spoonable	0.525	0.5%	1.6%	4.545																	
Dairy ice creams and similar	0.323	0.3%	1.0%	1.852																	
Fresh uncured cheese	0.757	0.7%	2.3%	4.667																	
Ripened cheese	0.439	0.4%	1.3%	1.818																	
Processed cheese and spreads	0.142	0.1%	0.4%	0.935																	
Vegetables, legumes, and starchy roots	**11.318**	**9.8%**		**41.439**		**missing data**							0.100	2.000	3.900	1.132	22.637	44.141	4.144	82.877	161.611
Carrots and similar-	1.147	1.0%	10.1%	4.354																	

Cucurbits fruiting vegetables	1.699	1.5%	15.0%	6.972																	
Solanacea	1.100	1.0%	9.7%	4.583																	
Processed tomato products	0.181	0.2%	1.6%	1.153																	
Onions and similar-	0.556	0.5%	4.9%	2.187																	
Head brassica	0.293	0.3%	2.6%	1.881																	
Broccoli and similar-	0.194	0.2%	1.7%	1.157																	
Pulses (dried legume seeds)	0.138	0.1%	1.2%	1.009																	
Legumes fresh seeds (beans, peas etc.)	0.217	0.2%	1.9%	1.116																	
Beans (with pods) and similar-	0.163	0.1%	1.4%	0.956																	
Potatoes and similar-	3.761	3.2%	33.2%	11.212																	
Dishes excluding pasta or rice dishes, sandwiches and pizza	0.231	0.2%	2.0%	1.140																	
Ready-to-eat mixed meal for children	0.366	0.3%	3.2%	0.000																	
Dairy imitates	0.410	0.4%	3.6%	0.000																	
Savoury sauces	0.268	0.2%	2.4%	1.500																	
Vegetable fats and oils, edible	0.394	0.3%	3.5%	1.353																	
Margarines and similar	0.199	0.2%	1.8%	0.864																	
Grain-based products and sugar	**9.789**	**8.5%**		**40.778**		**missing data**							0.008	0.224	0.441	0.073	2.195	4.317	0.306	9.144	17.983
Leavened bread and similar	3.467	3.0%	35.4%	9.091																	
Breakfast cereals, plain	0.942	0.8%	9.6%	4.427																	
Processed and mixed breakfast cereals	0.390	0.3%	4.0%	2.051																	
Simple cereals for infants or children, reconstituted	0.416	0.4%	4.3%	1.429																	
Cereal grains (and cereal-like grains)	0.574	0.5%	5.9%	2.462																	
Cereal and cereal-like flours	0.514	0.4%	5.2%	2.333																	
Cereals with an added high protein food reconstituted	0.701	0.6%	7.2%	4.091																	
Pasta and similar products	0.731	0.6%	7.5%	3.222																	
Cakes	0.204	0.2%	2.1%	1.538																	
Biscuits	0.623	0.5%	6.4%	2.727																	
Various pastry	0.263	0.2%	2.7%	1.923																	
Yeast leavened pastry	0.229	0.2%	2.3%	1.728																	

Pastry based on laminated dough	0.152	0.1%	1.6%	1.018																
Sugars (mono- and di-saccharides)	0.368	0.3%	3.8%	1.569																
Chocolate and chocolate products	0.218	0.2%	2.2%	1.169																
Meat and meat products																				
Mammals and birds meat	**0.084**	**0.1%**		**0.242**		**lit_2000**	**2**	**52**	**0.0**	**0.523**	**0.523**	**0.523**	0.000	0.523	3.322	0.000	0.044	0.278	0.000	0.127	0.805
Mammals meat	**1.578**	**1.4%**		**5.253**		**lit_2000**	**3**	**36**	**0.0**	**0.498**	**0.498**	**0.498**	0.000	0.498	3.322	0.000	0.786	5.241	0.000	2.618	17.451
Birds meat	**1.475**	**1.3%**		**5.941**		**lit_2000**	**3**	**16**	**0.0**	**0.580**	**0.580**	**0.580**	0.000	0.580	3.322	0.000	0.855	4.899	0.000	3.446	19.737
Preserved or partly preserved sausages	**0.736**	**0.6%**		**3.545**		**lit_2000**	**3**	**33**	**82.0**	**0.140**	**0.140**	**0.140**	0.004	0.140	1.874	0.003	0.103	1.379	0.014	0.496	6.643
Raw cured (or seasoned) meat	**0.138**	**0.1%**		**0.943**		**occurrence**	**3**	**66**	**98.5**	**0.009**	**1.875**	**3.740**	0.009	1.875	3.740	0.001	0.258	0.516	0.009	1.767	3.526
Sausages	**0.124**	**0.1%**		**0.317**		**lit_2000**	**2**	**42**	**81.1**	**0.115**	**0.115**	**0.115**	0.004	0.115	1.874	0.000	0.014	0.232	0.001	0.036	0.594
Sausages	0.052	0.0%	42.2%	0.317																
Fresh raw sausages	0.071	0.1%	57.8%	0.000																
Processed whole meat	**0.226**	**0.2%**		**1.333**		**occurrence**	**2**	**93**	**98.9**	**0.006**	**1.493**	**2.980**	0.006	1.493	2.980	0.001	0.337	0.672	0.009	1.991	3.973
Processed whole meat products	0.005	0.0%	2.4%	0.000																
Cooked cured (or seasoned) meat	0.220	0.2%	97.6%	1.333																
Other meat and meat products	**0.255**	**0.2%**		**1.081**		**occurrence**	**1**	**171**	**99.4**	**0.004**	**0.939**	**1.874**	0.004	0.939	1.874	0.001	0.239	0.478	0.004	1.015	2.026
Animal other slaughtering products	0.000	0.0%		0.000																
Meat and meat products	0.003	0.0%		0.000																
Marinated meat	0.004	0.0%		0.000																
Meat specialties	0.000	0.0%		0.000																
Liver based spreadable-textured specialities	0.167	0.1%		1.081																
Poultry liver	0.023	0.0%		0.000																
Poultry edible offal, non-muscle, other than liver and kidney	0.015	0.0%		0.000																
Mammals liver	0.013	0.0%		0.000																
Mammals other slaughtering products	0.008	0.0%		0.000																
Canned meat	0.006	0.0%		0.000																
Canned-tinned meat	0.001	0.0%		0.000																
Cured pork fat	0.006	0.0%		0.000																
Meat based spreadable-textured specialities	0.002	0.0%		0.000																
Luncheon spiced ham-type tinned meat	0.002	0.0%		0.000																

Mammals edible offal, non-muscle, other than liver and kidney	0.001	0.0%		0.000																
Poultry other slaughtering products	0.001	0.0%		0.000																
Ciccioli and similar	0.000	0.0%		0.000																
Mammals kidney	0.000	0.0%		0.000																
Mammals or birds dried meat	0.000	0.0%		0.000																
Preserved/processed fat tissues	0.000	0.0%		0.000																
Animal fresh fat tissues	0.000	0.0%		0.000																
Animal liver	0.000	0.0%		0.000																
Animal kidney	0.000	0.0%		0.000																
Animal blood	0.000	0.0%		0.000																
Animal edible offal, non-muscle, other than liver and kidney	0.000	0.0%		0.000																
Tinned bulk sausages	0.000	0.0%		0.000																
Processed fish or seafood																				
Processed or preserved fish (including processed offal)	**0.159**	**0.1%**		**1.000**		**occurrence**	**3**	**40**	**97.5**	**0.016**	**0.162**	**0.309**	0.016	0.162	0.309	0.003	0.026	0.049	0.016	0.162	0.309
Processed or preserved seafood	**0.002**	**0.0%**		**0.000**		**lit_2000**	**3**	**44**	**0.0**	**0.170**	**0.170**	**0.170**	0.015	0.170	0.308	0.000	0.000	0.001	0.000	0.000	0.000
Fish, seafood etc.	**0.705**	**0.6%**		**3.808**		**occurrence**	**1**	**43**	**97.7**	**0.015**	**0.161**	**0.308**	0.015	0.161	0.308	0.010	0.114	0.217	0.057	0.615	1.173
Fish (meat)	0.051	0.0%	7.3%	0.000																
Marine fish	0.469	0.4%	66.6%	3.119																
Diadromous fish	0.129	0.1%	18.4%	0.606																
Freshwater fish	0.037	0.0%	5.3%	0.000																
Fish roe	0.018	0.0%	2.5%	0.084																
Fish liver	0.000	0.0%	0.0%	0.000																
Other fish offal	0.000	0.0%	0.0%	0.000																
Eggs and egg products	**0.619**	**0.5%**		**3.991**		**missing data**							0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Whole eggs	0.399	0.3%	64.4%	2.082																
Hardened egg products	0.220	0.2%	35.6%	1.908																

3.2.3.4. Differences between national surveys:

The description of the contribution of different food categories to the NDEA exposure of different populations and national surveys can are shown on graph 1 of the opinion (Section 3.3.1).

European Population of Toddlers						NDEA intake of toddlers for different countries						
Age	**1 year**	**2 years**	**Toddler**	**relative**	**included in EA**	**N_Subjects**	**Mean LB**	**Mean MB**	**Mean UB**	**P95 LB**	**P95 MB**	**P95 UB**
Months	**13-24**	**25-36**	**13-36**									
Total	4157104	4258555	8415659	100.0%	72%							
Spain	363342	382090	745432	8.9%	8.9%	326	0.007	0.008	0.009	0.017	0.019	0.021
Portugal	87256	87913	175169	2.1%	2.1%	571	0.007	0.007	0.008	0.018	0.019	0.019
Latvia	18738	19353	38091	0.5%	0.5%	242	0.006	0.008	0.009	0.015	0.017	0.019
Cyprus	9538	9329	18867	0.2%	0.2%	275	0.006	0.007	0.007	0.015	0.017	0.017
Hungary	92882	93195	186077	2.2%	2.2%	535	0.007	0.008	0.009	0.014	0.016	0.018
Bulgaria	61688	62841	124529	1.5%	1.5%	428	0.007	0.008	0.008	0.016	0.016	0.017
Slovenia	19480	19847	39327	0.5%	0.5%	343	0.005	0.006	0.006	0.013	0.014	0.016
Estonia	14209	14545	28754	0.3%	0.3%	268	0.005	0.006	0.007	0.013	0.013	0.016
France	712846	721371	1434217	17.0%	17.0%	139	0.005	0.005	0.006	0.012	0.012	0.013
Finland	46120	48387	94507	1.1%	1.1%	500	0.005	0.005	0.005	0.011	0.011	0.011
Netherlands	170354	170474	340828	4.0%	4.0%	440	0.003	0.004	0.005	0.009	0.010	0.011
Denmark	61663	61967	123630	1.5%	1.5%	917	0.004	0.005	0.005	0.007	0.008	0.010
Germany including former GDR	783593	798366	1581959	18.8%	18.8%	348	0.003	0.003	0.003	0.007	0.007	0.008
Belgium	118594	120373	238967	2.8%	2.8%	36	0.005	0.006	0.008			
Italy	423269	443571	866840	10.3%	10.3%	36	0.004	0.005	0.006			
Czechia	112555	114739	227294	2.7%								
Ireland	60084	61647	121731	1.4%								
Greece	85706	90101	175807	2.1%								
Croatia	36132	36684	72816	0.9%								
Lithuania	27410	28309	55719	0.7%								
Luxembourg	6571	6705	13276	0.2%								
Malta	4453	4796	9249	0.1%								
Austria	85449	87087	172536	2.1%								
Poland	374101	389048	763149	9.1%								
Romania	205936	206869	412805	4.9%								
Slovakia	58544	59523	118067	1.4%								
Sweden	116591	119425	236016	2.8%								

3.2.3.5. List of identified uncertainties

Please consider the full list of uncertainties as identified in the table of the Appendix G of the scientific opinion.

3.2.3.6. Discussion on the exposure model of 9th March 2022

Uncertainties:

The simplified model was using further references of less relevance to the European situation

LOD/LOQ: Simplified calculations to estimate the LOD/LOQ effect

Limited sample size: the literature is reporting mainly small sample sizes

European toddler diet: Under- or overreporting of food items is possible

P95 and mean consumption of the simplified model: Not a representative sample for Europe

Uncertainty	**Low relative change scenario**	**high relative change scenario**
Missing food category: fruits, vegetables, grain products	• Literature data mainly report processed products	• Literature data are representative to diet of toddlers
Some literature reporting lower values for processed food than unprocessed	• Lower values are correct	• Higher values are correct
Not representative studies	• Literature is biased to high concentrations	• Literature is biased to low concentrations
Missing countries (mainly occurrence data from Northern countries)	• Products in Southern countries are not covered and may be lower contaminated	• Products in Southern countries are not covered and may be higher contaminated
Uncomplete reporting	• Studies only reporting upper limits of contamination	• Complete reporting
Risk assessment takes highest P95 across countries	• P95 for whole EU population would be lower	• EU P95 is equal to the highest country P95
Max survey from one country	• Max country approach is overestimating	•
Missing countries	• Missing countries may lead to lower P95, have lower intake	• Missing countries may lead to higher P95, have higher intake

3.2.3.7. Individual answers on the exposure model of 9th March 2022

NDEA exposure of toddlers (complete semi-formal EKE)

What is the relative change *of the 95th percentile of the daily exposures of European toddlers regarding the specified compound(s) (here NDEA)* after assuming perfect measurements for all food items in comparison to the existing assessment (expressed as middle bound) including all food categories?

Expert	Low	Q1	M	Q3	Upper
Expert A	0.1	1	6	7	10
Expert B	1.1	2	3	5	11
Expert C	1	1.3	1.4	1.5	4
Expert D	0.9	1	1.5	2	2
Consensus	0.2	1.3	2.5	4	8

3.2.3.8. Discussion points:

- Reasons for the lowest low factor being >1? Reasons identified in earlier discussion for exposure being higher, e.g. under-representation of NDEA levels in fish.
- Discussion of degree of reduction needed to adjust from P95 for max country to EU P95: need to take account of relative population sizes of max country and others, and any differences in diet

3.2.3.1. Individual answers on the revised exposure model of 17th August 2022

NDEA exposure of toddlers (EKE on probability bounds only)

What is the relative change *of the 95th percentile of the daily exposures of European toddlers regarding the specified compound(s) (here NDEA)* after assuming perfect measurements for all food items in comparison to the existing assessment (scenario 2) (expressed as middle bound [2]) including all food categories?

It was agreed that, for this revised assessment, it would be sufficient to elicit individual judgements and a consensus for the lower and upper plausible bounds. It was explained that the experts should judge that their probability for the true relative change being lower than their lower plausible bound was less than 1%, and that their probability for the true relative change being higher than their upper plausible bound was less than 1%

Expert	Low	Q1	M	Q3	Upper
Expert A	1	5	10	15	20
Expert B	0.2				10
Expert C	0.3				10
Expert D	0.5	0.75	1.5	1.75	2
Consensus	0.3				8

[2] As the lower and upper bounds already express the uncertainty of the use of left censored data, the factor in question is expressed in relation to the middle bound. Thus the factor is comprising all uncertainties, including also the uncertainty of the use of left censored data.

3.2.3.2. Overview of the results

Overview of the results of the Expert Knowledge Elicitation (1st EKE question, revised results)															
Parameter	UA factor of the exposure assessment of EU toddlers to NDEA														
Stratification	Population: Toddlers / Substance: NDEA														
Question	What is the relative change of the 95th percentile of the daily exposures of European toddlers regarding the specified compound(s) (here NDEA) after assuming perfect measurements for all food items in comparison to the existing assessment (scenario 2) (expressed as middle bound) including all food categories?														
Unit	[-] expressed as factors: 1/X or X														
Results	L (P<1%)	P2.5 %	**P5%**	P10%	P16.7 %	P25%	P33.3 %	**P50 %**	P66.7 %	P75%	P83.3 %	P90%	**P95 %**	P97.5 %	U (P<99 %)
EKE results	0.3														8
Fitted distribution	No distribution is fitted. The probability range of a factor from 0.3 to 8 covers with 98% probability the true value/answer to the question														
Summary of the evidence used for the evaluation															

- The exposure assessment on NDEA was reviewed; and the **age group of toddlers** was confirmed as **having highest exposure for TCNAs.**
- The handling of left-censored observations from surveys in the assessment was reviewed; the use of lower bound and upper bound imputation was confirmed. The **uncertainty is quantified by the range of the lower and upper bound assessment**.
- The handling of data from literature – in case of missing survey data – was reviewed, the **lower and upper bound were estimated**, if not given in the reference.
- The complete diet of European toddlers was reviewed and **main food categories comprising more than 95% of the diet were identified**. The mapping of contamination data to the diet showed, which food categories are not part of the exposure assessment. For each food category not included in the assessment the evidence for possible contaminations were discussed, using **theoretical reasoning and other indications from references**, e.g. publications on non-European contaminations. Lower and upper bounds were estimated per category. Indication for contaminations exist for **unbottled water, soft drinks, cheese, fruits and vegetables, grain-based products.**
- Using the complete diet of European toddlers and a **simplified exposure model**, the influence of additional food categories on the assessment, and the influence of left-censored data were explored. Different assumptions/estimates were tested by a sensitivity analysis. The simplified model **results in a factor of 11 (Lower 1.1, Upper 23)** between the "real" exposure and the existing assessment.
- The additional uncertainties due to use of the intake of toddlers for the country with the highest intake of all countries with surveys **(maximum approach)** were discussed. The **variation between the countries with surveys for toddlers (Range factor 2-3)**, and the **variation between different age groups (Factor range 4-7)** were used to judge the stability of results. The **coverage of the countries with surveys** on toddlers

for the whole European population of toddlers **(60% for P95)** were reviewed and regional/cultural differences discussed. The **main regional and cultural clusters are covered** by the surveys. • The additional uncertainties on contaminations with NDEA due to **"processing at home (e.g. cooking)"** were discussed and corresponding references were reviewed. The effect was **concluded to be minor** (compared to other uncertainties). • All other uncertainties identified in the checklist as existing, but with less relevance, were reviewed. **No further discussion was necessary.**	
Main uncertainties	
• Influence of **left-censored data** in the surveys. • Influence of the **use of data from literature**: Missing quantification of the influence of left-censored data in some references; • Influence of **missing food categories** on the exposure: Possible underestimation. • Influence of the use of the **maximum approach** on the estimation for the whole European population of the toddlers: Possible overestimation. • Influence of **"processing at home"** on the contamination of food categories	
Reasoning for a scenario which would lead to a reasonable high proportion	The **judgement on the upper limit** considers that • the upper bound for left-censored measurements are used • high values reported in the literature are used • missing food categories are contaminated with a high concentration, if evidence points to a contamination • the P95 European toddlers diet is similar to the diet of the country with maximum intake (from countries with surveys) • the "processing at home" contributes to the contamination, esp. also for missing food categories, e.g. vegetables
Reasoning for a scenario which would lead to a reasonable low proportion	The **judgement on the lower limit** considers that • the lower bound for left-censored measurements are used • low values reported in the literature are used • missing food categories are contaminated with a low concentration, if evidence points to a contamination • The P95 European toddlers is lower than the maximum intake (from countries with surveys)
Experts	Ron HOOGENBOOM, Marco IAMMARINO, Jean-Charles LEBLANC, Francesca RIOLO
Facilitator / Reporter	Olaf MOSBACH-SCHULZ / Andy HART
Date and place of the EKE	The EKE (semi-formal protocol) was done on the 25th March 2022 in a virtual meeting and revised using the updated exposure model (scenario 2) on 17th August 2022

4. Session "Overall uncertainty"

4.1. Elicitation group

Role	Name
Scientific officer	Anna CHRISTODOULIDOU
Elicitor	Andy HART
Recorder	Olaf MOSBACH-SCHULZ
Experts	Francesca RIOLO
	Marco IAMMARINO
	Jean-Charles LEBLANC
	Bettina GRASL-KRAUPP
	Margherita BIGNAMI
	Stephen HECHT
	Christina FORTES
	Aldo BENIGNI
Specialists	NA
Observers	Frans VERSTRAETE

4.2. Time and resources appropriate for this elicitation

- One half day total: 14:00-18:00, 7/4/2022
- Revision with updated BMDL and exposure assessment, 1-2 hours during PM of 3/5/2022
- Revision with updated exposure assessment, 1 hour 14:15-15:15, 17/8/2022

4.3. Step 1: Overall Uncertainty of Risk Characterisation – NDEA only

4.3.1. Context:

Critical endpoint: Carcinogenicity

Starting points for assessment of overall uncertainty:

Maximum middle bound estimate for 95th percentile of the daily exposures of European toddlers to NDEA, for scenario 2 of the exposure assessment: 9.6 ng/kg bw per day

Elicited consensus plausible bounds quantifying the impact of identified uncertainties on the estimated 95th percentile of the daily exposures of European toddlers to NDEA, expressed as the relative change (multiplicative factor): lower bound = 0.3, upper bound = 8 (see section 4.2.3.10 above).

Reference point: it was confirmed that the WG has agreed that the reference point for NDEA will be 10 µg/kg bw per day (changed from the initial value of 9 µg/kg bw per day) and that the plausible range of 0.95 - 1.0 previously elicited for the relative change (multiplicative factor) quantifying the impact of identified uncertainties on this reference point still represented the consensus judgement of the experts.

4.3.2. Calculations combining hazard and exposure uncertainties

Risk characterisation for NDEA was performed by the Margin of Exposure (MOE) approach. The MOE is the ratio of the Reference Point to the P95 exposure. Consequently, assessing uncertainty for the MOE required combination of the uncertainties influencing the Reference Point and the P95 exposure. The plausible bounds elicited for the Reference Point and P95 EU toddler exposure for NDEA were combined by probability bounds analysis. This method for combining uncertain quantities is described in section 14.1 of EFSA (2018a) and in more detail in Annex B.13 of EFSA (2018b). The advantage of this method is that it requires only a probability bound for each quantity: it does not require elicitation of complete probability distributions and allows for any degree of dependence of uncertainty between the quantities. It is conservative in the sense that it overestimates the probability of the actual MOE being outside the resulting bounds for the MOE, compared to a more refined probabilistic assessment, but avoids the need for refined methods when the conservative probabilities are sufficient for decision-making. Details follow of the application of the method to uncertainty about the MOE for NDEA.

A plausible range had been elicited for the multiplicative factor representing uncertainty about the Reference Point (MFRP). The lower and upper ends of that range are denoted MFRPL and MFRPU. Here MFRPL and MFRPU are lower and upper 1% probability bounds for the multiplicative factor. A 'lower 1% probability bound' is a value such that the experts judge there is at most 1% probability of lower values (i.e., Prob[MFRP < MFRPL]≤1%); and an upper 1% probability bound is a value such that the experts judge there is at most 1% probability of higher values (i.e., Prob[MFRP > MFRPU]≤1%). As a consequence, the experts judge that there is at least 98% probability that the multiplicative factor lies in the range between MRFPL and MRFPU.

The elicited plausible range for the multiplicative factor quantifying uncertainty about the Reference Point (MFRP) was combined with the value assessed for the Reference Point in the Opinion (RPO) to obtain lower and upper probability bounds for the reference point (RPL and RPU respectively), as follows:

$$\mathrm{RPL} = \mathrm{RPO} \times \mathrm{MFRPL}$$

and

$$\mathrm{RPU} = \mathrm{RPO} \times \mathrm{MFRPU}$$

so that RPL and RPU are lower and upper 1% probability bounds for the Reference Point, i.e., Prob[RP<RPL]≤1% and Prob[RP>RPU]≤1%. The experts judge that, if all the uncertainties were resolved, there is at least 98% probability that the Reference Point would lie between RPL and RPU.

Similarly, a plausible range was elicited for the multiplicative factor MFP95 quantifying uncertainty about the P95 exposure for EU toddlers, MFP95L and MFP95U being lower and upper 1% probability bounds for the multiplicative factor. The range was combined with the estimated P95 exposure (P95O, the maximum middle bound P95 from EFSA's Comprehensive Database, as reported in the Opinion) to obtain lower and upper probability bounds for the P95 exposure for EU toddlers (P95L and P95U respectively), as follows:

$$\mathrm{P95L} = \mathrm{P95O} \times \mathrm{MFP95L}$$

and

$$\mathrm{P95U} = \mathrm{P95O} \times \mathrm{MFP95U}$$

so that P95L and P95U are lower and upper 1% probability bounds for the P95 exposure for EU toddlers ('P95'), i.e., Prob[P95<P95L]≤1% and Prob[P95>P95U]≤1%.

An upper bound estimate for the Margin of Exposure (MOEU) was obtained by dividing RPU by P95L, which is equivalent to multiplying RPU by 1/P95L. MOEU is monotonic increasing with respect to RPU and 1/P95L. Consequently, the probabilities from the individual probability bounds can be combined using the second of the two simplest methods for probability bounds, described on page 177 of EFSA (2018b).

Specifically, the upper limit for the probability of MOE>MOEU is obtained by summing the upper limits of the probabilities for RP>RPU and 1/P95>1/P95L:

$$\text{Prob}[\text{RP} > \text{RPU}] \leq \mathbf{1}\%$$

$$\text{Prob}\left[\frac{1}{\text{P95}} > \frac{1}{\text{P95L}}\right] = \text{Prob}[\text{P95} < \text{P95L}] \leq 1\%$$

to give:

$$\text{Prob}[\text{MOE} > \text{MOEU}] \leq \text{Prob}[\text{RP} > \text{RPU}] + \text{Prob}\left[\frac{1}{P95} > \frac{1}{P95L}\right] \leq 1\% + 1\%$$

i.e.

$$\text{Prob}[\text{MOE} > \text{MOEU}] \leq \mathbf{2}\%$$

And therefore:

$$\text{Prob}[\text{MOE} \leq \text{MOEU}] \geq 98\%$$

A lower bound estimate for the Margin of Exposure (MOEL) was obtained by dividing RPL by P95U, which is equivalent to multiplying RPL by 1/P95U. Applying the same method as above, an upper limit for the probability of MOE<MOEL is obtained by summing the upper limits of the probabilities for RP<RPU and 1/P95<1/P95U, resulting in:

$$\text{Prob}[\text{MOE} < \text{MOEL}] \leq \mathbf{2}\%$$

And therefore:

$$\text{Prob}[\text{MOE} \geq \text{MOEL}] \geq 98\%$$

Calculation of the lower and upper bounds for the MOE and their probabilities was performed for European toddlers and NDEA using an Excel spreadsheet, which was displayed to the experts as shown below:

	A	B	C	D	E	F	G
1	PROBABILITY BOUNDS CALCULATIONS FOR NITROSAMINES WG MEETING 30 AUGUST 2022						
2							
3			Lower bound	Upper bound			
4	BMDL for NDEA:	10000			ng/kg bw per day		
5	Multiplicative factor for uncertainties affecting the BMDL:		0.95	1			
6	BMDL x plausible upper bound multiplicative factor:		9500	10000	ng/kg bw per day		
7	"Lost" probability for BMDL uncertainty factor:		1%	1%			
8							
9	Exposure uncertainty factor for Toddlers*		0.3	8			
10	"Lost" probability for exposure uncertainty factor:		1%	1%			
11							
12		P95 Exposure (Scenario 2)	Nominal MOE (Scenario 2)	Lower bound exposure	Upper bound exposure	Lower bound MOE	Upper bound MOE
13		ng/kg bw per day		ng/kg bw per day	ng/kg bw per day		
14	Toddlers	9.6	1042	2.88	76.8	124	3472
15							
16				"Lost" probability for MOE:		2%	2%
17							

The two columns to the lower right of the spreadsheet show the calculated lower and upper bounds for the MOE: there is less than 2% probability that the MOE is less than 124, and less than 2% probability that it is greater than 3472. It was noted that the lower bound for the MOE is an upper bound for risk, and vice versa.

It was explained to the experts that the probability bounds calculation makes no assumption about the distributions of the relative changes for exposure and hazard and allows for any possible dependence between them.

4.3.3. Elicited judgements on overall uncertainty

The lower and upper probability bounds derived from the calculations above are to be considered as initial estimates of the overall uncertainty for the MOE for EU toddlers and NDEA, quantifying the combined impact of all the sources of uncertainty that were included when eliciting judgements on the uncertainty factors for exposure and hazard. To arrive at a final assessment of overall uncertainty, the experts were asked to consider whether there are any additional sources of uncertainty, not yet taken into consideration, and if so, to adjust the initial probabilities to allow for these.

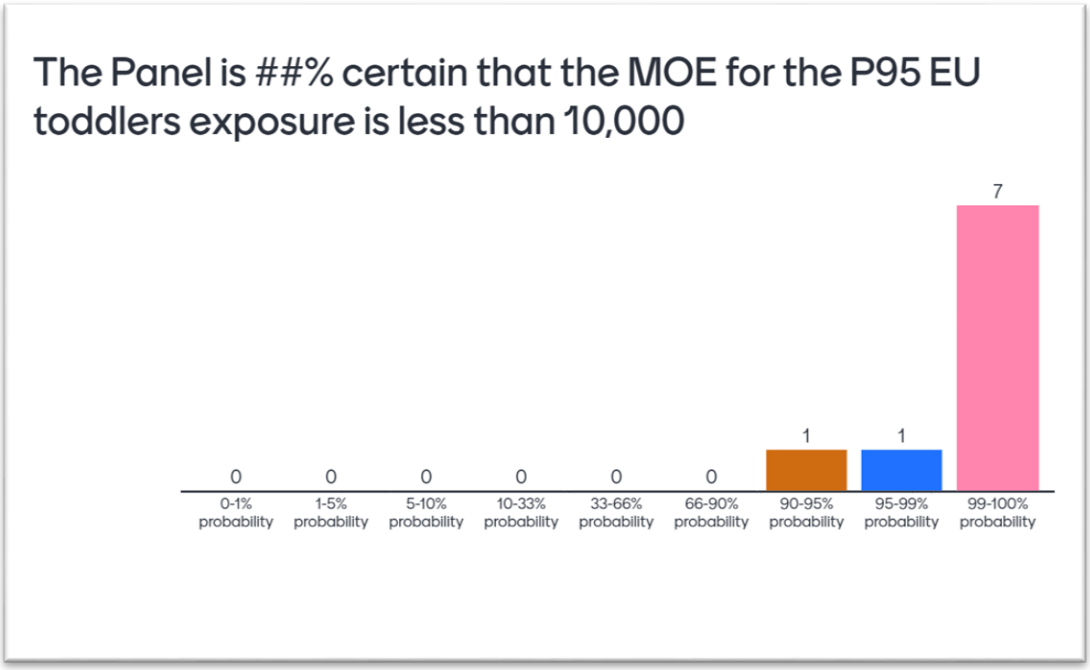
The EKE question for this judgement was framed as shown below.

Framing of MOE EKE question for NDEA

Topic	Description
Parameter	**MOE**
Strata	NDEA
Question	What should be the Panel's probability that the MOE for P95 EU toddlers exposure to NDEA is less than 10,000?
Unit	% probability, expressed as '% certainty'
Operationalisation	A perfect set of studies is conducted to evaluate the hazard of NDEA, perfect measurements of the complete diet of toddlers in whole Europe are included in the assessment, and the MOE for the P95 EU toddler is calculated. The probability of this MOE being below 10,000 is the answer.

The experts made and discussed individual judgements of the overall uncertainty for this question in the meeting of 3 May and agreed on a consensus, based on earlier versions of the exposure assessment. A revised assessment was elicited in the meeting of 30 August, based on the probability bounds calculation shown above. The experts were reminded of the nature of consensus required (what a rational impartial observer would judge, having seen the evidence, uncertainties and individual judgements and heard the discussion) and the need to guard against common heuristic biases affecting human judgement: anchoring and adjustment, availability, over-confidence and 'group think'. The experts' revised consensus judgement was elicited directly by discussion without first eliciting individual judgements. When making this judgement, the experts were asked to take into account any additional uncertainty arising from this semi-formal EKE approach.

The experts identified no additional uncertainties that were not already taken into account by the probability bounds calculation and agreed to base their consensus on the calculated upper bound: 98% probability the MOE was below 3472. It follows that at least the same probability or more applies to an MOE of 10000.



Consensus: The Panel* is 98-100% certain that the MOE for the P95 EU toddlers exposure to NDEA is less than 10,000.

* currently this is a consensus of the Working Group, for consideration by the Panel.

Step 2: Overall Uncertainty of Risk Characterisation – NDEA and other age groups

The procedure described above was repeated, considering all the other age groups other than toddlers and assuming that the uncertainty factors that were elicited for toddlers applied equally to the other age groups.

Calculated probability bounds were displayed as shown below:

	A	B	C	D	E	F	G	H	I	J
1	**PROBABILITY BOUNDS CALCULATIONS FOR NITROSAMINES WG MEETING 30 AUGUST 2022**									
2										
3			Lower bound	Upper bound						
4	BMDL for NDEA:	10000			ng/kg bw per day				* If experts consider exposure factor bounds differ for specific age groups, enter them below	
5	Multiplicative factor for uncertainties affecting the BMDL:		0.95	1						
6	BMDL x plausible upper bound multiplicative factor:		9500	10000	ng/kg bw per day					
7	"Lost" probability for BMDL uncertainty factor:		1%	1%						
8										
9	Exposure uncertainty factor for Toddlers*		0.3	8						
10	"Lost" probability for exposure uncertainty factor:		1%	1%						
11										
12		P95 Exposure (Scenario 2)	Nominal MOE (Scenario 2)	Lower bound exposure	Upper bound exposure	Lower bound MOE	Upper bound MOE		Group-specific exposure factor	
13		ng/kg bw per day		ng/kg bw per day	ng/kg bw per day				Lower	Upper
14	**Infants**	11.5	870	3.45	92	103	2899		0.3	8
15	**Toddlers**	9.6	1042	2.88	76.8	124	3472		0.3	8
16	**Children**	7.6	1316	2.28	60.8	156	4386		0.3	8
17	**Adolescents**	4.8	2083	1.44	38.4	247	6944		0.3	8
18	**Adults**	5.3	1887	1.59	42.4	224	6289		0.3	8
19	**Elderly**	4.6	2174	1.38	36.8	258	7246		0.3	8
20	**Very elderly**	3.2	3125	0.96	25.6	371	10417		0.3	8
21										
22				"Lost" probability for MOE:		2%	2%			

It was noted that both the lower and upper bounds for the MOE were below 10000 for all age groups except the very elderly, where the upper bound was 10417.

The facilitator pointed out that, for the very elderly, an exposure of 10000 ng/kg bw per day would lead to an MOE of precisely 10000. In view of this, to arrive at a probability for the MOE for this age group being less than 10000, the facilitator asked the exposure experts for their consensus judgement on the following EKE question: What is your probability that the P95 exposure to NDEA for EU very elderly is less than 1 ng/kg bw per day?

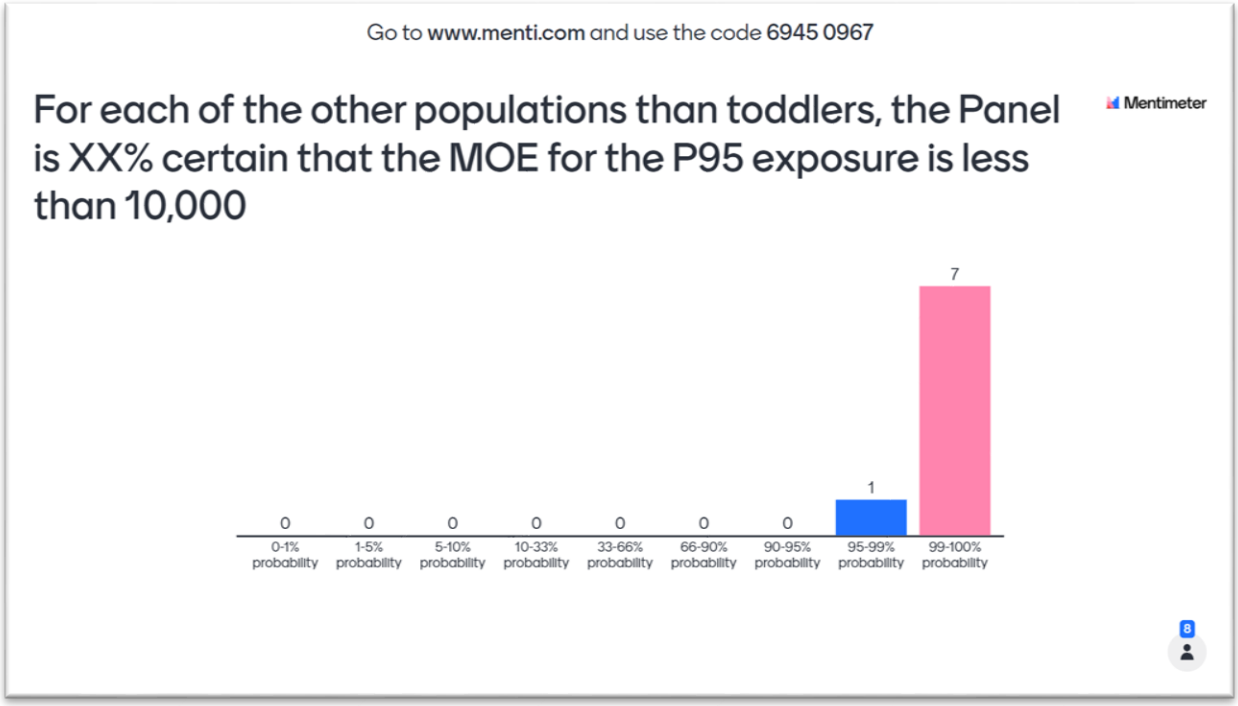
The exposure experts noted that 1 ng/kg bw per day is very close to the exposure of 0.96 ng/kg bw per day which is obtained when their lower plausible bound for the multiplicative factor for EU toddler P95 exposure is applied to the maximum middle bound estimate of exposure for the very elderly (as indicated in row 20 of the spreadsheet shown above), implying less than 1% probability that the exposure is lower. Considering the small difference between these values, they agreed that there is also less than 1% probability that the P95 exposure to NDEA for EU very elderly is lower than 1 ng/kg bw per day.

The facilitator explained that if this revised lower plausible bound of 1 ng/kg bw per day is substituted into the probability bounds calculation for the very elderly, this results in an upper bound MOE of 10000 for this age group (replacing the value of 10417 shown in the spreadsheet above).

To obtain a final assessment of overall uncertainty, the experts were asked to make judgements on the EKE question: What should be the Panel's probability that the MOE for P95 exposure to NDEA is less than 10,000 for each[3] of the other populations?

The experts' judgements on this question were elicited by the same procedure as for the toddler MOE, described above.

[3] Note that the question is asking for a probability that would apply separately to each of the populations, not a probability that the MOE is less than 10,000 for all of them (which would require additional considerations).



The experts identified no additional uncertainties that were not already taken into account by the probability bounds calculations described above and agreed to base their consensus on the results of those calculations.**Consensus: For each of the other populations than toddlers, the Panel* is 98-100% certain that the MOE for the P95 exposure to NDEA is less than 10,000.**

* currently this is a consensus of the Working Group, for consideration by the Panel.

Consideration of other nitrosamines

The draft Opinion contains tabulated MOEs for each of the other nitrosamines separately, as well as for NDEA. It was explained that it would be possible to make a more approximate assessment of uncertainty for these MOEs, repeating the same calculation as for NDEA, assuming the exposure and hazard uncertainty assessments for NDEA and toddlers apply equally to the other populations, and using either NDEA BMDL for every nitrosamine, or specific BMDLs where available.

The experts recalled the WG's earlier assessment of uncertainties affecting the reference values for *N*-other NAs relative to the proposed reference value of 9 ug/kg bw per day for NDEA (see section 4.1.3.2 above), which resulted in the following consensus judgement: **The WG is 95-99% certain that the lowest BMDL for carcinogenicity for any nitrosamine detected in food is 10 ug/kg bw per day.**

The experts noted that there are important differences in the uncertainties affecting assessment of nitrosamines other than NDEA. In particular, occurrence data are available for fewer food categories, and the occurrence levels of other nitrosamines could be higher than NDEA.

The WG concluded there is too much uncertainty about the reference point and exposure to make conclusions on the MOEs of nitrosamines other than NDEA.

Nevertheless, the WG agrees that probabilities of MOE<10,000 for *sum* of nitrosamines must be higher than those provided by the WG for NDEA alone. Therefore, the Panel concluded with 98-100% certainty that the MOE for the P95 exposure to all the carcinogenic *N*-NAs in food combined is less than 10,000.

5. References

EFSA (European Food Safety Authority) Scientific Committee, Benford D, Halldorsson T, Jeger MJ, Knutsen HK, More S, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Schlatter JR, Silano V, Solecki R, Turck D, Younes M, Craig P, Hart A, Von Goetz N, Koutsoumanis K, Mortensen A, Ossendorp B, Martino L, Merten C, Mosbach-Schulz O and Hardy A, 2018. Guidance on Uncertainty Analysis in Scientific Assessments. EFSA Journal 2018;16(1):5123, 39 pp. https://doi.org/10.2903/j.efsa.2018.5123.