Annex to: Risk assessment of *N*-nitrosamines in food. doi: 10.2903/j.efsa.2023.7884

Annex A – Protocol for human risk assessment related to the presence of *N*-nitrosamines in food

Introduction and scope of the protocol

The current protocol reports on the problem formulation and approach selected by the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel), for the risk assessment of *N*-nitrosamines in food. The protocol has been developed in accordance with the draft framework for protocol development for EFSA's scientific assessments (EFSA Scientific Committee, 2020). This framework foresees that the extent of planning in the protocol (i.e. the degree of detail provided for the methods that will be applied in the assessment) can be tailored to accommodate the characteristics of the mandate. This draft protocol has been developed with the aim of setting out as far as possible beforehand, the strategy to be applied for identifying, collecting and selecting data, appraising the relevant evidence, and analysing and integrating the evidence to draw conclusions that will form the basis for the scientific opinions.

Should the need to amend the protocol emerge as the assessment proceeds, such amendments will be documented and justified.

Supporting information

Iinformation on the chemistry, analytical methods, sources including non-dietary sources, EU legislation and previous risk assessments by international bodies, to frame and support the risk assessment will be collected from the literature via official websites, review papers, peer-reviewed publications and legal texts. The information will be summarised in a narrative way based on expert knowledge and judgement.

A.1. Problem formulation

Overall aim of the risk assessment

The overall aim is to assess the risk for adverse effects in humans associated with dietary exposure to *N*-nitrosamines in food.

N-nitrosamines in food have not been previously evaluated by EFSA as such.

Target populations

The target population of the human risk assessment is the European population, including specific vulnerable groups (fetus and breastfed infants) and consumer groups with high exposure due to dietary preferences, e.g. high and frequent processed meat consumers.

N-nitrosamines of concern and route of exposure

The risk assessments will focus on the dietary exposure to *N*-nitrosamines as reported in the literature.

Consideration will be given to potential non-dietary sources of exposure from literature reviews, e.g. drugs and tobacco products, to indicate the relative importance of the diet to the overall nitrosamine exposure.

Adverse effects

The human risk assessment will address the adverse health effects associated with the intake of *N*-nitrosamines as identified in the hazard identification and characterisation step.

Identification of risk assessment sub-questions

A series of sub-questions under each risk assessment pillar (i.e. hazard identification, hazard characterisation and exposure assessment) will be answered and combined to perform the risk assessment. The sub-questions identified are reported in Table A.1.

Table A.1. Sub-questions to be answered for the risk assessment.

Risk assessment step	No	Sub-questions
Hazard identification	1	What *N*-NAs could be found in food?
Hazard identification	2	What adverse outcomes are caused by exposure to *N*-NAs in experimental animals?
Hazard identification	3	What adverse outcomes are associated with exposure to *N*-NAs in humans?
Hazard identification	4	Can the different *N*-NAs be classified according to their genotoxic and carcinogenic potential?
Hazard characterisation	5	What is the absorption, distribution, metabolism and excretion (ADME) of *N*-NAs in experimental animal species/strains?
Hazard characterisation	6	What is the ADME of *N*-NAs in humans?
Hazard characterisation	7	What is the difference in ADME of *N*-NAs between humans and experimental animals?
Hazard characterisation	8	What is the dose-response relationship between *N*-NAs and relevant endpoints in experimental animals?
Hazard characterisation	9	What is the dose-response relationship between *N*-NAs and relevant endpoints in humans?
Hazard characterisation	10	What is the mode of action that can explain the observed adverse effects by *N*-NAs?
Hazard characterisation	11	Is chemical grouping possible?

Exposure assessment	12	What are the analytical methods to be used to detect the occurrence of *N*-NAs in food products?
Exposure assessment	13	What is the effect of processing and processing conditions on the levels of *N*-NAs in food?
Exposure assessment	14	What are the levels of *N*-NAs in food in Europe?
Exposure assessment	15	What are the consumption levels of foods among the European population?
Exposure assessment	16	What is the estimated exposure to *N*-NAs from the diet in the European population including specific vulnerable groups and groups with high exposure?
Exposure assessment	17	What are the concentrations of *N*-NAs in, e.g., urine, blood, breast milk, adipose tissue andplacenta in the European population?
Exposure assessment	18	What is the relationship between the exposure levels and biomarkers measured in human tissues?
Risk characterisation	19	What is the margin of exposure (MOE)? Is the derivation of health-based guidance values (HBGVs) possible?

Studies on both humans and experimental animals will be considered for the hazard identification and characterisation. The potential association between the compound(s) administered and the endpoints of interest for the human risk assessment will be evaluated. It will include an assessment of the dose-response relationship for the derivation of a chronic Reference Point and an evaluation of uncertainties; for example those derived from consideration of the toxicokinetic and toxicodynamic properties of the compounds assessed and from considerations of the inter-species differences and intraspecies variability. The next step will be to estimate the human dietary exposure to the target compounds. The last step will be the calculation of margins of exposure (MOEs) or the comparison of the exposure estimates to a health-based guidance value (HBGVs, e.g. a tolerable intake).

A.2. Method for answering the sub-questions on hazard identification and characterisation

The sub-questions formulated in Table A.1 will be answered by a comprehensive narrative approach. An extensive literature search will be performed to identify primary research studies as well as reviews and meta-analysis relevant to the sub-questions formulated. In addition, the bibliography of the key full text papers will be checked for further, potentially, 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.

To inform the sub-questions related to the hazard identification and characterisation (sub-questions 1 to 11), studies reporting associations with effects in humans (e.g. epidemiological studies), and *in vivo* studies in experimental animals that reported effects after exposure to the *N*-NAs will be considered. The eligibility criteria related to the study

characteristics are listed in Table A.2 (and apply to all sub-questions). The additional eligibility criteria related to study characteristics are listed in Table A.3, A.4 and A.5 for studies in humans, in experimental animals and toxicokinetic studies.

The details of the studies will be reported in tables and discussed in the corresponding section of the Opinion. The experimental animal studies will be reported by: (i) compound of interest tested; (ii) animal species; (iii) study duration and (iv) endpoint. The human epidemiological studies will be reported by: (i) compound of interest analysed; (ii) study design; and (iii) endpoint.

The selection of the scientific studies for inclusion or exclusion will be done by the relevant domain experts from the CONTAM Working Group (WG) on *N*-NAs in food and the CONTAM Panel. It will be based on consideration of the extent to which the study is relevant to the assessment, and on general study quality considerations (e.g. sufficient details on the methodology, performance and outcome of the study, on dosing, substance studied and route of administration and on statistical description of the results), irrespective of the results. Major limitations in the information used will be documented in the scientific Opinion.

Table A.2. Eligibility criteria related to the selection of the reports (all sub-questions).

Language	In	English (a)
Time	In	No time limit
Publication type	In	Peer-reviewed primary research studies (i.e. studies generating new data), systematic reviews, reviews, meta-analyses, extended abstracts, conference proceedings, PhD Theses
	Out	Editorials, letters to the editor

(a): Studies in languages other than English might also be cited if considered relevant by the experts from the CONTAM WG on *N*-NAs or the CONTAM Panel.

Table A.3. Eligibility criteria for the selection of human epidemiological studies.

Sub-questions 3 and 9		
Study design	In	Cohort studies Case-control studies including nested case-control studies
	Out	Animal studies *In vitro* studies
Study characteristics:	In	Any study duration Any number of subjects
	Out	/
Population	In	All population groups, all ages, males and females Study location: all countries
	Out	/

Exposure/ intervention	In	Oral exposure from food Exposure: - Studies in which levels of the *N*-NAs, analysed in food, have been compared to biomarkers. - Studies in which the dietary exposure to the *N*-NAs, analysed in food, has been estimated
	Out	/
Specific outcome of interest	In	All endpoints
	Out	/

Table A.4. Eligibility criteria for the selection of toxicological studies in experimental animals and *in vitro* studies.

Sub-question 2, 4 and 8		
Study design	In	Experimental animal studies in mammals (rats, mice, monkeys, guinea pig, mini pigs, rabbit, hamster, dog, cat, mink) *In vitro* studies in relevant systems (mammalian (including human) primary cells, and cell lines, subcellular interaction studies and bacterial strains used in genotoxicity studies)
	Out	Human studies, studies in non-relevant species.
Study characteristics:	In	Any study duration Any number of animals Any human culture cells/models
	Out	/
Population	In	Any age, males and females
	Out	/
Exposure/ intervention	In	Route of administration: Oral (feeding, gavage studies), i.p. Compounds: *N*-NAs analysed in food Estimated exposure validated Single or repeated administration
	Out	Inhalation, dermal application, i.v, s.c Studies on *N*-NAs not analysed in food
Specific outcome of interest	In	All endpoints
	Out	/

Table A.5. Eligibility criteria for the studies on toxicokinetics.

Sub-questions 5, 6 and 7		
Study design / Test system	In	*In vivo* studies in humans *In vivo* studies in experimental animals *In vitro* studies in mammalian cells/models
	Out	/
Exposure/ intervention	In	Any of the classes of *N*-NAs under evaluation, individually or as mixtures
	Out	/
Specific outcome of interest	In	Any outcome related to the absorption, distribution, metabolism and elimination of the target compounds

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

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 guidance documents pertaining to risk assessment will be followed for the development of the risk assessment:

☐ 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, 2009),

☐ Management of left-censored data in dietary exposure assessment of chemical substances (EFSA, 2010a),

☐ Guidance of EFSA on the use of the EFSA Comprehensive European Food Consumption Database in exposure assessment (EFSA, 2011a),

☐ Overview of the procedures currently used at EFSA for the assessment of dietary exposure to different chemical substances (EFSA, 2011b),

☐ Scientific Opinion on genotoxicity testing strategies applicable to food and feed safety assessment (EFSA Scientific Committee, 2011)

☐ 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 SC, 2012a),

☐ Scientific Opinion on Risk Assessment terminology (EFSA SC, 2012b).

☐ Update: use of the benchmark dose approach in risk assessment (EFSA Scientific Committee, 2017b)

☐ Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA SC, 2019).

☐ Scientific Opinion on the guidance on the use of the weight of evidence approach in scientific assessments (EFSA Scientific Committee, 2017b).

☐ Guidance on the assessment of the biological relevance of data in scientific assessments (EFSA Scientific Committee, 2017c).

☐ Guidance on Uncertainty Analysis in Scientific Assessments (EFSA Scientific Committee, 2018a).

A.2.1 Literature searches

The literature searches to inform the risk assessments on *N*-NAs will be performed searching the following bibliographic databases or scientific citation research platforms:

☐ PubMed

☐ Web of ScienceTM, encompassing the following databases:

☐ Web of ScienceTM Core Collection

☐ BIOSIS Citation IndexSM

☐ CABI: CAB Abstracts®

☐ Current Contents Connect®

☐ Data Citation IndexSM

☐ FSTA® – the food science resource

☐ MEDLINE®

☐ SciELO Citation Index

☐ Zoological Record®

The literature searches for studies relevant to *N*-NAs will be outsourced to an external contractor.

The output from the searched databases, i.e., the bibliographic references wth relevant information, e.g. title, authors, abstract, will be exported into separate Endnote files, allowing a count of the individual hits per database. Files will then be combined, and duplicate records will be removed. The selection process will be performed either in a web-based systematic review software, e.g. with DistillerSR® (Evidence Partners, Ottawa, Canada) or using xls or word files.

A.2.2 Integration of the lines of evidence for hazard identification and method to perform hazard characterisation

The final critical endpoints will be identified by integrating evidence from both human and experimental animal lines of evidence considering the respective levels of confidence. If possible, raw data on these critical endpoints from pivotal studies will be obtained. A 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 ($BMDL_{10}$) for a particular incidence of effect. The lowest relevant Reference Point will be considered to calculate the MOE or for the possible derivation of an HBGV.

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 considered when establishing an MOE or an HBGV.

Information on mode of action will also support this step, as mode of action studies can establish the key events and their relationships required for the various adverse outcomes due to the exposure to *N*-NAs and inform the human relevance of effects observed in *in vivo* and *in vitro* experimental models.

A.3. Method to address the exposure assessment sub-questions

To address sub-question 14 on the levels of *N*-NAs in food in European countries, a structured approach will be followed to collect and evaluate the evidence. The available occurrence data on *N*-NAs in food will be extracted from the EFSA database by the EFSA Evidence Management Unit. Occurrence data are collected through the continuous annual call for data issued by EFSA requesting data on a list of prioritised chemical contaminants2. National food authorities and research institutions, academia, food business operators and other stakeholders are invited to submit data occurrence by the 1st of October each year. Due to time restrictions, the deadline for the collection of data on *N*-NAs will be shorten. The data submission to EFSA must follow the requirements of the EFSA Guidance on Standard Sample Description for Food and Feed ver 2. (EFSA, 2013b) and the chemical monitoring reporting guidance: 2021 data collection (EFSA, 2021); occurrence data will be managed following the EFSA standard operational procedures (SOPs) on 'Data collection and validation' and on 'Data analysis and reporting'.

To guarantee an appropriate quality of the occurrence data used in the exposure assessment, the initial dataset will be evaluated before being used to estimate dietary exposure. This includes, among others, re-codification of any food category misclassification and/or correction of errors in other reported variables , e.g., unit of measure, the exclusion of suspect samples or those samples with incomplete information (e.g., absence of detailed analytical methodology). These steps will be carried out by the EFSA officer in charge of the exposure assessment in collaboration with the members of the Working Group and/or the Scientific Committee.

In the case of lack of data for certain food categories in the EFSA database, the WG may choose, based on clearly specified criteria, to extract data from selected literature studies and include them in the exposure assessemnt.

Left-censored data (results below LOD or below LOQ) will be treated by the substitution method as recommended in the "Principles and Methods for the Risk Assessment of Chemicals in Food" (WHO/IPCS, 2009). The same method is indicated in the EFSA scientific report "Management of left-censored data in dietary exposure assessment of chemical substances" (EFSA, 2010b) as an option in the treatment of left-censored data. The guidance suggests that the lower bound (LB) and upper bound (UB) approach should be used for chemicals likely to be present in the food (e.g. naturally occurring contaminants, nutrients and mycotoxins). The LB is obtained by assigning a value of zero (minimum possible value) to all samples reported as lower than the LOD (< LOD) or LOQ (< LOQ). The UB is obtained by assigning the numerical value of LOD to values reported as < LOD and LOQ to values reported as < LOQ (maximum possible value), depending on whether LOD or LOQ is reported by the laboratory.

Regarding the consumption levels of foods among the European population (sub-question 15), the EFSA Comprehensive European Food Consumption Database (Comprehensive

Database) will be the source of food consumption information. This database provides a compilation of existing national information on food consumption at an individual level. It was first built in 2010 (EFSA, 2011a; Huybrechts et al., 2011; Merten et al., 2011) and then last updated in July 2021. Details on how the Comprehensive Database is used are published in the Guidance of EFSA (EFSA, 2011a).

As indicated by the EFSA Working Group on Food Consumption and Exposure (EFSA, 2011b), 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 from the chronic exposure assessment.

To estimate the human dietary exposure (sub-question 16), both occurrence and consumption data will be codified and classified according to the FoodEx2 classification system (EFSA, 2011c).

The FoodEx2 classification system consists of a large number of standardized basic food items aggregated into broader food categories in a hierarchical parent-child relationship. Additional descriptors, called facets, are used to provide additional information about the codified foods (e.g., information on food processing and packaging material).

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 for of each food at individual level in each dietary survey.

The estimates will be performed by the EFSA Evidence Management Unit. All analyses will be run using the SAS Statistical Software.

The sub-question 12 will be addressed narratively following the evaluation of reviews as well as of other peer-reviewed single studies published in the literature and evaluation of analytical methods reported by data providers during the collection of the occurrence data by relevant domain experts from the Working Group.

Sub-questions 13, 17,18 and 19 will be addressed narratively by carrying out a literature search to identify reviews as well as other peer-reviewed single studies published in the open literature that will be screened or any other reliable information (e.g. accredited laboratory results) and evaluated by relevant domain experts from the Working Group.

A.4. Method to address uncertainties in risk assessment

The evaluation of the inherent uncertainties in the risk assessments on *N*-NAs will be performed based on the guidance of the Opinion of the Scientific Committee related to Uncertainties in Dietary Exposure Assessment (EFSA, 2007), the report on 'Characterising and Communicating Uncertainty in Exposure Assessment' (WHO/IPCS, 2008) and the new guidance on uncertainties of the EFSA Scientific Committee (EFSA Scientific Committee, 2018) and the guidance on communication of uncertainty in scientific assessments (EFSA, 2019b).

Uncertainties will be collected, assessed qualitatively and prioritised if needed. The prioritised and all uncertainties will be quantified as appropriate for the hazard identification and characterisation and the exposure assessment. The overall uncertainty will be calculated and reported for the overall conclusion.

Recommendations will be included in the Scientific Opinion for the generation of additional data that could decrease the impact of the identified uncertainties on the conclusions of the risk assessment.

A.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 above and sub-question 21).

A.6. Plans for updating the literature searches and dealing with newly available evidence

The literature searches performed will be repeated approximately 2 months before the planned date of adoption of the Opinion. The scientific papers retrieved by these additional searches will be screened for relevance by the members of the Working Group and EFSA staff and included in the draft Opinion as appropriate by the Working Group experts.

A.7. Public Consultation

The draft protocol and the draft Opinion will be subject to a public consultation to receive input from interested parties. The comments will be considered in the finalisation of the protocol and the Opinion.

A.8. History of the amendments

The following amendments were introduced:

Text added under A.3 : "In the case of lack of data for certain food categories in the EFSA database, the WG may choose, based on clearly specified criteria, to extract data from selected literature studies and include them in the exposure assessment."

The paragraph under A.4 : "Uncertainties will be assessed qualitatively and quantitatively as appropriate. The uncertainties will be considered with reference to the Risk Assessment Roadmap and the tables of uncertainties for hazard identification and characterisation and exposure commonly found in CONTAM opinions." was modified as following: "Uncertainties will be collected, assessed qualitatively and prioritised if needed. The prioritised and/or all uncertainties will be quantified as appropriate for the hazard identification and characterisation and the exposure assessment. The overall uncertainty will be calculated and reported for the overall conclusion."

Question 19 'What is the contribution of non-dietary exposure (e.g. from medicines, tobacco products) to total exposure?' was removed from table A.1 and also the following sentence: 'In addition, exposure from other sources than food will be considered e.g., specific categories of medicines, smokers, and users of other tobacco products.' Indicative comparison of the dietary exposure with other sources of exposure will be provided under the supporting information section.

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