Vitenskapskomiteen for mat og miljø
Norwegian Scientific Committee for Food and Environment

Protocol for risk assessment of "other substances"

The Norwegian Scientific Committee for Food and Environment

Technical report from the Norwegian Scientific Committee for Food and Environment (VKM)
Protocol for risk assessment of "other substances"
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Protocol for risk assessment of "other substances"

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Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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Abbreviations

ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and excretion
EEA	European Economic Area
EFSA	European Food Safety Authority
HBGV	health based guidance value
NFSA	Norwegian Food Safety Authority
POD	point of departure
QSAR	quantitative structure-activity relationship
VKM	Norwegian Scientific Committee for Food and Environment

Glossary

Acceptable daily intake
An estimate of the amount of a substance in food or drinking water that can be consumed daily over a lifetime without presenting an appreciable risk to health. It is usually expressed as milligrams of the substance per kilogram of body weight and applies to chemical substances such as food additives, pesticide residues and veterinary drugs (EFSA Glossary).

Absorption, distribution, metabolism and excretion
The four key processes which describe how drugs and chemicals get into the body, what happens to them while they are there, and how they are eliminated (EFSA Glossary).

Adverse health effect
A change in morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences (WHO, 1994).

Health-based guidance value
Guidance on safe consumption of substances that takes into account current safety data, uncertainties in these data, and the likely duration of consumption (EFSA glossary).

"Other substances"
A substance other than a vitamin or mineral that have a nutritional or physiological effect (Regulation (EC) No 1925/2006 of the European Parliament and of the Council).

Point of departure
The point on a dose-response curve established from experimental data used to derive a safe level (EFSA Glossary).

"Positive list"
Annex to Regulation (EC) No 1925/2006 including "other substances" and levels thereof allowed for addition to foods.

Quantitative structure-activity relationship
The quantitative/qualitative structure activity relationships are a set of methods by which the effects of different compounds are related to their molecular structures. It allows the likely adverse or beneficial effects of a particular chemical to be predicted by comparing it with others which have similar structures (EFSA Glossary).

1 Background

"Other substances" are substances that have a nutritional or physiological effect but are not vitamins or minerals. Examples of "other substances" include fatty acids, amino acids, coenzyme Q10 and caffeine. Excessive intake of certain "other substances" may be associated with health risks.

In the European Economic Area (EEA), the provisions on the addition of "other substances" to foods are currently only partially harmonised in Regulation (EC) No 1925/2006. This means that Member States may lay down national supplementary provisions on the aspects that are not harmonised. Any national supplementary provisions must comply, inter alia, with the general principles of EEA law on the free movement of goods, "mutual recognition" and the legal exceptions to these EEA principles.

In Norway, new supplementary national provisions regarding the addition of certain "other substances" to foods including food supplements entered into force on 1 January 2020. The new national supplementary provisions are included in the Norwegian regulation "Forskrift 26. februar 2010 nr. 247 om tilsetning av vitaminer, mineraler og visse andre stoffer til næringsmidler" (Lovdata, 2019), which also implements Regulation (EC) No 1925/2006 in Norwegian internal law.

A so-called "positive list" for the addition of certain "other substances", was included as an Annex to the regulation. The intention is to reduce health risks that can occur when consuming certain "other substances" in foods, including food supplements.

The new national supplementary provisions only apply to the addition of "other substances" that a) have a purity of at least 50% or are concentrated 40 times or more, and b) are not normally consumed as a food in themselves and not normally used as an ingredient in foods.

Furthermore, the supplementary national provisions do not apply to the addition of the following "other substances":

a) plants or parts of plants in fresh, dried, chopped, cut or powdered form
b) extracts of plants or parts of plants exclusively made through basic aqueous extraction, possibly followed by dehydration
c) enzymes and microorganisms and
d) "other substances" listed in Parts A and B of Annex III to Regulation (EC) No 1925/2006

It is only permitted to add "other substances" that are listed in the "positive list" in Annex 3 to foods, including food supplements. Such addition to foods must be in accordance with the terms and conditions set in the "positive list", including the limits that are set for the different substances. Substances regulated by other legislations like those for novel foods,

food additives, flavourings, foods for special medical purposes, etc. is outside the scope of the national supplementary provisions.

If a food business operator wants to add different quantities or use different conditions of a substance that is included in the "positive list", the food business operator must notify the Norwegian Food Safety Authority (NFSA). If a food business operator wants to add new substances, not currently included in the "positive list", the food business operator must apply for authorisation to the NFSA.

When needed for the NFSA to process an application or notification, the Norwegian Scientific Committee for Food and Environment (VKM) is requested to perform a risk assessment so that new substances or higher amounts of substances listed in the "positive list" are risk assessed.

2 Aim and objectives

The overall aim is to examine whether exposure to a specific "other substance", as covered by the national supplementary provisions, may constitute a health risk to the Norwegian population.

The objectives:

- Identify and characterise adverse health effects (hazards) related to oral intake of an "other substance"
    - If possible, identify or establish a health-based guidance value or describe point of departure
    - Describe uncertainty related to the health-based guidance value or point of departure
- Estimate the exposure
    - Estimate exposure for the dose(s) given by NFSA for the included age groups
    - Where relevant, describe exposure from other sources
    - Describe uncertainty related to the exposure estimates
- Assess health risks associated with exposure to the substance, based on exposure and potential hazard, and describe uncertainty that may have an impact on the conclusions
- Identify and describe main knowledge gaps that may have an impact on the conclusions

2.1 Limitations

- The assessment is performed for a given substance, and only for the dose(s) in the mandate given by NFSA.
- The assessment covers the general healthy population, not groups in the population that may have a high exposure due to e.g. certain dietary habits, or population groups that may be especially vulnerable due to e.g. certain genetic variants, diseases, drug use or age/life stages.
- The age groups to be included are given in the mandate from the NFSA.
- Exposure from other sources of the substance, such as e.g. food or cosmetics, is not estimated.
- Documentation of any claimed beneficial effects is not evaluated.
- Stability of the substance in a product is not addressed.
- Interaction with other components in a product is not addressed.
- Potential impurities are not addressed.

3 Substance specifications

3.1 Name and other identifiers of the substance

We will address the following:

- Substance name
- CAS number
- EINECS number
- Molecular formula
- Molecular weight
- Structural formula
- Configuration

3.2 Physical and chemical properties

We will address the following:

- Physical state
- Boiling point (liquids), melting point (solids)
- Relative density
- Vapour pressure
- Water solubility
- Partition coefficient

4 Absorption, distribution, metabolism and elimination

The absorption, distribution, metabolism and elimination (ADME) of the substance will be described. We aim to answer the following questions:

1. What is the ADME of the substance in humans?
2. Is the substance metabolised to innocuous metabolites?
3. If the substance is an endogenous metabolite, is the dose given in the mandate from NFSA within normal physiological metabolisation and elimination (homeostasis)?

If data on ADME are only available from animal studies, their relevance for humans will be evaluated.

When considered necessary, VKM will perform literature searches in the electronic databases from MEDLINE (Ovid) and Embase (Ovid) (see Appendix, Section 9, for search terms).

When considered necessary and feasible, quantitative structure activity relationship (QSAR) models may be used to predict ADME. Using QSAR data simulation, information on possible metabolites and properties can be obtained based on the chemical structures and similarities to chemicals for which such information is known. The information can be used to find structurally and mechanistically defined analogues and chemical categories, serving as sources for read-across when actual data is missing.

5 Hazard identification and characterisation

We aim to identify and characterise potential hazards related to oral intake of the substance. The extent of toxicity data needed will be considered for each substance.

The research questions for the hazard identification and characterisation are presented in Table 5-1.

Table 5-1. Hazard: Research questions.

Hazard	No	Research questions
Identification	1	Is there a concern for genotoxicity?
	2	Is exposure to the substance associated with adverse health effects?
Characterisation	3	What is the dose-response relationships between exposure to the substance and the adverse effects?
	4	Can a health-based guidance value be established or a point of departure be identified?

A brief overview of the hazard identification and characterisation is given in Figure 5-1.

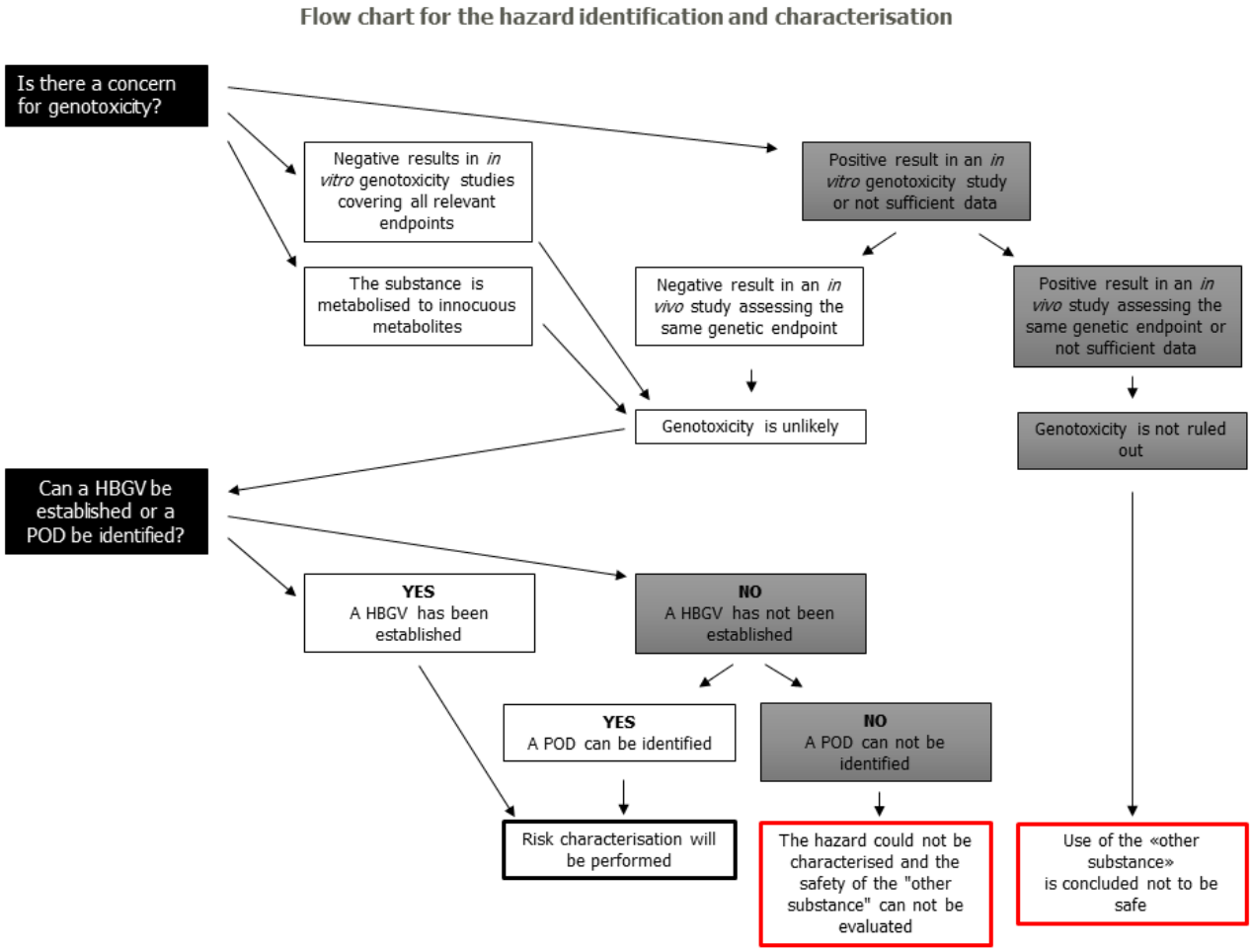

Figure 5-1. Flow chart for the hazard identification and characterisation. HBGV = health-based guidance value; POD = point of departure.

5.1 Evaluation of genotoxic potential

For substances metabolised to innocuous metabolites (Section 4), genotoxicity is considered to be unlikely and therefore no further evaluation of genotoxic potential will be performed. For all other substances, the genotoxic potential will be further evaluated (research question 1, table 5-1). For adequate evaluation of the genotoxic potential of a chemical substance, the endpoints induction of gene mutations, structural and numerical chromosomal alterations will be assessed. If data are not sufficient to conclude that genotoxicity is unlikely, we will conclude that use of the "other substance" may not be safe and further assessment of the substance will therefore not be performed.

5.1.1 General considerations for the evaluation of genotoxicity

Negative results for the substance in *in vitro* genotoxicity studies with adequate quality and covering all relevant endpoints (gene mutations, structural and numerical chromosomal alterations), are sufficient to rule out genotoxic potential. This only applies if the standard

exogenous metabolising system used in the *in vitro* study is considered to adequately reflect the metabolism *in vivo*.

A positive result in an *in vitro* genotoxicity study needs to be followed by an *in vivo* study assessing the same genetic endpoint.

Further *in vivo* testing may be required to assess whether the genotoxic effect observed *in vitro* is also expressed *in vivo*. The choice of *in vivo* follow-up tests should be guided by effects observed in the *in vitro* studies (genetic endpoint) as well as by knowledge of bioavailability, reactivity, metabolism and target organ specificity of the substance.

Whether a positive *in vitro* genotoxicity finding can be over-ruled by a negative rodent carcinogenicity study will be evaluated on a case-by-case basis. However, a negative rodent carcinogenicity study cannot over-rule a positive *in vivo* genotoxicity test result.

In the case of *in vivo* studies, when negative results are obtained, it is important to demonstrate that the substance reaches the target tissue.

5.1.2 Identification of relevant data for the evaluation of genotoxicity

To identify relevant data of sufficient quality for answering research question 1 (Table 5-1) we will search the websites of international risk assessment organisations for opinions, risk or safety assessments of the substance. When needed, we will perform literature searches in the electronic databases from MEDLINE (Ovid) and Embase (Ovid) (see Appendix for search terms).

The search result will be screened based on predefined eligibility criteria (Table 5.1.2-1).

Table 5.1.2-1. Eligibility criteria for studies on genotoxicity.

Exposure	The substance assessed
Outcome of interest	Genotoxicity
Publication type	Primary studies

Screening of titles and abstracts

Pairs of reviewers will screen titles and abstracts independently. A publication will be included when there is doubt whether the publication meets the eligibility criteria.

Screening of full texts

Pairs of reviewers will screen the full text publications independently. In case of disagreement, the two reviewers will discuss the paper to reach consensus. If the disagreement persists, the project group will reach a final decision.

5.1.3 Evaluation of genotoxicity when sufficient data are lacking

If genotoxicity data are lacking or when there is not sufficient data for all endpoints, the evaluation of genotoxic potential can be based on one of the below options (i, ii or iii):

i. Rodent carcinogenicity data. This should be a 2-year repeated dose study with good quality, i.e. following OECD Test No. 451 (OECD, 2018b).
ii. Information on the following two points
    a. Application of QSAR in prediction of genotoxicity (structural alerts for genotoxicity) for the substance and its metabolites
    b. Physical and chemical characteristics.

    Data obtained from QSAR should not be used alone to predict the genotoxic potential, but has to be considered in combination with ADME and physical and chemical properties of the substance. If there is only information on ADME for experimental animal studies, potential differences in biotransformation in animals and humans should be considered.

iii. Application of read-across. The application of read-across will be evaluated on case-by-case basis.

5.2 Adverse health effects

When genotoxicity is unlikely, the potential to induce other adverse effects will be evaluated to answer research questions 2-4 (Table 5-1).

We aim to identify previously established health-based guidance values (HBGV) defining the level of the substance to which people can safely be exposed over a specified period. If no HBGV is available, we aim to identify a point of departure (POD) for the substance, that is, a point on a dose-response curve that can be used to derive a safe level, when possible, or used for assessing a margin of exposure (MOE).

If no HBGV can be established or no POD can be identified, further assessment of the substance will not be performed.

5.2.1 Health-based guidance value

If opinions, risk or safety assessments of the substance exists and a HBGV such as an acceptable daily intake (ADI) has been established, the current evaluation can be based on this value. An evaluation of date and quality of the opinion/assessment and the need for an updated literature will be decided on a case-by-case basis.

5.2.2 Point of departure

If a HBGV has not been established, a POD for adverse effects should be identified. The type of toxicological data required depends on the following questions:

1. Is the substance expected to be metabolised to innocuous substances?
2. Is the substance endogenous, and is the dose within an acceptable range (e.g. within a physiological/homeostatic range, case-by-case evaluation)?

If questions 1 and 2 can be answered yes, less toxicological data is required to establish a POD.

If the answer is no to both questions, toxicity studies such as repeated dose 90-day oral toxicity study in rodents, i.e. OECD Test No. 408 (OECD, 2018a), is required.

If one of the questions is answered "yes", toxicological data is required, however, e.g. randomised control studies (RCT) with sufficient follow-up time and which include also adverse outcomes and analyses of relevant clinical and clinical biochemistry parameters (haematological and clinical biochemistry parameters) or a repeated dose 28-day oral toxicity study in rodents, may be sufficient to establish a POD. This will be evaluated on a case-by-case basis.

5.2.3 Identification of relevant data for the evaluation of adverse effects

To identify relevant data for answering research questions 2-4 (Table 5-1) we will search the websites of international risk assessment organizations for opinions, risk or safety assessments of the substance published outside the traditional publishing channels. When needed, we will perform literature searches in the electronic databases from MEDLINE (Ovid) and Embase (Ovid) (see Appendix for search terms).

Animal studies will be used to describe (dose response relationship for) i) acute and subacute toxicity, ii) subchronic toxicity, iii) chronic toxicity, and iv) reproductive toxicity (including developmental toxicity and fertility).

Human data will be used to identify relevant effects to the human population. We will include experimental studies (randomised controlled studies and other controlled studies) and observational studies (cross-sectional studies, case-control studies and cohort studies

5.2.3.1 Publication selection

Literature retrieved from the searches will be screened based on the eligibility criteria presented in Tables 5.2.3.1-1 (animal studies) and 5.2.3.1-2 (human studies).

Table 5.2.3.1-1. Hazard: eligibility criteria for animal studies.

Study design	Animal studies testing more than one dose of the substance

Animal models	Mammalian animals
Exposure	The substance is tested alone (not part of a mixture) Exposure route in prioritised order: 1. Oral 2. Intraperitoneal, intravenous, subcutaneous
Outcome of interest	Any adverse health effect associated with the substance assessed
Language of the full text	English, Norwegian, Swedish, Danish, German
Publication type	Scientific publications

Table 5.2.3.1-2. Hazard: eligibility criteria for human studies.

Study design	Human experimental studies (RCTs and other controlled studies) Human observational studies (cross-sectional studies, case-control studies and cohort studies)
Population	All age groups, males and females
Exposure	The substance is tested alone (not part of a mixture) Exposure route in prioritised order: 1. Oral 2. Intraperitoneal, intravenous, subcutaneous
Outcome of interest	Any adverse health effect related to exposure to the substance
Language of the full text	English, Norwegian, Swedish, Danish, German
Publication type	Scientific publications

An overview of the results of the study selection will be presented in a flowchart.

The publication selection process will be as follows:

Screening of titles and abstracts

Pairs of reviewers will screen titles and abstracts independently. A publication should be included when there is doubt whether the publication meets the eligibility criteria.

Evaluation of full texts

Pairs of reviewers will screen the full text publications independently. In case of disagreement, the two reviewers will discuss the paper to reach consensus. If the disagreement persists, the project group will reach a final decision.

5.2.3.2 Evaluation of internal validity

The included studies will be divided between pairs of reviewers for evaluation of internal validity/risk of bias (RoB) (OHAT, 2015; OHAT, 2019).

5.2.3.3 Rating of confidence in evidence

The rating of confidence in evidence will be performed according to the "Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration" (OHAT, 2019).

- For each study, an initial confidence rating will be performed to determine the ability of the study design to ensure that exposure preceded and was associated with the outcome. We will follow the method suggested by OHAT (2019) and evaluate whether 1) the exposure was experimentally controlled, 2) the exposure occurred prior to the development of the outcome, 3) the outcome is assessed on the individual level (i.e., not through population aggregate data) and 4) an appropriate comparison group is included in the study. Fulfilment of all features will receive an initial rating of high confidence (++++). Lower ratings, i.e. moderate (+++), low (++) or very low (+), correspond to the number of features fulfilled. Studies rated high or moderate will be included for further analysis.
  Studies rated low or very low will be excluded.
- Factors that may downgrade the initial level of confidence in evidence will be evaluated for each study, and are internal validity/risk of bias, bias related to funding/conflict of interest, unexplained inconsistency and imprecision.
- Factors that may upgrade the initial level of confidence in evidence will be evaluated for each study, and are large magnitude of effect (e.g. incidence, degrees of severity), the presence of a dose-response relationship, residual confounding (if a study reports an effect or association despite the presence of residual confounding and there are indications that such confounding or bias would underestimate the effect, confidence in the association is increased) and consistency across study design type/dissimilar populations for the relevant studies combined.
- Following downgrading and upgrading, for each study the confidence in the evidence for a given effect will be determined using the following terms (OHAT, 2019):
  - "High confidence (++++) in the association between exposure to the substance and the outcome. The true effect is highly likely to be reflected in the apparent relationship.
  - Moderate confidence (+++) in the association between exposure to the substance and the outcome. The true effect may be reflected in the apparent relationship.
  - Low confidence (++) in the association between exposure to the substance and the outcome. The true effect may be different from the apparent relationship.
  - Very low confidence (+) in the association between exposure to the substance and the outcome. The true effect is highly likely to be different from the apparent relationship."

  Studies rated low or very low will be excluded.

- All studies addressing a given outcome will be grouped, and the overall level of confidence in evidence across all studies will be determined using the same rating terms as for single studies.

5.2.3.4 Level of evidence for health effect

The overall confidence in evidence for a given outcome (Chapter 3.1.4) will be translated into level of evidence for health effect according to OHAT (2019). Five descriptors are used to categorise the level of evidence: "high," "moderate," "low," "evidence of no health effect," and "inadequate evidence". The definition of the descriptors, as given by OHAT (2019) is as follows:

- "High Level of Evidence. There is high confidence in the body of evidence for an association between exposure to the substance and the health outcome(s).
- Moderate Level of Evidence. There is moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome(s).
- Low Level of Evidence. There is low confidence in the body of evidence for an association between exposure to the substance and the health outcome(s), or no data are available.
- Evidence of No Health Effect. There is high confidence in the body of evidence that exposure to the substance is not associated with the health outcome(s).
- Inadequate Evidence. There is insufficient evidence available to assess if the exposure to the substance is associated with the health outcome(s)".

The level of evidence for a health effect should be categorised as high, moderate or evidence of no health effect to be used for the risk characterisation.

5.2.4 Data charting

An overview of data items to be extracted is given in Tables 5.2.4-1 and 5.2.4-2.

Table 5.2.4-1. Data items to be extracted from animal studies.

Study characteristics	• Title • Author(s) • Year • Country • Funding source(s) • Reported conflict of interest
Type of study	• Good laboratory practice (yes/no) • Guideline study (yes/no; if yes, specify) • Study design (including number of groups/ number of animals per group)

Animal model	• Species/(sub)strain/line • Disease models (e.g. allergy)
Study design and exposure	• Sex and age • Feed (name, source) • Compound purity • Vehicle used • Dose regimen and frequency • Route of administration • Period of exposure (e.g. pre-mating, mating, gestation, lactation, adult) • Exposure duration
Results and statistical analysis	• Main outcome(s) • Period of outcome assessment (premating, mating, gestation, lactation, adult) • Parameters measured and methods used • Statistical test(s)
Comments	

Table 5.2.4-2. Data items to be extracted from human studies. Note that not all data extraction information listed is relevant for all study designs

Study characteristics	• Title • Author(s) • Year of publication • Country • Funding • Reported conflict of interest
Methods/ intervention	• Study design (e.g. RCT, cohort, etc.) • Type of blinding • Method for randomization • Doses
Participants	• Number of participants and completion rate (invited, accepted, drop out, included in follow-up if applicable) • Inclusion/exclusion criteria for participants • Gender • Age • Number of exposed/non-exposed • Confounders and other variables as reported • Health and socioeconomic status of participants • Other (e.g. selection bias and representativeness for the general Norwegian population)

Results	• Reported outcome (including measures of variance) • Parameters measured and methods used • Measurement time points
Statistical analysis	• Power analysis • Statistical test
Comments	

One project group member will extract the data with a second project group member independently checking the data extraction for accuracy and completeness. In case of disagreement, the two project group members will discuss to reach consensus. If the disagreement persists, the project group will reach a final decision.

5.2.5 Synthesis of results – adverse effects

The main results on adverse health outcomes from the included literature will be presented in table format summarising the main findings.

6 Exposure assessment

The research question is presented in Table 6-1.

Table 6-1. Exposure: Research questions.

Exposure	**Research question**
	What is the estimated daily exposure for the substance?

We will estimate the exposure resulting from oral intake of the dose(s) given in the mandate from the NFSA.

The default body weights (bw) determined by EFSA, the median and the 5th percentile, will be used for the exposure calculations (EFSA Scientific Committee, 2012).

We will not estimate the exposure from other sources of the substance, such as e.g. food or cosmetics. However, when estimates of exposure from other sources are available, it will be reported.

7 Risk characterisation

The risk characterisation will be based on the HBGV or POD and the estimated exposure (e.g. given doses and other sources of exposure).

For "other substances" with a HBGV, the risk characterisation will be based the exposure and the HBGV. An exposure below the HBGV will be judged as acceptable.

For POD the margin of exposure (MOE) approach, i.e. the ratio of the POD to the exposure (MOE=POD/Exposure), will be used for the risk characterisation. The acceptability of the margins will be evaluated on a case-by-case basis.

8 References

EFSA Glossary. European Food Safety Authority, https://www.efsa.europa.eu/en/glossary-taxonomy-terms.

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9 Appendix: Literature searches

9.1 Absorption, distribution, metabolism and excretion

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to date of the search>

((("Name of the substance" or "synonyms for the name of the substance*").ti.) AND (absorption/ or absorption, physicochemical/ or Metabolism/ or Biotransformation/ or (Absorption or distribution or metabol* or elimination or excretion or degradation or biotransformation? or bioconversion? or "biological transformation?" or toxicokinetic? or clearance or detoxification or detoxication or adme).tw,kf)) NOT (comment or editorial or letter).pt.

Embase 1974 to date of the search

((((("Name of the substance" or "synonyms for the name of the substance*").ti.) AND (absorption/ or metabolism/ or excretion/ or degradation/ or biotransformation/ or toxicokinetics/ or clearance/ or detoxification/ or metabolite/ or (Absorption or distribution or metabol* or elimination or excretion or degradation or biotransformation? or bioconversion? or "biological transformation?" or toxicokinetic? or clearance or detoxification or detoxication or adme).tw,kw)) NOT (conference abstract* or letter* or editorial*).pt.) AND Elsevier.cr.

9.2 Genotoxicity

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to date of the search>

((("Name of the substance" or "synonyms for the name of the substance*").ti.) AND (Mutation/ or Mutagens/ or Mutagenesis/ or Mutagenicity Tests/ or DNA damage/ or dna breaks/ or dna breaks, double-stranded/ or dna breaks, single-stranded/ or Comet Assay/ or Chromosome Aberrations/ or Cytogenetics/ or Aneugens/ or Micronucleus Tests/ or Sister Chromatid Exchange/ or DNA Adducts/ or Frameshift Mutation/ or Point Mutation/ or Chromosome Duplication/ or Gene Duplication/ or Chromosome Breakage/ or Aneuploidy/ or Noxae/ or (Mutation? or mutagen* or (gene? adj2 alteration?) or mutator? or Genotoxi* or "Genetic Toxicity Test?" or "Ames test*" or "ames salmonella assay?" or "mouse lymphoma tk assay?" or "mouse lymphoma assay?" or "mouse spot test" or mutamouse or (Muta adj2

Mouse) or "Big Blue" or "LacZ mouse" or "LacI mouse" or "cII gene" or "gpt delta" or (("deoxyribonucleic acid" or DNA) adj (damage* or injur* or lesion? or break* or adduct? or reactivity)) or "strand break*" or "doublestrand break*" or "singlestrand break*" or "comet assay*" or "single cell gel electrophoresis" or "singlecell gel electrophoresis" or SCGE or "alkaline elution" or "unscheduled DNA synthesis" or "unscheduled deoxyribonucleic acid synthesis" or "Rec assay? with Bacillus subtilis" or "SOS test with Escherichia coli" or ((chromosom* or autosom*) adj (aberration? or abnormalit* or anomal* or defect? or error? or duplication? or break* or endoreduplication?)) or cytogen* or clastogen* or aneugen* or "Aneuploidyinducing Agent?" or "Polyploidy Inducing Agent?" or "Polyploidyinducing Agent?" or "micronucleus assay?" or "micronucleus test*" or "MN assay?" or "SOS chromotest*" or "sister chromatid exchange*" or ((Frameshift or "Frame Shift" or "reading frame" or point) adj Mutation?) or "reading frame shift" or ((OutofFrame or "Out of Frame") adj (Mutation? or Insertion? or Deletion?)) or gentox* or "gene duplication?" or "gene doubling?" or Aneuploidy or aneuploid* or (toxic adj (substance? or agent? or chemical? or compound?)) or noxae).tw,kf)) NOT (comment or editorial or letter).pt.

Embase 1974 to date of the search

((((("Name of the substance" or "synonyms for the name of the substance*").ti.) AND (gene mutation/ or mutation/ or mutagenic agent/ or mutagenic activity/ or mutagenesis/ or mutagenicity/ or mutagen testing/ or Ames test/ or genotoxicity/ or DNA damage/ or dna strand breakage/ or double stranded dna break/ or single stranded dna break/ or comet assay/ or unscheduled DNA synthesis/ or chromosome aberration/ or cytogenetics/ or clastogen/ or aneugen/ or micronucleus test/ or SOS chromotest/ or sister chromatid exchange/ or DNA adduct/ or Frameshift Mutation/ or point mutation/ or toxic substance/ or aneugen/ or chemical mutagen/ or (Mutation? or mutagen* or (gene? adj2 alteration?) or mutator? or Genotoxi* or "Genetic Toxicity Test?" or "Ames test*" or "ames salmonella assay?" or "mouse lymphoma tk assay?" or "mouse lymphoma assay?" or "mouse spot test" or mutamouse or (Muta adj2 Mouse) or "Big Blue" or "LacZ mouse" or "LacI mouse" or "cII gene" or "gpt delta" or (("deoxyribonucleic acid" or DNA) adj (damage* or injur* or lesion? or break? or adduct? or reactivity)) or "strand break*" or "doublestrand break*" or "singlestrand break*" or "comet assay?" or "single cell gel electrophoresis" or "singlecell gel electrophoresis" or SCGE or "alkaline elution" or "unscheduled DNA synthesis" or "unscheduled deoxyribonucleic acid synthesis" or "Rec assay? with Bacillus subtilis" or "SOS test with Escherichia coli" or ((chromosom* or autosom*) adj (aberration? or abnormalit* or anomal* or defect? or error? or duplication? or break* or endoreduplication?)) or cytogen* or clastogen* or aneugen* or "Aneuploidyinducing Agent?" or "Polyploidy Inducing Agent?" or "Polyploidyinducing Agent?" or "micronucleus assay?" or "micronucleus test*" or "MN assay?" or "SOS chromotest*" or "sister chromatid exchange*" or ((Frameshift or "Frame Shift" or "reading frame" or point) adj Mutation?) or "reading frame shift" or ((OutofFrame or "Out of Frame") adj (Mutation? or Insertion? or Deletion?)) or gentox* or "gene duplication?" or "gene doubling?" or Aneuploidy or aneuploid* or (toxic adj (substance? or agent? or

chemical? or compound?)) or noxae).tw,kw)) NOT (conference abstract* or letter* or editorial*).pt.) AND Elsevier.cr.

9.3 Adverse health effects

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((("Name of the substance" or "synonyms for the name of the substance*").ti.) AND (risk/ or risk assessment/ or risk factors/ or "Chemical and Drug Induced Liver Injury"/ or Immunosuppression/ or Endocrine Disruptors/ or Hypersensitivity/ or Food Hypersensitivity/ or Food Intolerance/ or Anaphylaxis/ or Inflammation/ or Poisoning/ or (adverse effects or toxicity or poisoning).fs. or (risk* or safety or adverse or "side effect?" or sideeffect? or hazard* or harm* or negative or toxicity or toxic or hepatotox* or "liver tox*" or nephrotox* or "nephro tox*" or "kidney tox*" or "renal tox*" or immunotox* or "immune system tox*" or "immune tox*" or "immuno tox*" or "immunosystem tox*" or "reproductive tox*" or "developmental tox*" or embryotox* or "embryo tox*" or "lung tox*" or pulmotox* or "pulmonary tox*" or "respiratory tox*" or respirotox* or neurotox* or "skin tox*" or "dermal tox*" or dermatox* or teratogenicity or teratogeneity or "endocrine tox*" or "immune effect" or "immune respons*" or "immuno respons*" or immunorespons* or immunogenesis or "immunologic respons*" or immunosuppress* or "immuno suppress*" or "immune suppress*" or "endocrine disrupt" or anaphylax* or anaphylactic or anaphylactoid or anaphylatoxin or "immune fever" or "food intoleranc*" or "Food Sensitivit*" or "nutritional intolerance*" or "nutrient intolerance*" or hypersensitiv* or hypersensitization or hypersensitisation or hyperergic or hyperergy or erethism or Allergy or Allergies or Allergic or allergen? or allergenic or sensitization or inflammation* or inflammatory or serositis or poisoning?).tw,kf)) NOT (comment or editorial or letter).pt.

Embase 1974 to date of the search

((((("name of the substance" or "synonyms for the name of the substance*").ti.) AND (risk/ or risk assessment/ or risk factor/ or exp side effect/ or exp adverse drug reaction/ or adverse event/ or toxicity/ or acute toxicity/ or exp health hazard/ or hazard assessment/ or liver toxicity/ or nephrotoxicity/ or immunotoxicity/ or reproductive toxicity/ or chronic toxicity/ or embryotoxicity/ or lung toxicity/ or neurotoxicity/ or skin toxicity/ or teratogenicity/ or immune response/ or immunosuppressive treatment/ or endocrine disruptor/ or hypersensitivity/ or allergy/ or food allergy/ or food allergen/ or anaphylaxis/ or nutritional intolerance/ or inflammation/ or (risk* or safety or adverse or "side effect?" or sideeffect? or hazard* or harm* or negative or toxicity or toxic or hepatotox* or "liver tox*" or nephrotox* or "nephro tox*" or "kidney tox*" or "renal tox*" or immunotox* or "immune system tox*" or "immune tox*" or "immuno tox*" or "immunosystem tox*" or "reproductive

tox*" or "developmental tox*" or embryotox* or "embryo tox*" or "lung tox*" or pulmotox* or "pulmonary tox*" or "respiratory tox*" or respirotox* or neurotox* or "skin tox*" or "dermal tox*" or dermatox* or teratogenicity or teratogeneity or "endocrine tox*" or "immune effect" or "immune respons*" or "immuno respons*" or immunorespons* or immunogenesis or "immunologic respons*" or immunosuppress* or "immuno suppress*" or "immune suppress*" or "endocrine disrupt" or anaphylax* or anaphylactic or anaphylactoid or anaphylatoxin or "immune fever" or "food intoleranc*" or "Food Sensitivit*" or "nutritional intolerance*" or "nutrient intolerance*" or hypersensitiv* or hypersensitization or hypersensitisation or hyperergic or hyperergy or erethism or Allergy or Allergies or Allergic or allergen? or allergenic or sensitization or inflammation* or inflammatory or serositis or poisoning?).tw,kw)) NOT (conference abstract* or letter* or editorial*).pt.) AND Elsevier.cr.