ANSES Opinion
Request No 2020-SA-0106
Related Request Nos 2019-SA-0178 and 2021-SA-0176

The Director General

Maisons-Alfort, 6 July 2022

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on the risks associated with the consumption of nitrites and nitrates[1]

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.
It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).
Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 6 July 2022 shall prevail.

On 29 June 2020, ANSES received a formal request from the Directorate General for Health (DGS), the Directorate General for Food (DGAL) and the Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF) to conduct the following expert appraisal: formal request on the risks associated with the consumption of nitrites and nitrates.

1. BACKGROUND AND PURPOSE OF THE REQUEST

1.1. Background

The context of this expert appraisal is presented below according to the terms of the formal request (in italics and inverted commas).

"The presence of nitrites in the body can lead to haemoglobin oxidation, reducing the ability of red blood cells to carry oxygen. It can also contribute to the formation of other compounds, such as nitrosamines, some of which are carcinogenic.

There are various sources of consumer exposure to nitrites, mainly:

[1] This version cancels and replaces the version of 1July 2022

i) The conversion of nitrates into nitrites in certain foodstuffs.

Nitrates are found in water mainly because of their use in primary production. They occur naturally in some foodstuffs, particularly leafy vegetables such as spinach or lettuce. In humans, some of the nitrates consumed can be converted to nitrites by bacteria in the oral cavity.

ii) The unintentional presence of nitrites in foodstuffs.

Nitrites may be found in vegetables in particular, but at levels that are generally much lower than those for nitrates.

iii) The use of nitrites and nitrates as additives in foodstuffs.

Potassium and sodium nitrites (E249, E250) and sodium and potassium nitrates (E251, E252) are commonly used to preserve meat and other perishable products. They also help limit the proliferation of harmful micro-organisms, in particular Clostridium botulinum, which causes botulism. These food additives are authorised in the European Union. As such, they have undergone scientific assessments to characterise the risks associated with their use.

The European regulations[2] currently provide for a maximum level of incorporation of 150 mg/kg for processed meat products, excluding traditional products. For traditional products, which are produced in smaller volumes than the industrially produced ones and therefore contribute less to consumer exposure, the regulations provide for a residual nitrite and nitrate content of up to 250 mg/kg. The residual content varies according to various factors related to the processing method (processing temperature, pH, presence of ascorbic acid, etc.) and does not depend solely on the levels initially incorporated. The Danish authorities wished to maintain a lower level of use, at 60 mg/kg, which they had set prior to European harmonisation.

The combination of haem iron and added nitrites has in particular been considered as an explanation for the observed increased risk of developing colon or rectal cancers associated with the consumption of certain meat products (IARC-INCa 2018 data)[3]. *The haem iron contained in the meat is thought to promote the conversion of nitrites into nitrosamines, substances classified as probably carcinogenic to humans (Group 2A).*

In response to consumer demand, industry has developed solutions presented as alternatives to the use of nitrate or nitrite salts (shortened UBD[4]s, vegetable broths, plant extracts, etc.). In addition, operators have committed more generally to reducing the use of additives in line with the objectives set by the national food and nutrition programme (PNAN).

[2] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives.
[3] IARC/INCa 2018 study "Cancer cases in France attributable to lifestyle and environmental factors". Lyon: International Agency for Research on Cancer, 2018.
[4] Use-by date

As part of its re-evaluation of additives, the European Food Safety Authority (EFSA) issued opinions in June 2017[5] and concluded, based on the available evidence, that the existing levels for nitrites and nitrates intentionally added to meat and other foods were sufficiently protective for consumers.

More specifically:

- *regarding nitrates used as food additives, and with "realistic data" (i.e. the concentration levels actually observed in food), the experts estimated that consumer exposure to nitrates used as food additives was less than 5% of the overall exposure to nitrates in food and did not exceed the Acceptable Daily Intake (ADI);*
- *regarding nitrites used as food additives, the experts estimated that exposure was within safe limits for all population groups, with the exception of children whose diet is rich in foods containing these additives, in whom the limits were exceeded slightly.*

  In addition, when all sources of dietary exposure (natural occurrence in food, environmental contamination, use as additives) were taken into account, the EFSA panel stressed that:
- *for nitrates, exposure may exceed the ADI for all age groups (medium to high exposure assumption);*
- *for nitrites, exposure may exceed the ADI for all age groups under the assumption of high exposure, and for specific age groups (infants, young children and children) under the assumption of medium exposure.*

EFSA also issued recommendations to address some of the uncertainties."

Alongside EFSA's expert appraisal[5] work had been undertaken at ANSES to characterise dietary exposure to nitrates (mainly from vegetables and drinking water) specific to France, in response to formal request 2015-SA-0029. This work resulted from a formal request to ANSES from the *Eaux et Rivières de Bretagne* association (15/01/2015), the *Coordination Rurale* agricultural trade union (19/01/2015) and then the National Federation of Farmers' Unions (FNSEA, 26/01/2015) on the health impacts of nitrates found in food and the environment. This is because in France, both dietary habits and the presence of nitrates in food (especially vegetables) and water may differ significantly from the European data used by EFSA. This is particularly true for the drinking water supply, in which the concentrations of analytes characterising its physico-chemical quality vary according to the resources exploited and the treatments applied. The aim of this work was to assess the French population's exposure to nitrates in relation to toxicological benchmarks. The results would be used to identify situations warranting attention, so as to recommend useful measures where possible, in particular through the identification of foods (including drinking water) contributing the most to nitrate

[5] European Food Safety Authority (2017). Scientific Opinion on the re-evaluation of sodium nitrate (E 251) and potassium nitrate (E 252) as food additives. EFSA Journal 2017;15(6):4787, 123 pp. https://doi.org/10.2903/j.efsa.2017.4787
European Food Safety Authority (2017). Scientific Opinion on the re-evaluation of potassium nitrite (E 249) and sodium nitrite (E 250) as food additives. EFSA Journal 2017;15(6):4786, 157 pp. https://doi.org/10.2903/ j.efsa.2017.4786

exposure in France. This work previously initiated on nitrates has been integrated into the present expert appraisal on dietary exposure to nitrites and nitrates.

The Agency also states that it is currently addressing a formal request from the Ministry of Health on the more specific issue of nitrates in drinking water, for those water supply facilities where the quality limit is exceeded, drawing on some of the work presented below.

1.2. Purpose of the request

Following on from the work carried out by the various health authorities, as part of the present expert appraisal ANSES was asked to:

"*1) take account of EFSA's work on the preservation of meat products with respect to the risk of contamination by Clostridium botulinum, in order to establish, if possible, the situations – including the use of processes presented by industry as a means of replacing nitrate or nitrite salts – in which a reduction in the levels of nitrites/nitrates found in foodstuffs could significantly increase the risks associated with the proliferation of pathogenic bacteria in certain foods;*

2) identify the courses of action that could help reduce overall consumer exposure by ingestion to nitrites and nitrates, regardless of their origin, and thus ultimately to nitrosamines, based on exposure specific to France;

3) assess whether new scientific knowledge, especially in response to EFSA's recommendations, could resolve uncertainties about the transformation mechanisms of nitrates and nitrites in the body and in foodstuffs, and to justify re-examination of the ADIs/Health-Based Guidance Values (HBGVs) determined by EFSA;

4) assess whether, since the 2018 IARC/INCa publication, new scientific knowledge could better characterise the link between human carcinogenesis and intake of haem iron combined with nitrites via consumption of meat products. To do this, ANSES will contact INCa as necessary."

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)".

2.1. Procedure: means implemented and organisation

This expert appraisal mainly falls within the sphere of competence of the Expert Committee on "Assessment of physico-chemical risks in food" (CES ERCA). ANSES entrusted examination of this request to the Working Group on "Risks associated with the consumption of **N**itr**i**tes and **N**itr**a**tes" (NiNa WG), established by decision of 20 November 2020 following a public call for applications. This WG reported to the CES ERCA.

The methodological and scientific aspects of the formal request and the NiNa WG's expert appraisal work were regularly submitted to the CES ERCA between September 2020 and June

2022. The work was also presented to and validated by the experts of the CES on "Assessment of the biological risks in foods" (BIORISK) with regard to the expert appraisal responding to question 1. The experts of the CES on "Water" and the CES on "Health reference values" were also consulted. The report produced by the Working Group takes account of the observations and additional information provided by the CES members.

The results were therefore produced by a group of experts with complementary skills.

The work was adopted by the CES ERCA at its meeting on 17 June 2022.

2.2. Prevention of risks of conflicts of interest

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are made public on the following website: https://dpi.sante.gouv.fr/.

2.3. Expert appraisal method

2.3.1. Discussion group prior to the formal request

Prior to the creation of the WG, a group of four rapporteurs from the CES on "Health reference values" and the CES ERCA, who were appointed with a view to undertaking preparatory work, carried out a literature review to take stock of toxicological and epidemiological knowledge on nitrates and nitrites.

This group of rapporteurs noted the complexity and interactions of the mechanisms involved in carcinogenesis, and the need to clearly understand their functioning in order to take them into account in the expert appraisal. This group also highlighted the possible involvement of various newly-formed compounds.

2.3.2. Working method of the WG

To answer the questions in the formal request, the WG identified the following work themes:

1. assess the impact of reducing or withdrawing nitrite additives on the microbiological risks associated with the presence of certain pathogens in meat and processed products (*Clostridium botulinum, Salmonella* spp.*, Listeria monocytogenes*);
2. collect data on concentrations of nitrates, nitrites and newly-formed compounds in food and water;
3. assess exposure to nitrates and nitrites through food and water;
4. identify nitroso compounds[6] formed in meat products treated with nitrates and nitrites;
5. identify nitroso compounds formed in the consumer's body according to their nitrate/nitrite intake via meat products, *i.e*. not from other foods and water;

[6] Different terms are used in the literature to describe the compounds resulting from the conversion of nitrites. For the sake of harmonisation and consistency between the different parts of the document, the WG has chosen to use the term "nitroso compounds".

6. compile knowledge on the toxicity of nitroso compounds;
7. update the review of epidemiological studies on the links between carcinogenesis and exposure to nitrates and nitrites via water and food;
8. assess the relevance of the health-based guidance values used by EFSA in its 2017 reports;
9. characterise the risk to the French population from dietary exposure to nitrates and nitrites;
10. recommend measures for managing the risks associated with the presence of naturally occurring nitrates and nitrites, or nitrate and nitrite additives in food and their newly-formed compounds.

To implement the methodological approach, three sub-groups were formed within the WG to address the following parts:

- Microbiology;
- Chemistry/Exposure assessment;
- Toxicology/Epidemiology.

Hearings were also held for this expert appraisal with representatives of the meat and processed meat industries (ADIV[7], IFIP[8], FICT[9], ACTIA[10]), and with research teams from INRAE[11] (QuaPA[12], Toxalim[13]), Inserm[14] (EREN[15]) and INCa[16].

Each stage in the response to the formal request was discussed within the relevant expert committees during the expert appraisal work, as part of a process of collective scientific validation.

This opinion is based on the collective expert appraisal report on the assessment of the risks associated with the consumption of nitrates and nitrites.

[7] Association for the development of the meat industry
[8] French pork and pig institute
[9] French federation of industrial pork butchers, caterers and meat processors
[10] French network of technical institutes in the food industry
[11] French National Research Institute for Agriculture, Food and the Environment
[12] Animal products quality unit
[13] Food toxicology unit
[14] French National Institute for Health and Medical Research
[15] Inserm-Nutritional epidemiology research team
[16] National Cancer Institute

3. ANALYSIS AND CONCLUSIONS OF THE CES ERCA AND THE NINA WG

The presentation of the answers to the questions in the opinion does not strictly follow the order of the questions as posed in the text of the formal request. After presenting the substances of interest, their origin and the regulatory framework, this opinion sets out the conclusions of the microbiological risk assessment. This is followed by a presentation of the conclusions relating to the assessment of the available epidemiological and toxicological data, enabling the risks associated with ingested nitrates and nitrites to be characterised after exposure has been estimated.

3.1. Substances of interest addressed in the context of the request

In general, this formal request concerns the problem of nitrate and nitrite ions in food, as well as newly-formed substances, which are potentially harmful to consumer health.
Nitrates, Nitrites and nitroso compounds are therefore the beacons of a holistic and pragmatic approach based on concrete documented facts and using the most relevant scientific data currently available.
The above considerations place the problem and its approach in a descriptive and dynamic perspective focused on nitrate and nitrite ions, including their origin, metabolism and transformation, as shown in the overview diagram below (Figure 1). The presence of nitrates and nitrites in food:

1. is due to the contamination of water resources by human activities (use of nitrogen fertilisers, spreading of liquid manure, discharges of urban or industrial waste);
2. results from bioaccumulation in plants;
3. results from intentional use (nitrate and nitrite additives incorporated as preservatives in foodstuffs, mainly meat products).

The issues addressed in this opinion required a dynamic consideration that was as inclusive as possible of all the pathways by which nitrate and nitrite ions are transformed into newly-formed nitroso compounds, and of their effects on human health. At the same time, the effects of a reduction in the use of nitrites on the microbiological risk associated with meat products was also assessed.

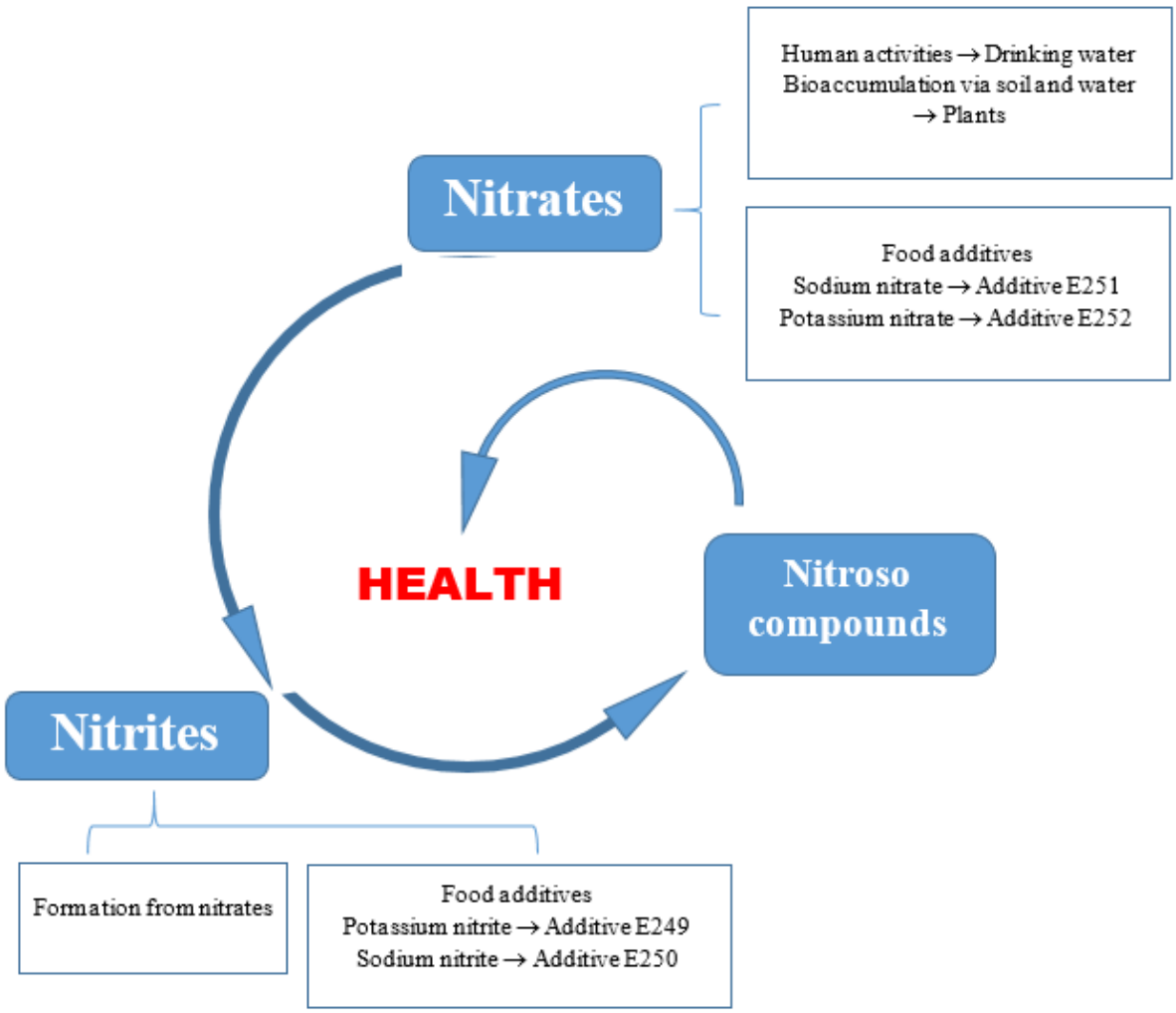

Figure 1. Substances of interest addressed in the context of the request: overview

3.2. Origin and fate of nitrates and nitrites in water and food

Nitrates in raw water mainly come from natural processes associated with the nitrogen cycle (mineralisation of organic matter), agricultural activities (through the spreading of mineral fertilisers and livestock manure) and discharges from urban or industrial sources. Activities in certain industry sectors can also lead to the discharge of water that is very high in nitrates. These include the food industry, especially slaughterhouses and dairies, the chemical and pharmaceutical industries, and the paper industry.

Nitrates in plant organs and products should not be regarded as contaminants but as natural constituents essential for the development of plant tissue. However, excessive nitrogen fertilisation practices can lead to an accumulation of these ions. As a result, nitrate levels in

leafy vegetables, especially lettuce, can be very high and exceed the plants' physiological needs (Escobar-Gutiérrez et al., 2002)[17].

The presence of nitrates and nitrites in meat products is mainly due to their use as additives for their antioxidant and antimicrobial properties and their effect on the colour of the products. Nitrates and nitrites contribute to the production of nitrosating agents ($NO°$, NO^+), which lead to the formation in foodstuffs of nitroso compounds, including:

- nitrosamines, especially in products that are cooked or fried at high temperatures;
- nitrosothiols;
- nitrosyl-haem.

3.3. Regulations

Nitrate and nitrite levels are regulated in water, in foodstuffs of plant origin and in meat products.

At the European level, mains-supplied drinking water, spring water and water made drinkable through treatment are regulated by Directive (EU) 2020/2184 of the European Parliament and of the Council of 16 December 2020 on the quality of water intended for human consumption[18], while natural mineral waters are regulated by Directives 2003/40/EC[19] and 2009/54/EC[20].

In France, the regulations distinguish between natural mineral waters on the one hand, and drinking water on the other, which includes mains-supplied water (tap water), water made drinkable through treatment and bottled spring water. In drinking water, the quality limits for nitrates and nitrites are respectively 50 mg L^{-1} and 0.50 mg L^{-1} (Ministerial Order of 11 January 2007). If the quality limit is exceeded, a temporary derogation to use the water may be granted under certain conditions (Articles R1321-26 to 36 of the French Public Health Code). For nitrates, *"a derogation procedure may be considered for levels between 50 and 100 mg L^{-1} in the distributed water*. *This derogation must then be accompanied by a recommendation that pregnant women and infants avoid consumption"*[21].

The European Union has set maximum levels for nitrates in foodstuffs of plant origin[22], expressed in mg of nitrate ion per kg. However, there are no regulatory levels for nitrites in the EU Regulation on contaminants in foodstuffs. The regulations currently cover six categories of

[17] Escobar-Gutiérrez, A. J., I. G. Burns, A. Lee & R. N. Edmondson (2002). Screening lettuce cultivars for low nitrate content during summer and winter production, The Journal of Horticultural Science and Biotechnology, 77:2, 232-237. http://dx.doi.org/10.1080/14620316.2002.11511485
[18] Directive (EU) 2020/2184 of the European Parliament and of the Council of 16 December 2020 on the quality of water intended for human consumption
[19] Commission Directive 2003/40/EC of 16 May 2003 establishing the list, concentration limits and labelling requirements for the constituents of natural mineral waters and the conditions for using ozone-enriched air for the treatment of natural mineral waters and spring waters
[20] Directive 2009/54/EC of the European Parliament and of the Council of 18 June 2009 concerning the exploitation and marketing of natural mineral waters
[21] Instruction No. DGS/EA4/2018/79 of 21/03/18 on the procedures for managing non-conformities in water intended for human consumption provided for by information notes for the year 2018.
[22] Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs

plant products, considered to be of greatest concern with regard to nitrate intake: spinach whether fresh or not (preserved, deep-frozen or frozen), lettuce, iceberg lettuce, rucola (rocket), and processed cereal-based foods and baby foods for infants and young children.

With regard to the use of nitrates and nitrites as food additives, among the 27 functional classes of food additives currently provided for in Regulation (EC) No 1333/2008 of the European Parliament and of the Council (EU, 2008)[23], potassium or sodium nitrite (E249 or E250 respectively) and sodium or potassium nitrate (E251 or E252 respectively) are included in the "preservatives" class ("*substances which prolong the shelf-life of foods by protecting them against deterioration caused by micro-organisms and/or which protect against growth of pathogenic micro-organisms*"). Under this EU regulation, nitrites are permitted in certain meat preparations (as defined in Regulation (EC) No 853/2004[24]) and in heat-treated and non-heat-treated meat products, while nitrates are permitted in certain fish (pickled herring and sprats), in certain categories of cheese and in non-heat-treated meat products. Nitrates and nitrites are also permitted in some traditional immersion-cured or dry-cured products. Regulation (EC) No 1333/2008 provides for maximum amounts, either for use or as residual amounts, of nitrate and nitrite salts for the different product categories in which they are authorised. In France, the regulatory values for the use of these additives in processed meat products are taken into account in the "Code of practice for processed meat, cured meat and canned meat" drawn up by the industry in order to standardise practices.

3.4. Conclusions and recommendations from the assessment of the microbiological risks associated with reducing nitrate/nitrite levels as additives in certain foods – Question 1 of the formal request

3.4.1. Conclusions

Due to their antimicrobial and technological properties, nitrites and nitrates (as precursors of nitrites) are commonly used as food additives in a wide variety of foodstuffs, mainly meat products (processed meats and cured meats). The inhibitory and antimicrobial activity of nitrites is exerted on a large number of micro-organisms, especially pathogenic bacteria. The impact of reducing the use of nitrates/nitrites in foodstuffs on spoilage micro-organisms[25] was not assessed for this opinion.

The present expert appraisal was conducted by identifying, within the categories of processed meat and cured meat products and the associated microbiological hazards, certain

[23] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives
[24] Regulation (EC) No 853/2004 of the European Parliament and of the Council of 29 April 2004 laying down specific hygiene rules for food of animal origin
[25] Micro-organism (bacterium, yeast, mould) which will grow or modify the organoleptic properties of a food during storage.

hazard/food pairs[26] regarded as relevant examples for estimating the microbiological risks to consumers associated with a reduction or elimination of the nitrites used.

This assessment was based on predictive microbiology models for three hazard/food pairs and provided estimates of the potential increase in risk under the nitrite reduction scenarios tested. This expert appraisal was by nature non-exhaustive: further quantitative risk assessments including other hazard/food pairs and the availability of new knowledge could enable these initial results to be developed and lead to recommendations, in particular for the categories of foodstuffs not yet explored.

On the basis of this work, the experts of the WG and the CES ERCA and CES BIORISK consider that reducing or eliminating the use of nitrites:

- in ready-to-eat cooked processed meat products would not increase the risk of listeriosis, provided that the storage temperature is effectively controlled and the shelf life of the products in question is reduced;
- in dry-cured sausages should necessarily and as a priority be accompanied by measures to reduce the *Salmonella* load in pigs on the farm and hygiene measures at the slaughterhouse, as recommended in ANSES's 2018 opinion[27], without prejudice to the implementation of other measures;
- in dry-cured hams is compatible with preventing the risk of botulism, subject to strict control of salt levels and temperatures during the product's salting, rest and ripening stages.

The experts of the WG and the CES ERCA and CES BIORISK point out that the greater the reduction in the use of nitrites, the higher the microbiological risk to consumers. Consequently, the additional control measures to be implemented by operators should be drastic and/or more numerous. The feasibility of their application and effectiveness will therefore need to be assessed.

The effectiveness of alternatives to the use of nitrates/nitrites in meat products that are currently being studied or applied was not assessed for this opinion. However, the experts of the WG and the CES ERCA and CES BIORISK underline that, for most of these alternatives there is a lack of data on both antimicrobial efficacy and toxicological assessment.

3.4.2. Recommendations

The experts of the WG and the CES ERCA and CES BIORISK reiterate that the application of good hygiene practices and the implementation of a HACCP system are effective measures and remain a legal obligation in production units.

[26] *Listeria monocytogenes*/cooked ham – *Salmonella*/dry-cured sausage – *Clostridium botulinum*/dry-cured ham

[27] ANSES. 2018. Opinion and report on *Salmonella* control measures in the pig sector: review of knowledge and quantitative risk assessment https://www.anses.fr/fr/system/files/BIORISK2016SA0037Ra.pdf.

They recommend that:

- any elimination or reduction of the use of nitrates/nitrites be systematically combined with compensatory control measures that are authorised, validated, monitored, verified and shared by the industry and the authorities;
- validation of these compensatory measures be based on predicted data (using predictive microbiology tools) and/or experimental data on the matrices in question;
- any change in the use of nitrates/nitrites be accompanied by a revision of the guides to good hygiene practice for the sectors in question.

The experts of the WG and the CES ERCA and CES BIORISK also recommend:

- carrying out work to improve knowledge of *Salmonella* contamination of raw materials and its development during the dry-cured sausage manufacturing process;
- acquiring data on the prevalence and concentrations of *Clostridium botulinum* in fresh meat;
- establishing a framework for assessing alternative measures to the use of nitrates/nitrites as antimicrobials;
- acquiring data on alternative measures to the use of nitrates/nitrites regarding their antimicrobial efficacy, possible toxicity and impact on the organoleptic properties of the foodstuffs in question.

The experts of the WG and the CES ERCA and CES BIORISK note that some alternative processes to the direct addition of nitrites involve the addition of naturally occurring nitrates (plant extracts, vegetable broths, etc.), which are converted to nitrites by bacterial enzymes. This type of alternative does not therefore lead to a reduction in consumer exposure to nitrites.

3.5. Conclusions and recommendations from the assessment of new scientific knowledge that could better characterise the link between human carcinogenesis and nitrate/nitrite intake via food and water consumption – Question 4 of the formal request

When addressing question 4 of the formal request, the Working Group thought it appropriate to broaden its analysis to include studies dealing with exposure to nitrates and nitrites via all food sources (water, plant and animal, including processed meats). The WG's methodology consisted in systematically identifying in the literature all articles published subsequent to the research presented in EFSA's opinions[5] (which covered the period up to the end of December 2014).

3.5.1. Methodological approach

The extraction identified 187 articles over the period January 2015 to March 2022 with the keywords presented in Table 1 (search performed in PubMed and Scopus).

Table 1. List of keywords used in the in-depth literature review

Type	Key words
Substances	Nitrates, nitrites, NOCs, nitrosylated heme
Response	Neoplasm, cancer
Population	Cohort, case-control
Period	January 2015 to March 2022
Language	English

The articles taken into account are based on the results of cohort or case-control studies. Regarding exposure, the indicator varied, nitrates, nitrites, by source (dietary, water, animal or plant foods) and nitroso compounds (e.g. NDMA, NDEA, FeNO).

Some articles were not included for the following reasons:

- they did not present results from a cohort and/or case-control study or did not present original results (meta-analysis);
- the study design did not enable the relative risks or odds ratios (ORs) to be attributed to the substances of interest;
- the risks of bias were not or were only insufficiently taken into account in the calculation of the ORs.

When only one study described an association between an exposure and the development of cancer, or when several articles provided inconsistent results, the level of evidence was considered to be inadequate to conclude on the existence or absence of an association.

3.5.2. Results

The results of this systematic literature review are shown in the Prisma diagram in Figure 2.

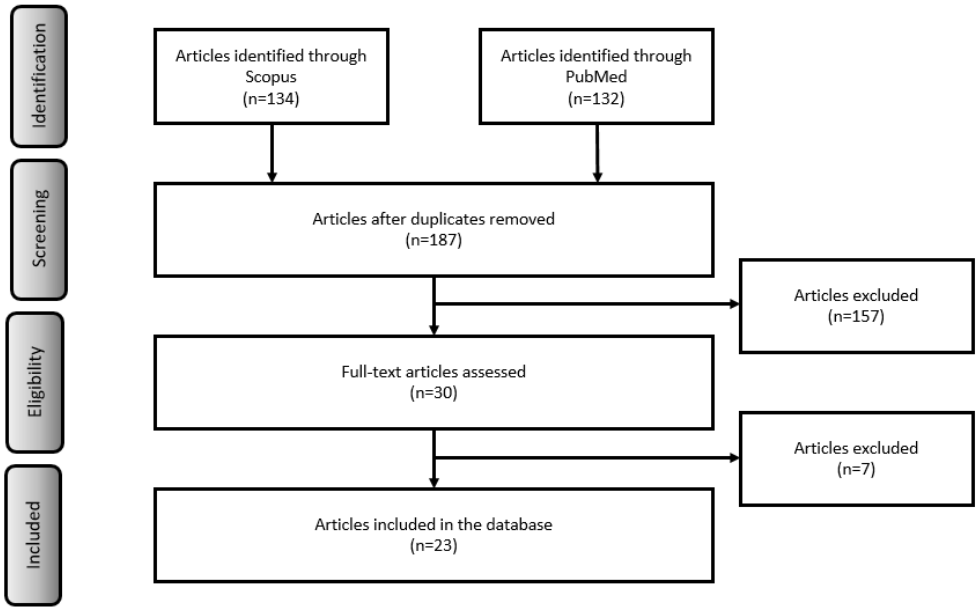

Figure 2. Prisma diagram of the literature review on the epidemiological data (January 2015 to March 2022)

3.5.3. Conclusions

The Working Group concluded that there is:

- a positive association between exposure to **nitrates** via **drinking water** and the risk of colorectal cancer;
- a positive association between exposure to **nitrates and/or nitrites** via **processed meat** and the risk of colorectal cancer.

For the first time, a recent study reported the impact of perinatal exposure to nitrates on the risk of paediatric cancer. As this is the only study available, the WG was unable to conclude on this point.

Since only one article was available, the WG considers that it is not possible on the basis of current knowledge to confirm any association between exposure to nitrates and nitrites and the risk of cancers other than colorectal cancer, but notes:

- ✓ a suspected positive association between:
  - exposure to **nitrates** in **drinking water** and the risk of ovarian and kidney cancers;
  - exposure to **nitrates** in **food** (excluding drinking water), whether in natural form or from the use of additives, and the risk of ovarian cancer;
  - exposure to ***N*-nitrosodiethylamine (NDEA) and *N*-nitrosodimethylamine (NDMA)** in **food** (excluding drinking water), whether in natural form or from the use of additives, and the risk of pancreatic cancer;
  - exposure to **NDEA** and **NDMA** in **foods of plant origin** and the risk of liver and biliary tract cancers;

- exposure to **nitrates** in **processed meat** and the risk of breast and bladder cancer, and cancer mortality;
- exposure to **nitrites** in **processed meat** and the risk of pancreatic, stomach, oesophageal, breast, bladder and prostate cancers, and cancer mortality.

✓ a suspected inverse association between exposure to **nitrites** through consumption of **foods of plant origin** and the risk of liver and biliary tract cancers.

Since several articles provided inconsistent results for the postmenopausal population, the Working Group was unable to conclude as to the positive association observed in some studies between nitrate exposure via drinking water and the risk of bladder and breast cancers.

3.5.4. Recommendations

The positive associations found above, from an in-depth review of the epidemiological studies, underline the need to limit dietary exposure:

- to nitrates and nitrites via processed meat;
- to nitrates via drinking water.

For paediatric cancer and cancer in postmenopausal women, particular attention should be paid to the impact of exposure to nitrates in drinking water. Further research should be conducted.

For the specific case of cancer in postmenopausal women, further studies seem to be necessary with regard to the potential role of nitrates in endocrine disruption.

3.6. Conclusions and recommendations on the need to re-examine EFSA's HBGVs and the transformation mechanisms of nitrates/nitrites in the body and in foodstuffs – Question 3 of the formal request

3.6.1. Conclusions on the re-examination of EFSA's HBGVs

EFSA[3] currently recommends using acceptable daily intakes (ADIs) for nitrates of 3.7 mg nitrate ions (kg bw)$^{-1}$ d^{-1}, and for nitrites of 0.07 mg nitrite ions (kg bw)$^{-1}$ d^{-1}. As with nitrates, the ADI for nitrites is based on the increase in methaemoglobin levels following exposure of rodents to nitrites in water (NTP, 2001)[28].

Genotoxicity studies do not indicate any genotoxic potential of nitrates and nitrites. The NTP's carcinogenicity studies on nitrites in drinking water (2001) concluded that there was no evidence of carcinogenic activity in male and female F344/N rats and male B6C3F1 mice. The results were ambiguous in female B6C3F1 mice based on the positive trend in the incidences of squamous cell papilloma or (combined) carcinoma of the forestomach. However, the NTP

[28] NTP (National Toxicology Program), 2001. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Nitrite (CAS No. 7632-00-0) in F344/N Rats and B6C3F1 Mice (drinking water studies).

stressed that the studies were conducted under conditions that do not foster the endogenous formation of nitrosamines.

In the absence of any other data, the Working Group concluded that the doubling of basal blood methaemoglobin levels could be identified as an early marker of exposure to nitrates and nitrites (oxidation indicator). At this stage, taking this early marker of exposure into account is justified by the fact that it is the effect that can be observed at the lowest level.

3.6.2. Conclusions on the transformation mechanisms of nitrates/nitrites in foodstuffs and in the body

The International Agency for Research on Cancer (IARC, 2010)[29] has classified nitrates and nitrites as "probably carcinogenic to humans" (Group 2A) if ingested under conditions that result in endogenous nitrosation.

Thanks to current knowledge, the formation of nitroso compounds has been identified, in particular from the consumption of meat products treated with nitrate and nitrite additives. After oral exposure, 75% of the absorbed dietary nitrates are excreted in the urine, and the remaining 25% are secreted by the salivary glands into the mouth cavity where bacterial action reduces some of them to nitrites. Nitrites are unstable and, in excess, can lead to the formation of nitroso compounds in the gastrointestinal tract such as:

- *S*-nitrosothiols (RSNO), formed mainly in the stomach where they act as nitric oxide (NO) donors;
- *N*-nitroso compounds, mainly nitrosamines, which can be formed throughout the digestive tract either at acidic pH in the stomach or at neutral pH and in the presence of iron in the intestine. *N*-nitroso compounds can lead to the formation of DNA adducts;
- nitrosylated iron (FeNO) or nitrosyl-haem formed in the intestine, mainly in the colon.

Consumption of **red meat**, which is very rich in haem iron, is directly and dose-dependently associated with the formation of nitroso compounds in the colon and the formation of DNA adducts specific to these compounds. Consumption of **processed meat products** increases the formation of nitroso compounds compared with consumption of red meat. Consumption of **processed meat products with a reduced nitrite content and to which compounds with antioxidant properties have been added** leads to a significant reduction in the formation of nitroso compounds compared with conventional processed meats.

Nitrosamines are the best characterised of the nitroso compounds. Toxicological data highlight their genotoxicity and carcinogenicity in experimental studies. *N*-nitrosodimethylamine (NDMA) is identified as having the highest carcinogenic potential. The benchmark dose

[29] IARC (International Agency for Research on Cancer), 2010. Ingested nitrate and nitrite, and cyanobacterial peptide toxins. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 94, v–vii, 1–412.

($BMDL_{10}$), estimated from experimental data in rats (SCCS, 2011)[30], was used in subsequent work to estimate the level of health concern based on the margin of exposure (MOE) after estimating the amount of endogenous nitrosamines formed after cumulative nitrate and nitrite ingestion.

There is a lack of data on the identification and quantification of exogenous[31] and endogenous[32] nitroso compounds. Data are also lacking on the toxicological potential of these compounds, in particular nitrosylated haem iron and nitrosothiols.

In conclusion, the new knowledge available is not sufficient to justify changing the ADI proposed by EFSA[3] and it was therefore used for the risk assessment in this expert appraisal.

3.6.3. Recommendations

The Working Group recommends:

- conducting a debate on the establishment of health-based guidance values taking account of co-exposure to nitrates, nitrites and endogenous and exogenous nitroso compounds, and considering food matrices;
- conducting experimental studies to identify the critical effects of nitrates and nitrites under conditions reflecting the formation of endogenous nitroso compounds;
- carrying out further experimental studies of chronic toxicity and carcinogenesis in animal models to assess the potential link with consumption of meat products whether or not treated with different levels of added nitrates/nitrites;
- identifying exogenous and endogenous nitroso compounds other than nitrosamines, quantifying them and assessing their potential toxicity;
- studying the factors influencing toxicity associated with the consumption of processed meat products (diet, ageing, microbiota, disease, etc.).

[30] SCCS (EU Scientific Committee on Consumer Safety), 2011. Opinion on nitrosamines and secondary amines in cosmetic products. European Commission. Health & Consumer Protection. SCCS/1458/11. ISSN 1831-4767
[31] In the food matrix
[32] In the consumer's body

3.7. Conclusions and recommendations for courses of action that would help reduce exposure to nitrates and nitrites in the French population – Question 2 of the formal request

3.7.1. Conclusions on exposure to nitrates and nitrites

Based on the available data on nitrate and nitrite concentrations in water[33] and food[34] between 2010 and 2019, data on food consumption in the French population (adults and children over 3 years of age in metropolitan France excluding Corsica)[35] and data on the presence of nitrate and nitrite additives in food products sold on the French market[36], the expert appraisal work led to the following considerations.

Concerning nitrates:

- they are largely provided through food (75-80%) while water, mainly drinking water distributed through the supply network, contributes 20-25% of consumer exposure;
- their use as additives accounts for less than 4% of total exposure from all sources;
- they are always present in plants, however, in some cases they accumulate at very high concentrations. Vegetables are therefore the main contributors (between 62 and 69%) to total nitrate exposure. In adults, leafy vegetables are the main contributors, while in children, pulses, leafy vegetables, fruits and sprouted seeds each contribute similar amounts to nitrate exposure;
- total exposure exceeds the ADI for nitrates in less than 1.5% of adults and children.

Concerning nitrites:

- they are mainly provided through food (99%), particularly processed meat products such as cooked ham and cooked sausages, which represent from 41 to 63% of intake depending on the consumers and/or the censoring assumptions;
- their use as additives accounts for between 45 and 65% of total exposure from all sources;
- total exposure to nitrites exceeds the ADI in less than 0.4% of children. The ADI is not exceeded in adults.

The Working Group assessed cumulative exposure to nitrates and nitrites using the margin of exposure (MOE) approach. The MOE for endogenous NDMA (based on the $BMDL_{10}$) in adults was above 10,000 at the 97.5th percentile (17,656 [15,258-20,153]). For children over 3 years of age, the median of the 97.5th percentile distribution was below 10,000 (8,636 [5,170-13,870]), but this was not significant. Furthermore, the approach used in children, which was based on a nitrate to nitrite conversion rate of 9%, is considered more protective than the kinetic model used for adults.

[33] SISE-EAUX data (source: Directorate General for Health)
[34] CONTAMINE data (source: surveillance and control plans / Directorate General for Competition Policy, Consumer Affairs and Fraud Control)
[35] ANSES. 2017. Opinion and report of the French Agency for Food, Environmental and Occupational Health & Safety on the Third Individual and National Study on Food Consumption (INCA3)
[36] INRA and ANSES. 2019. Review and use of additives in processed products

3.7.2. Courses of action studied

3.7.2.1. "Water"

Drinking water contributes between 20 and 25% of total dietary exposure to **nitrates**. The impact of systematic compliance with the quality limit for nitrates in the drinking water supply was tested by considering that no individual consumed water containing more than 50 mg L^{-1} of nitrates (all nitrate concentrations in drinking water exceeding this limit were set at 50 mg L^{-1}).

This simulation had a minimal impact on the total dietary exposure of the French population. This can be explained by the small number of DWSFs[37] for which the average nitrate concentration was higher than 50 mg L^{-1}.

However, for populations served by DWSFs distributing water with nitrate concentrations above this quality limit, the level of exposure via the drinking water supply was more than three times higher than for the rest of the population. For these populations, the drinking water supply contributed more than 47% of total dietary exposure[38].

Since water contributes very little to **nitrite** exposure (0.6% at the lower bound), it does not constitute a course of action for reducing total nitrite exposure.

3.7.2.2. "Additives"

Processed meat products contribute between 42 and 63% of total nitrite exposure. Without prejudice to the consequences on the microbiological risk, the experts assessed a theoretical "no added nitrites" scenario in the two processed meat products contributing most to exposure, i.e. "cooked ham" and "cooked sausages".

This scenario reduced total nitrite exposure for adults by 18-29% and for children by 25-40%. In this scenario, regardless of the population, the ADI for nitrites was never exceeded.

Reducing the use of these additives is a course of action for which the implementation procedures should be specified in order to determine the residual content in the finished products according to the amounts added. Due to the lack of data on the relationship between the amount added and the residual amount, it was not possible to reassess the use levels of these additives that would limit both the microbiological and chemical risks associated with consumption of the product, with priority given to the major contributors.

[37] Drinking water supply facility
[38] This scenario has been addressed in a specific opinion (ANSES 2022).

3.7.2.3. "Consumer recommendations"

In this scenario, the recommendation to limit consumption of processed meat to 150 g per week, as recommended by *Santé Publique France* based on ANSES's work[39,40], was applied to the two major contributors, i.e. "cooked ham" and "cooked sausages".

A 4-7% reduction in total nitrite exposure was then observed in adults and children. This reduction meant that the ADI was no longer exceeded in children.

3.7.3. Recommendations

In view of the results observed and the simulations carried out, the WG and the CES ERCA recommend **reducing nitrate and nitrite intakes via water and food, mainly by limiting the amounts of nitrate and nitrite additives incorporated into processed meat products**.

In addition, the WG and the CES ERCA recommend:

- following ANSES's recommendations on consumption of processed meat, which advise limiting it to 150 g per week[39,40]. This would ensure that the acceptable daily intake for nitrites of 0.07 mg (kg bw)$^{-1}$ d^{-1} was not exceeded;
- continuing studies to better characterise the relationship between the amounts added[41] and the residual concentrations[42] of nitrates and nitrites in treated meat products, in order to more precisely assess the impact of their reduction on consumer exposure;
- reassessing the relevance of the maximum derogation value used in management (100 mg L^{-1}) for nitrates in drinking water;
- diversifying vegetable consumption in the total diet. This is because certain foodstuffs of plant origin, such as leafy vegetables, can have high nitrate concentrations. However, due to their high fibre, vitamin and mineral content, vegetables provide protection against various diseases (cancer, diabetes, cardiovascular diseases, etc.). ANSES recommends consuming five portions of fruit and vegetables per day, based on 80 to 100 g per portion (ANSES, 2016)[39].

3.8. General conclusions and recommendations on the risks associated with the consumption of nitrates and nitrites

Based on the expert appraisal conducted in response to this formal request, the WG and the CES ERCA and CES BIORISK recommend **reducing nitrate and nitrite intakes through water and food**.

[39] ANSES, 2016. Updating of the PNNS guidelines: revision of the food-based dietary guidelines. ANSES opinion and collective expert appraisal report.
[40] *Santé Publique France*, 2019. Recommendations for adults on diet, physical activity and sedentary behaviour. 62 p. https://www.santepubliquefrance.fr/content/download/186841/document_file/42466_spf00000619.pdf
[41] Maximum permitted amounts of an additive in a food product (Regulation (EC) No 1333/2008).
[42] Residue content at the end of the production process, expressed as $NaNO_2$ or $NaNO_3$ according to Regulation (EC) No 1333/2008 (and its amendments), Annex II Part E.

Regarding processed meat products, the Working Group concludes that:

- nitrites are mainly provided through processed meat products, and their use as additives represents between 45 and 65% of total exposure from all sources;
- consumption of processed meat products contributes to the formation of endogenous nitroso compounds of concern (nitrosamines, nitrosothiols, nitrosyl-haem);
- exposure to nitrates and/or nitrites through the consumption of processed meat products is positively associated with a risk of colorectal cancer, based on an analysis of epidemiological data from an in-depth literature review;
- there are insufficient studies to confirm or refute any association between exposure to nitrates and/or nitrites through consumption of processed meat products and the risk of pancreatic, stomach, oesophageal, breast, bladder and prostate cancers, and cancer mortality.

Furthermore, the analysis of the microbiological risks arising from the reduction or elimination of nitrates and nitrites in processed meat led the experts of the WG and the CES ERCA and CES BIORISK to point out that the greater the reduction in the use of nitrites, the higher the microbiological risk to consumers. Consequently, the additional control measures to be implemented by operators should be drastic and/or more numerous. They also noted that some alternative processes to the direct addition of nitrites involve the addition of naturally occurring nitrates (plant extracts, vegetable broths, etc.), which are converted to nitrites by bacterial enzymes. This type of alternative does not therefore lead to a reduction in consumer exposure to nitrites.

In view of these conclusions, the Working Group and the CESs recommend:

- **limiting dietary exposure to nitrates and nitrites via processed meat products** by limiting the use of nitrate and nitrite additives and complying with consumption recommendations;
- systematically combining any **elimination or reduction of the use of nitrates/nitrites** with **compensatory control measures** that are authorised, validated, monitored, verified and shared by the industry and the authorities;
- continuing studies to establish the relationship between the residual level of nitrates/nitrites and the level of nitrate and nitrite additives incorporated into meat products;
- studying alternative measures to the use of nitrates/nitrites for their antimicrobial efficacy, possible toxicity and impact on the organoleptic properties of the foodstuffs in question;
- improving consumer information on the use of alternatives to nitrates and nitrites, such as vegetable broths, which can also be a source of exposure to these compounds;
- conducting further epidemiological studies to improve knowledge of the association between nitrate and nitrite exposure through the consumption of processed meat products and cancer risk.

Regarding water, the Working Group and the CES ERCA conclude that:

- nitrates from drinking water contribute 20-25% of total nitrate intake;
- there is evidence from epidemiological studies of an association between exposure to nitrates via drinking water and the risk of colorectal cancer;
- there are insufficient studies to confirm or refute any association between exposure to nitrates via drinking water and the risk of kidney, bladder, breast and ovarian cancers, as well as paediatric cancer.

The Working Group and the CES ERCA recommend:

- reassessing the relevance of the maximum derogation value used in management (100 mg L^{-1}) for nitrates in drinking water;
- in order to limit exposure to nitrates via mains-supplied drinking water:
    - strengthening actions to protect the quality of water resources from nitrate contamination;
    - pursuing and strengthening actions to restore water quality for contaminated resources;
    - if the above actions are not sufficient, adapting drinking water production processes (mixing water, using suitable treatments, or even abandoning perennially contaminated catchments) in order to guarantee permanent compliance with the quality limit in the water supply;
- conducting further studies to investigate the association between nitrates in drinking water and the risk of cancer (other than colorectal) as revealed by the epidemiological studies. This relates to paediatric cancer following perinatal exposure, and kidney, ovarian, breast and bladder cancers in postmenopausal women;
- assessing, in light of new epidemiological and toxicological data, the relevance of the quality limit of 50 mg L^{-1} of nitrates in drinking water.

Regarding plants, the Working Group and the CES ERCA conclude that:

- vegetables are the main contributors (between 62 and 69%) to total nitrate exposure;
- some plants, particularly leafy vegetables, can accumulate large amounts of nitrates.

The WG and the CES ERCA recommend diversifying vegetable consumption in the total diet.

The WG and the CES ERCA noted a lack of data in several areas, mainly concerning:

- exogenous (in the food matrix) or endogenous (in the consumer's body) nitroso compounds formed following ingestion of nitrates and nitrites via the consumption of water and food:
    - because the formation mechanisms and toxicity associated with these substances are still poorly understood and need to be investigated;

  - analytical methods for identifying and quantifying these compounds in food and biological matrices need to be developed.
- the establishment of health-based guidance values taking account of co-exposure to nitrates, nitrites and endogenous and exogenous nitroso compounds, and considering food matrices. To this end, experimental studies to identify the critical effects of nitrates and nitrites under conditions reflecting the formation of nitroso compounds should be conducted.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The presence of nitrates and nitrites in foodstuffs concerns both drinking water and plant and meat products.

With regard to drinking water, the contamination of raw water resources is mainly due to nitrates. The nitrates come firstly from natural processes associated with the nitrogen cycle, and secondly from human activities, in particular those associated with agricultural activities such as the spreading of mineral fertilisers or livestock manure.

Nitrates in plant products are natural constituents essential for their development. Bioaccumulation of nitrates, leading to levels exceeding their physiological needs, can occur in the event of excessive nitrogen fertiliser inputs.

The presence of nitrates and nitrites in processed meat products is mainly due to their use as additives for their antioxidant and antimicrobial properties, as well as for their effect on the colour of the products.

After ingestion, some of the nitrates are converted into nitrites. Nitrites are unstable compounds that, when present in excess, generate the formation of nitroso compounds in the digestive tract, particularly following consumption of meat products. These nitroso compounds are known for their genotoxicity and carcinogenicity.

The multiple sources of exposure to nitrates and nitrites and the mechanisms by which they are transformed into nitroso compounds in the body justified the need for a comprehensive approach to assessing their effects on human health, which constitutes a step forward in taking the exposome into account. This comprehensive approach also took into account the antimicrobial activity of nitrates and nitrites for the safety of certain foods.

The French Agency for Food, Environmental and Occupational Health & Safety **endorses the conclusions and recommendations of the WG and the CES ERCA and CES BIORISK,** which respond to each of the questions raised in the formal request, **and recommends reducing the population's exposure to nitrates and nitrites by taking proactive measures to limit dietary exposure**.

With regard to the question on the **risks induced by reducing nitrate/nitrite levels used as additives** in the preparation of meat products, it should be noted that this use, particularly for processed meat and cured meats, is able to effectively control the growth of pathogenic bacteria responsible for foodborne illness. As such, it is included in the guides to good hygiene

practice. The effect of nitrites is specific to the food and pathogen in question, and the three most relevant food/pathogen pairs were assessed in this expert appraisal: cooked ham/*Listeria*, dry-cured sausage/*Salmonella*, and dry-cured ham/*C. botulinum*. Although a reduction in the additive level could significantly increase the microbiological risk associated with the consumption of these products, **the Agency believes that it can be considered, subject to the implementation of validated compensatory measures to control this risk**. These measures should be taken mainly at the manufacturing stage, but for the cooked cuts of meat category, could also involve a reduction in the products' shelf lives (shorter use-by dates). The Agency also stresses that the greater the reduction, the higher the risk to the consumer, which calls for more drastic and/or more numerous additional control measures, including beyond the manufacturing-distribution chain. Also, regarding alternative solutions to the use of nitrates/nitrites, ANSES specifies that they should undergo a specific assessment (for each hazard/food pair) based on impact data concerning their effectiveness and safety for human health. Furthermore, without having carried out a systematic analysis or examined a precise industrial alternative, the experts noted that certain processes substitute the direct addition of nitrites with inputs of nitrates of natural origin which, under the effect of bacterial enzymes, are converted into nitrites. These processes do not constitute a real reduction in consumer exposure to nitrites.

Concerning **the update of knowledge in oncology,** since the work carried out by EFSA (2017) and IARC (2018), **the analysis of the literature data confirms that there is an association between the risk of colorectal cancer and exposure to nitrates and nitrites**, whether ingested through drinking water or processed meat. The analysis is consistent with the classification of the International Agency for Research on Cancer (IARC). ANSES notes the existence in the literature, subsequent to the works mentioned above, of studies characterising a link with other types of cancer. Because there is only one of each type of study, it is not possible to confirm the qualification of this link. The Agency strongly supports the recommendations for further work in this area to confirm or refute these relationships, particularly in relation to perinatal exposure.

With regard to the question about updating knowledge in the field of toxicology, and in particular knowledge on the transformation mechanisms of nitrates and nitrites into nitroso compounds, the experts noted that on the basis of current knowledge, the marker of exposure associated with the doubling of blood methaemoglobin levels can be identified both as an early marker and as the effect that can be observed at the lowest level of exposure to nitrates and nitrites. Therefore, the acceptable daily intakes (ADIs) proposed by EFSA were endorsed for the risk assessment in this opinion. However, while they are still considered relevant, the current ADIs were defined separately for each of these substances, whereas the biochemical mechanisms involved constitute a series of transformations towards nitroso compounds. **The Agency therefore recommends conducting a debate to establish a health-based guidance value that takes co-exposure to nitrates, nitrites and nitroso compounds into account**. In the meantime, the expert appraisal used an approach that was able to add together the amounts of endogenous nitrosamines formed after combined exposure to nitrates and nitrites by means of a "margin of exposure" (MOE) approach,

Lastly, ANSES points out that EFSA is currently responding to a formal request from the European Commission on a specific assessment of the toxicity of the various nitroso compounds, which should improve knowledge of the transformation mechanisms and even lead to a revision of the ADI, and which is expected to be completed by the end of 2022.

The question on **assessing the courses of action for reducing overall consumer exposure** required the use of the available databases and studies to reconstruct all exposure to nitrates and nitrites contained in a large number of foods and ingredients consumed. For nitrates, 65% of dietary exposure is associated with the consumption of plant products, particularly leafy vegetables, 25% with drinking water and less than 4% with foods containing them as additives. For nitrites, over half of the exposure of adults and children comes from the consumption of processed meat products, due to the nitrite additives used to prepare them.

All sources of exposure taken into account, **the Agency notes that almost 99% of the population (adults and children) do not exceed the ADI**. Implementation of the MOE approach leads, under conservative assumptions, to a margin above 10,000 at the 97.5% percentile for adults, and slightly below 10,000 for about 3% of children.

In light of these exposure results and the known effects of exposure to nitrates and nitrites, **the Agency considers that limiting the intentional addition of these compounds to food in an ALARA[43] approach constitutes a food safety objective to reduce overall population exposure as much as possible, and stresses that actions are available to implement it**.

The effectiveness of the various proposed courses of action was assessed by the expert committees, leading to variable results depending on the population, particularly with regard to drinking water. Controlling exceeded quality limits for nitrates in certain drinking water supply facilities should help limit exposure of the users concerned. In general, the continued optimisation of certain practices, such as agricultural practices related to the spreading of fertilisers and livestock manure within the framework of the European directive concerning the protection of waters against pollution caused by nitrates from agricultural sources, can help reduce nitrate concentrations in raw water and drinking water, and nitrate levels in plant products. An ANSES opinion on this specific subject of exceeded quality limits in drinking water is being finalised, in response to a formal request from the Directorate General for Health.

In addition, the Agency reiterates its recommendations and those of *Santé Publique France*, under the National Nutrition and Health Programme, for a well-balanced and varied diet, with at least five portions of fruit and vegetables per day from a variety of sources, and no more than 150 grams of processed meats per week, which constitute an effective course of action on an individual basis.

Dr Roger Genet

[43] As low as reasonably possible

KEY WORDS

French: Nitrates, nitrites, eau, aliment, produits carnés traités, microbiologie prévisionnelle, scénarios, risque microbiologique, exposition alimentaire, caractérisation du risque, valeur toxicologique de référence.

English: Nitrates, nitrites, water, food, processed meat, predictive microbiology, scenarios, microbiological risk, dietary exposure, risk characterisation, health-based guidance value.

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ANNEX 1

Tracking of the changes made to the 1July 2022 version

Page number	Change made
Page 8	Correction to Figure 1 on the names of food additives
Page 14	Correction to Figure 2 on the number of articles included for the conclusion (n=23 instead of n=22)
Page 24	Editorial change *C. botulinum* (instead of *botulinum*)