

# EFSA Nitrosamine Opinion

**This is a paper for discussion.**

**This does not represent the views of the Committee and should not be cited.**

## Background

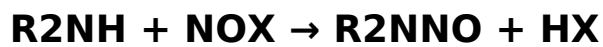
1. EFSA published a public consultation on a draft Opinion on N-nitrosamines (N-NAs) in food on 12<sup>th</sup> October, closing on 22<sup>nd</sup> November ([Annex A](#)). The COT are being asked to review this draft opinion and provide any comments which will then be fed back to EFSA. If Members have any further comments, there will be a document provided in the Teams folder. Please provide any comments by Wednesday 16<sup>th</sup> November. This document provides a brief overview of the draft EFSA Opinion based on the EFSA summary due to the limited time available to review the draft Opinion.

## Introduction

2. The EFSA CONTAM Panel had been requested by the European Commission, to provide a scientific Opinion on the human health risks related to the presence of N-NAs in food. The Opinion evaluates the toxicity of N-NAs to animals and humans, estimates the dietary exposure of the European Union (EU) population to N-NAs and assesses the human health risks to the EU population due to the estimated dietary exposure.

3. EFSA had evaluated 32 N-NAs and investigated their presence in food. Quantifiable amounts had only been measured for a certain number of the N-NAs. The risk characterisation was therefore limited to the ten carcinogenic N-NAs (TCNAs) occurring in food (i.e. N-nitrosodimethylamine (NDMA), N-nitrosomethylethylamine (NMEA), N-nitrosodiethylamine (NDEA), N-nitrosodipropylamine (NDPA), N-nitrosodibutylamine (NDBA), N-nitrosomethylaniline (NMA), N-nitrososarcosine (NSAR), N-nitrosomorpholine (NMOR), N-nitrosopiperidine (NPIP) and N-nitrosopyrrolidine (NPYR) (TCNAs)).

4. N-NAs are the reaction products formed from nitrosating agents (NOX) such as nitrites or nitrogen oxides and amino-based substances (R<sub>2</sub>NH) such as secondary amines. They may be formed in a variety of foods under processing conditions in the presence of these reactants.



5. N-NAs have been detected, e.g., in cured meat products, processed fish, beer and other alcoholic and non-alcoholic beverages, cheese, soy sauce, oils, processed vegetables and human milk. Heat treatment also produces and increases the levels of N-NAs in food with findings mainly focussing on meat and fish products.

6. The EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS) concluded in its opinion on the re-evaluation of potassium nitrite (E249) and sodium nitrite (E250) as food additives, that the formation of N-NAs in the body from nitrites added at approved levels to meat products was of low concern for human health. In this draft opinion the CONTAM Panel has been asked to assess the risks of N-NAs to public health as a contaminant.

## **Absorption, Distribution, Metabolism and Excretion (ADME)**

7. Data for absorption and distribution of many of the N-NAs are scarce. However, there are studies that show that NDMA, NDEA, NPYR, N-nitrosothiazolidine (NTHZ) and N-nitrosoproline (NPRO) are readily and completely absorbed and distributed mainly to the liver but also to other organs in experimental animals. Most N-NAs undergo a CYP-mediated oxidation which is a key event in bioactivation.

8. NDMA is metabolized to  $\alpha$ -hydroxydimethylnitrosamine via  $\alpha$ -hydroxylation, catalyzed mainly by CYP2E1.  $\alpha$ -Hydroxydimethylnitrosamine spontaneously decomposes to methyldiazonium ions that react easily with DNA bases producing DNA adducts such as 7-Me-Gua and O<sup>6</sup>-Me-Gua. The DNA repair enzyme O<sup>6</sup>-Me-Gua-DNA-methyltransferase removes the O<sup>6</sup>-Me-Gua adducts. If unrepaired, O<sup>6</sup>-Me-Gua adducts cause miscoding and generate principally G>A transition mutations which can lead to the initiation of carcinogenesis.

9. The liver plays a major role in clearing and metabolising NDMA; extrahepatic distribution is also possible for this and other N-NAs and is enhanced

by co-exposure to other CYP substrates such as ethanol. CYP enzymes of different families convert NDEA, NMEA, NDPA, NDBA, NMA, NSAR, NMOR, NPIP and NPYR mostly via  $\alpha$ -hydroxylation to alkylating agents which are capable of binding to DNA. The same enzymes also perform denitrosation, which is mainly considered a detoxification pathway. Extrahepatic bioactivation of other N-NAs mainly in the upper gastrointestinal (GI) and respiratory tract has been shown. Quantitative and qualitative species-and tissue related differences in N-NAs biotransformation have been documented.

10. Overall, unmetabolised N-NAs and their stable metabolites (e.g. glucuronides) are mainly and rapidly excreted via urine; for N-nitroso-thiazolidine-4-carboxylic acid (NTCA), N-nitroso-2-methyl-thiazolidine-4-carboxylic acid (NMTCA), N-nitrosohydroxyproline (NHPRO), NPRO, NSAR and NMA urinary excretion accounts for up to 90% of the administered dose. Biliary excretion is considered of minor importance and has been documented for NDMA, NDEA, NDPA, NPYR and N-nitrosodiphenylamine (NDPheA). Direct or indirect evidence for transfer via milk has been reported for NDMA, NDEA and NDBA; in addition, NDMA, NDEA, NDBA and NDPA undergo placental transfer.

11. Very little is known about the fate of N-NAs in humans and most of the available information concerns NDMA. The presence of measurable N-NA levels has been reported in blood, gastric juice, urine and milk. The origin of these N-NAs is unknown, and their endogenous formation could not be excluded. In the few studies in which human volunteers were offered meals with known N-NA (NDMA) content, only trace amounts of the ingested dose were recovered in biological fluids, except in the case of ethanol co-administration. This suggests that in humans, ethanol may decrease the hepatic clearance of NDMA, as demonstrated in rodents. The in vivo extrapolation of the in vitro hepatic NDMA intrinsic clearance measured in human liver microsomes resulted in a calculated hepatic extraction ratio of about 90%, which is very similar to that measured in vivo in the rat. Finally, quantitative differences between humans and rats were reported in the ability of the same tissue to biotransform and activate (as measured by DNA-binding) different N-NAs.

12. Earlier studies performed with human tissue subfractions or tissue cultures have demonstrated the bioactivation of several N-NAs not only by the liver but also by extrahepatic organs and tissues, including oesophagus, colon, bladder, bronchi, pancreatic duct and nasal mucosa. The most common N-NAs found in food (NDMA, NMEA, NDEA, NDPA, NDBA, NMA, NSAR, NMOR, 94 NPIP and NPYR) are mostly biotransformed by CYP2E1 and 2A6, while CYP2B1 and CYP1A1

are involved to a lesser extent. CYP genetic polymorphisms may, at least partly, explain the large interindividual variation in the biotransformation of certain N-NAs observed in in vitro studies.

13. Most studies on DNA adducts in human tissues do not specifically identify N-NAs as their source. It is also unclear to which extent exposure to N-NAs reflects their endogenous formation or occurs via food/water.

## **Toxicity**

14. In short-term toxicity studies, NDMA, NDEA, NMOR and NPIP exerted pronounced hepatotoxic effects, reduced body weight gains and the reduced survival of experimental animals.

## **Genetic Toxicity**

15. The genotoxic properties of the acyclic volatile NDMA, NMEA, NDEA and NDPA have been extensively investigated both in vitro and in vivo. Following metabolic activation, these N-NAs induce gene mutations in both bacteria and mammalian cells in vitro. Mutations have also been observed in the liver of transgenic animals with GC>AT transitions being the main mutational class. These base substitutions are consistent with the well-known miscoding properties of DNA bases alkylated at the O<sup>6</sup> position of guanine.

16. Information on the genotoxicity of the acyclic non-volatile N-NAs is more limited. Induction of mutations in vitro was shown for NDBA while increased levels of DNA breaks in several organs confirmed the in vivo genotoxicity of NDBA.

17. The cyclic volatile NMOR, NPIP and NPYR were mutagenic both in vitro and in vivo. For all these N-NAs, increased levels of DNA strand breaks were observed in several mouse organs (stomach, colon, liver, lung, kidney and urinary bladder). In addition, the clastogenic potential of NMOR has been demonstrated by its ability to induce micronuclei in the bone marrow cells. The reported in vitro mutagenicity of NPYR has been confirmed in vivo in transgenic rats (increases mainly of AT>GC transitions but also of mutations at G:C base pairs).

18. Overall the available data for N-NAs includes:

(i) evidence of in vitro and in vivo genotoxicity of NDMA, NMEA, NDEA, NDPA, NDBA, N-nitrosodibenzylamine (NDBzA), NMOR, NPIP and NPYR,

- (ii) evidence of genotoxicity limited to in vitro studies for N-nitrosodiisopropylamine (NDIPA), N-nitrosomethylbutylamine (NMBA), NMA, N-nitroso-N-(1-methylacetyl)-3-methyl-butylamine (NMAMBA), NTHZ, N-nitroso-3-hydroxypyrrolidine (NHPYR), and N-nitroso-2-hydroxymethylthiazolidine (NHMTHZ),
- (iii) indirect evidence (gained by read-across and structure activity relationships (SAR) analyses) that N-nitrosoethylisopropylamine (NEIPA), N-Nitrosomethylvinylamine (NMVA), N-nitrosodiisobutylamine (NDIBA), N-nitrosoethylaniline (NEA), N-nitroso-N-(1-methylacetyl)-2-methyl-propylamine (NMAMPA), NSAR and N-nitroso-2-methylthiazolidine (NMTHZ) may exert genotoxic activity,
- (iv) experimental and/or indirect evidence (gained by read-across and SAR analyses) that NPRO, NHPRO, NTCA, NMTCA, N-nitroso-2-hydroxymethyl-thiazolidine-4-carboxylic acid (NHMTCA), N-nitrosooxazolidine-4-carboxylic acid (NOCA), N-nitroso-5-methyloxazolidine-4-carboxylic acid (NMOCA) and N-nitrosopiperic acid (NPIC) may not exert significant genotoxic activity and,
- (v) insufficient information to conclude on the genotoxic potential of NDPheA.

## **Long-term toxicity**

- 19. The acyclic volatile N-NAs NDMA, NMEA, NDEA, NDPA, NDIPA, NEIPA, NMBA and NMVA induced tumour formation in several mammalian species and many different organs, such as liver, pharynx, oesophagus, forestomach, the upper respiratory tract and the lung. In monkeys NDEA and NDPA induced hepatocellular carcinoma (HCC). The acyclic non-volatile N-NAs NDBA, NDIBA, NMA, NMAMBA and NSAR were carcinogenic in many rodent organs/tissues, including liver, the upper and lower respiratory tract, oesophagus and/or forestomach. NDBzA did not induce tumour formation in rodents.
- 20. The cyclic volatile N-NAs caused tumour formation in rat liver, the respiratory and/or the GI tract (NMOR, NPIP, NPYR and NHPYR). Furthermore, NPIP induced hepatocellular carcinoma (HCC) in livers of monkeys.
- 21. For the cyclic N-NAs: NPRO, NHPRO and NPIC, no clear evidence for carcinogenicity could be obtained in rodents. NDPheA induced malignant tumours of the urinary bladder in male and female rats.

22. Overall, NDMA, NMEA, NDEA, NDPA, NDIPA, NEIPA, NMBA, NMVA, NDBA, NDIBA, NMA, NMAMBA, NSAR, NMOR, NPIP, NPYR, NHPYR and NDPheA are carcinogenic in experimental animals. Genotoxic mechanisms are the underlying mode of action for the carcinogenic activity of N-NAs, except for NDPheA. The most frequent target organ in animals is the liver followed by the upper digestive, urinary and the respiratory tract.

23. Some of the 32 N-NAs had no or limited carcinogenicity data. Based on a large database of N-NAs with known carcinogenic potency (parametrised as TD50s (median toxic dose)), knowledge of the most likely mode of action and genotoxicity and toxicokinetic information:

- carcinogenic activity was predicted for NEA, NMAMPA, NMAMBA, NTHZ, NMTHZ, NHMTHZ, and NDBzA, and
- lack of carcinogenic potential for NTCA, NMTCA, NHMTCA, NOCA, and NMOCA.
- TD50s were predicted also for NMVA, NEIPA, NMBA, NDIPA, NDIBA, and NSAR, whose carcinogenic activity was known but TD50s were not reported.

## **Developmental and reproductive toxicity**

24. Reports on transplacental carcinogenesis as well as developmental and reproductive toxicity show effects of N-NAs, tested at high doses in several rodent species. However, the studies often applied only one dose, did not cover several critical phases and were small in number and quality limiting conclusions on potential risks for human health. The documented transplacental transfer and bioactivation of N-NAs in fetal tissues provides a mechanistic explanation for the transplacental carcinogenic effects of NDMA, NDEA, NDPA, NDBA and NPIP in rodents. Furthermore, a high rate of cell replication in the liver of neonatal animals is increasing the susceptibility towards the carcinogenic activity of N-NAs.

## **Observations in humans**

25. In all the epidemiological studies on associations between dietary intake of N-NAs and cancer, selection bias, information bias, and confounding were present to some degree. In addition, in all studies N-NA intake was estimated from data obtained from food frequency and food history questionnaires. Food intake questionnaires are imperfect measures of exposure and thus misclassification of exposure is likely to occur. It is important to note that food frequency questionnaires are used for ranking subjects according to food or

nutrient intake, but not for estimating absolute levels of intake. Based on the exposure tools used in these studies and the possibility of residual confounding by other exposure sources (e.g. smoking, occupation) 6 and/or other unmeasured factors (e.g. helicobacter infection, fruits and vegetables intake, chemicals in meat other than N-NAs) the possibility of using data from these studies for hazard characterisation is limited. Due to limitations in study design, these studies cannot be used to establish tumour target sites and Reference Points for N-NAs.

## **Mode of action**

26. The main mode of action for the carcinogenic activity of N-NAs is genotoxicity. The key step is metabolic activation by  $\alpha$ -hydroxylation and the subsequent formation of highly reactive diazonium ions which can form DNA-adducts. Acyclic N-NAs with dimethyl- and diethyl-groups were reported to be more genotoxic and mutagenic than N-NAs with longer chains and cyclic N-NAs. In rodents, the liver is the main target tissue for the carcinogenic activity of N-NAs, followed by the upper GI and respiratory tract. However, these tissues have not been identified consistently as N-NA targets in human epidemiological studies. This may be due to species-specific differences in absorption, distribution and elimination and species-/tissue-specific differences in bioactivation and repair of DNA adducts. Analysis of 900 human colorectal cancer (CRC) cases identified the mutational signature of DNA O<sup>6</sup>-alkylguanine, the most mutagenic adduct induced by N-NAs. This signature was associated with the development of CRC and with high intakes of processed and unprocessed red meat.

## **Benchmark dose modelling and possible grouping for carcinogenic potency**

27. With regard to the individual ten carcinogenic NAs (TCNAs) reported to occur in food, experimental data for five of these NAs allowed the derivation of BMDL10 values (in mg/kg bw per day) for NDMA (0.035), NDEA (0.010), NMOR (0.014), NPIP (0.062), and NPYR (0.127). The dose response modelling was based on the critical effect identified as liver tumour incidence.

28. For 9 carcinogenic N-NAs, TD50 values (in mg/kg bw per day) were reported: NDMA (0.0959), NMEA (0.05), NDEA (0.0265), NDPA (0.186), NDBA (0.691), NMA (0.142), NMOR (0.109), NPIP (1.11) and NPYR (0.799). The TD50 was predicted (as there was no reported value) only for NSAR (0.982). By any criterion, NDEA, NMEA, NDMA and possibly NMOR are in the group of highest

carcinogenic potency. The derived BMDL10 and TD5 values are summarised in Table 1.

Table 1. The ten carcinogenic N-NAs reported to occur in food and their derived BMDL10 values and reported (and predicted for NSAR) TD50 values.

Chemical BMDL10 values TD50 values

NDMA	0.035	0.0959
NMEA	0.010	0.05
NDEA	n/a	0.0265
NDPA	n/a	0.186
NDBA	n/a	0.691
NMA	n/a	0.142
NMOR	0.014	0.109
NPIP	0.062	1.11
NPYR	0.127	0.799
NSAR	n/a	0.982 (predicted)

29. In a conservative approach the CONTAM Panel applied the same carcinogenic potency to all TCNAs as for NDEA (0.0265 mg/kg bw per day). In an alternative approach, the ratio between the lowest BMDL10 of N-NAs with the highest concern (0.010 mg/kg day for NDEA, NMEA, NDMA and NMOR) and the lowest BMDL10 of the remaining N-NAs (0.062 mg/kg per day for NDPA, NDBA, NMA, NPYR, NPIP, NSAR) was used to calculate a potency factor of 0.2 between



the two subgroups. Despite the differences in experimental systems, NDEA, NMEA, NDMA and possibly NMOR are the most potent by any criterion measured.

30. Therefore, the CONTAM Panel selected the BMDL10 of 10 µg/kg bw per day for the induction of any liver tumour (benign and malignant tumours combined) in female rats as a Reference Point for the risk characterisation of the most potent N-NA, NDEA, but also of the TCNAs, by applying a conservative approach in which the same potency has been attributed to all of them.

## **Occurrence data**

31. Considering the occurrence of N-NAs in food, 2,817 results for food samples analysed from four European countries between 2003-2021 were available for the assessment. Besides the EFSA occurrence dataset, the CONTAM Panel considered also analytical results from EU countries (n = 3,976) and non-EU countries (n = 27) extracted from articles published between 1990 and 2021, selected based on quality criteria.

## **Exposure assessment**

32. From this dataset, the dietary exposure assessment could be performed for the following food categories: 'Alcoholic beverages', 'Coffee, cocoa, tea and infusions', 'Fish, seafood, amphibians, reptiles and invertebrates', 'Meat and meat products' and 'Seasoning, sauces and condiments'. The percentage of left-censored data in these food categories at the Level 1 of the Foodex2 classification, across N-NAs, ranged from 3% to 99%.

33. No occurrence data were available to EFSA or selected from the literature for any of the N- NAs for the following food categories: "Fruit and fruit products", "Fruit and vegetable juices and nectars (including concentrates)", "Grains and grain-based products", "Legumes, nuts, oilseeds and spices", "Milk and dairy products", "Starchy roots or tubers and products thereof, sugar plants", "Vegetables and vegetable products", "Water and water-based beverages".

34. Among the five food categories considered in the dietary exposure assessment "Meat and meat products" was the only food category for which data were available for all the individual TCNAs.

35. NDMA was the only N-NA for which data were available for all five Foodex2 Level 1 food categories. Data were available for 3 food categories for

NPYR, NPIP, NDEA and NDBA; for 2 food categories for NMOR and one food category for NSAR, NMEA, NDPA and NMA.

36. Although unprocessed and uncooked meat may contain trace amounts of N-NAs, evidence is found in literature which shows the increased presence of N-NAs in these foods after cooking (baking, frying, grilling, microwaving) indicating that cooking generates N-NAs.

37. However, data availability on cooked unprocessed meat and fish are limited and there is also some uncertainty regarding the potential presence or absence of nitrite/nitrate added in the products that were cooked and/or bought already as cooked. For this reason, the Panel decided to estimate exposure using two scenarios, excluding (scenario 1) or including cooked unprocessed meat and fish (scenario 2).

38. In scenario 1 (excluding cooked unprocessed meat and fish) the TCNA mean middle-bound (MB) dietary exposure ranged from 0.1 ng/kg bw per day in infants to 12.0 ng/kg bw per day in toddlers. The TCNA P95 upper-bound (UB) dietary exposure ranged from zero to 54.8 ng/kg bw per day, both in infants. The highest P95 dietary exposure to TCNAs assessed using potency factors was 1.7 times lower than the highest P95 dietary exposure to TCNA assessed without using potency factors (both found in infants).

39. In scenario 2 (including cooked unprocessed meat and fish) the TCNA mean MB dietary exposure ranged from 7.4 ng/kg bw per day in infants to 87.7 ng/kg bw per day in toddlers. The TCNA P95 UB dietary exposure ranged from 34.7 ng/kg bw per day in infants to 208.8 ng/kg bw per day in toddlers. The highest P95 dietary exposure to TCNAs assessed using potency factors was 3.3 times lower than the highest P95 dietary exposure to TCNA assessed without using potency factors (both found in toddlers).

40. In both scenarios, NPYR, NSAR, NDMA, NPIP and NDEA are the five individual N-NAs contributing the most to the highest mean TCNA exposure across surveys and age groups (> 80%).

41. The highest P95 UB dietary exposure to TCNAs in scenario 2 was about 3 times higher than in scenario 1.

42. For the individual compounds, in both scenarios the main contributing food category at the Foodex2 Level 1 was "Meat and meat products" for all N-NAs. "Alcoholic beverages" (beer and unsweetened spirits and liqueurs) was also a main contributor for NDBA, NDMA and NMOR in adolescents, adults, elderly and

very elderly in both scenarios. “Fish, seafood, amphibians, reptiles and invertebrates” (processed fish and seafood categories only) was also a main contributor in scenario 1 for NDMA, NPIP and NPYR in all age groups and for NDEA in adults, elderly and very elderly and in scenario 2 for NDMA and NPIP in all age groups.

43. Due to the uncertainty with regard to the high proportions of results below LOD/LOQ and/or only limited availability of data considered in the dietary exposure assessment for TCNAs, the CONTAM Panel noted that exposure calculations should be interpreted with caution.

## **Risk characterisation and conclusions**

44. For substances that are both genotoxic and carcinogenic, the EFSA Scientific Committee stated that a margin of exposure (MOE) of 10,000 or higher, if based on the BMDL10 from an animal carcinogenicity study, would be of low concern from a public health point of view (EFSA, 2005).

45. The CONTAM Panel characterised the risk for scenario 1 (excluding cooked unprocessed meat and fish) and scenario 2 (including cooked unprocessed meat and fish). The NDEA BMDL10 of 10 µg/kg bw per day, for increased incidence of liver tumours (benign and malignant tumours combined) in rodents, was used as the Reference Point for the TCNAs in the MOE approach. MOE values ranged (minimum LB-maximum UB at the P95 exposure) in scenario 1 from 3,242 to 183 and in scenario 2 from 322 to 48, across dietary surveys (excluding some infant surveys with P95 exposure equal to zero) and age groups. The CONTAM Panel concluded that these calculated MOEs for the TCNAs are below 10,000 in both scenarios which may indicate a health concern. Attributing a lower potency factor to NMA, NDPA, NDBA, NSAR, NPIP, NPYR would not change the above conclusion.

46. The assessment of P95 exposure was subject to significant sources of uncertainty, which could make the true value up to a factor of three lower or a factor of eight higher. The uncertainty contributing most to the potentially large under-estimation was the lack of occurrence data for important food categories, especially vegetables, cereals and milk and dairy products. Only minor uncertainties were identified for the Reference Point (BMDL10) for NDEA. The toxicity of some other N-NAs was more uncertain due to limitations in the available toxicity data. Taking account of the identified uncertainties, the CONTAM Panel concluded that the MOE for TCNAs at the P95 exposure is highly

likely (98%-100% certain) to be less than 10,000 for all age groups, which may indicate a health concern.

47. The CONTAM Panel recommends that the following should be undertaken:

- fill the gaps in ADME of N-NAs relevant to human exposure.
- Fully characterise the metabolic activation pathways and DNA adducts formed 276 in human and animal tissues.
- Determine the relative mutagenic potencies of some N-NAs present in food for which the genotoxic/carcinogenic mechanisms have not been fully clarified (for example NMOR, NPIP, NPYR). This would include: i) the use of metabolic activation systems of human origin, ii) characterisation of DNA adducts, and iii) comparison of mutational spectra obtained by whole genome sequencing to mutational signatures present in human cancer.
- Perform epidemiological studies implementing a molecular approach and endorsing omics investigation on the association between N-NAs and cancer with control of confounding factors (e.g. use of medicines, occupational exposure, smoking).
- Standardise a sensitive analytical method to quantify the carcinogenic N-NAs, both volatile and non-volatile, in different food products.
- Collect data on N-NAs in processed foods other than processed meat (i.e. vegetables, cereals, milk and dairy products, fermented foods, pickled preserves, spiced foods etc.) and on cooked products with and without the addition of nitrate and nitrite. In addition, more data on human milk are needed to enable the exposure assessment in infants.

## **Questions on which the views of the Committee are sought**

- i. Do Members agree with the methodology used by EFSA to determine the Reference Point and derived BMDL10 values and the values selected/calculated?
- ii. Do Members agree with the methods used to calculate the MOEs for the TCNAs?
- iii. Do members have any other comments that they would like included in the public consultation?

## **Secretariat**

**October 2022**

## **TOX/2014/XX Annex A**

### **EFSA Public Consultation on their draft opinion on N-Nitrosamines in Food**

The EFSA Public consultation and draft opinion: [Public Consultation: \(europa.eu\)](#)

**Secretariat**

**October 2022**