COMMENTS AND RESPONSE TO COMMENTS ON OEL: PROPOSAL AND JUSTIFICATION

All comments and attachments including confidential information received during the consultation have been provided in full to the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Last data extracted on 19.06.2023

Substance name: Nitrosamines
EC number:
CAS number:

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
14.06.2023	Austria	<confidential>	Company-Downstream User	1
Comment received				
Comment on "6.1. Monitoring methods (external exposure)", p. 46: The sampling method for ambient air, as referenced to in chapter 6.1., is prone to formation of artifacts, therefore leading to incorrect (too high) values for N-Nitrosomorpholine (CAS 67587-56-8) and especially for N-Nitrosomethylethanolamine (CAS 26921-68-6). A method for artifact-free air monitoring, by using an impregnated filterpaper prior to the Thermosorb cartridge, as described in the patent AT523589 A2 2021-09-15 is attached. Comment on "4.1 Occupational exposure limits", p. 24, table 13: Unit should be microgram µg /m³ instead of milligram mg /m³ ECHA note – An attachment was submitted with the comment above. Refer to public attachment PL0749_AT523589A2.pdf				
ECHA/RAC Response				
The method provided includes only the sampling part and as such cannot be reported (complete procedures including the sampling and the analysis method (where possible including validation data) should be included. However, the possibility of artifacts created in the sampling media is an issue and a comment explaining that the Thermosorb N is designed to prevent them has been added. The OSHA method reports the test performed to test the resistance to artifact formation of the Thermosorb N tube. Editorial corrections have been made.				

Date	Country	Organisation	Type of Organisation	Comment number

07.06.2023	Germany	Federal Institute for Occupational Safety and Health (BAuA)	National Authority	2
Comment received				
p. 47, chapter 6.2.1: there is information on background levels in the general population available by the CDC (https://www.cdc.gov/exposurereport/) for the nitrosamines: NDEA, NMEA, NMOR, NPiP, NPyr. p.49, chapter 6.2.3: Biomonitoring analytic methods: please take into account the analytical methods published by CDC (https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/labmethods.aspx?BeginYear=2013 Methode: Volatile N-Nitrosamine Compounds).				
ECHA/RAC Response				
Thank you, information from the CDC added on the background levels in section 6.2.1 and biomonitoring analytical methods in section 6.2.3.				

Date	Country	Organisation	Type of Organisation	Comment number
23.04.2023	United States of America		Individual	3
Comment received				
Monitoring exposure				
ECHA/RAC Response				
No details in the comment beyond “monitoring exposure”.				

Date	Country	Organisation	Type of Organisation	Comment number
16.06.2023	Germany	Deutsche Gesetzliche Unfallversicherung (DGUV)	National NGO	4
Comment received				
Statement of the German Statutory Accident Insurance (Deutsche Gesetzliche Unfallversicherung, DGUV) on OEL for Nitrosamines On request of the Commission, ECHA has prepared a scientific report on OELs for nitrosamines at the workplace. In its report, ECHA provide information on a cancer exposure-risk relationship instead of recommending OELs. The DGUV supports this approach as no health based OELs can be recommended for nitrosamines as they are non-threshold carcinogens. For this reason, risk-related acceptable (statistical probability of developing cancer 4:10000) and tolerable concentrations (statistical probability of developing cancer 4:1000) of N-Nitrosodimethylamin (NDMA) were derived in Germany by the Committee on Hazardous Substances (AGS) and published by the Federal Ministry of Labour and Social Affairs (BMAS), which can be found in the TRGS 910 „Risk-related concept of measures for activities involving carcinogenic hazardous substances”. The tolerable concentration in effect is 0.75 µg/m3 and the acceptable concentration is 0.075 µg/m3. According to TRGS 552 „Carcinogenic nitrosamines categories 1A und 1B” (TRGS 552 „Krebserzeugende N-Nitrosamine der Kategorie 1A und 1B“) the tolerable and acceptable concentration apply to all carcinogenic N-nitrosamines. Furthermore, the sum of all N-				

nitrosamines that co-occur at a workplace must not exceed these values. Similar regulation should also be considered on EU level.

N-nitrosamines are usually not used as raw material. They mainly develop during manufacturing or application processes under conditions where secondary amines and nitrosating agents react with each other. Therefore, main protective measures to minimize the exposure of workers to N-nitrosamines include the substitution of secondary amines or the implementation of inhibitors which prevent the origin of N-nitrosamines. Further information can be found in the TRGS 552 (section 4.2; Annex II, table 2 (substitution) and Annex IV, section 3.2 (inhibitors)). Through consequent substitution the formation of N-nitrosamines during working activities can be prevented.

Therefore, we mainly support similar regulations on EU level, that ensure the prohibition of secondary amines that can react to N-nitrosamines.
In this context, however, the DGUV would like to point out that exceptions are necessary for distinct industrial sectors, such as underground mining work areas: Ongoing research suggests that N-nitrosamines may play a role in underground mining work areas. Since substitution cannot be applied here, an independent solution for regulating the hazards would have to be found.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment OEL nitrosamine.zip

ECHA/RAC Response

We acknowledge your support to consider the substances as non-threshold carcinogens and present exposure-risk relationships.

As noted, ECHA has developed the background document to support the RAC opinion on OELs for selected nitrosamines as requested by the Commission. Suggestions such as the prohibition of secondary amines (with exemptions) are outside the scope of this work, but could be made to the Commission so that they can be taken into account in the further steps of their processes.

Date	Country	Organisation	Type of Organisation	Comment number
16.06.2023	Sweden	Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG)	International NGO	5

Comment received

See attachment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment NEG comments on nitrosamines 15 June 2023.pdf

ECHA/RAC Response

Your detailed comments have been considered and several corrections, clarifications or editorial changes have been implemented and further details (e.g. on the carcinogenicity key study of Klein et al, 1989, 1991) have been provided in the in the Opinion and/or Annex 1.

We acknowledge your support to consider the substances as non-threshold carcinogens and present exposure-risk relationships. Also, your support to base the NDMA ERR on the inhalation study with nasal tumour findings is acknowledged.

NMor is now included in the opinion.

Considerations on potency differences and use of ERRs for the setting of OELs are included in the final opinion.

The different toxicological studies on NDMA were assessed by RAC in detail. A detailed discussion on uncertainties in the inhalation studies, and basis for ERR calculations, are presented in the Opinion.

Date	Country	Organisation	Type of Organisation	Comment number
16.06.2023	Germany	Occupational Toxicology Taskforce (Chem Leg)	Industry or Trade Association	6

Comment received

Public Comment on the ECHA Scientific report for evaluation of limit values for Nitrosamines at the workplace Prepared by the European Chemicals Agency (released 18 April 2023)

Comments on the Draft 'ECHA Scientific report for evaluation of limit values for Nitrosamines at the workplace' were received from Occupational Toxicology Taskforce members.

Comment 1

Raw data used for BMD modelling, studies performed by Peto et al., 1991:

a) proposal to adjust the wording in the Table 31 (p.87) where it is applicable, instead of ''Liver: hepatocellular tumours (liver cell)'' to ''Liver: hepatocellular tumours: liver cells (malignant + benign)''

b) Minor errors in the dataset for NDEA. Group size for dose levels: 2124 ppm, n= 66, not 60; 16894 ppm, n= 54, not 60. Also, incidence for Oesophagus (malignant + benign) in males, groups 2.640 & 3.168 ppm, incidence should be 47 and 49, respectively (instead of 45 and 48).

c) Overall, adjustment of the size group will result in minor change in the PoD: from 0.0142 mg/kg to 0.0146 mg/kg (see attached BMD report), change is proposed for consistency across published reports

Comment 2

In the current draft, an exposure risk relationship (ERR) approach is used to derive additional cancer risk calculations (risk-based OELs) for NDEA and NDMA (acceptable cancer risk level: 1 per 100 000). The no-threshold assumption is the default approach, but "when subsequent analysis of the data allows refinement in the sense that overall, the data actually points to a threshold, then a threshold approach can be followed" (ECHA, 2017, 2019). DNA repair systems have limited capacity, but their ability to repair low levels of adducts has been shown in multiple studies. Based on available literature, thresholds for genotoxicity for NDEA and NDMA can be demonstrated, and this approach should be also taken into consideration in the assessment. The most recent studies, which show a dose response relationship, should be included (e.g. No-Observed-Genotoxic-Effect Levels (NOGELs) for particular nitrosamines). Several references are listed at the

end of the document.

Comment 3
p. 24, table 13, Existing OELs:
An error in units: Please check units/values in the table – either change unit to µg/m³ or change values to e.g. 0.000075 for Germany. For Austria, the TWA according to GESTIS is 0.0025 mg/m³. No limit from Slovenia is in the current GESTIS list.
Listed limits set by the German Research Foundation (DFG), for specific nitrosamines were replaced with the recommendation that "… exposure should be minimized due to carcinogenicity concerns" (DFG, 2015) - Similarly, ACGIH and OSHA now recommend that OELs for N-nitrosamines be "… as low as reasonably achievable (ALARA)" (ACGIH, 2012; COC, 2020; NIOSH, 2005).

Comment 4
p. 24 – 5.1. 'Occurrence':
Proposal to add: NDMA is produced endogenously through both acid-catalyzed nitrosation of amine precursors (primarily in the stomach) and through biologically catalyzed nitrosation, in other tissues including the oral cavity, intestine, liver, blood, and bladder (Hrudey et al. 2013 from ASTDR, 2017). Estimates of the amount of NDMA produced endogenously vary widely.
Exposure to nitrosamines and their precursors from other external sources (e.g., food) – potential occupational exposure seems to be marginal, when compared to a total exposure (including all sources of the exposure).

Comment 5
p. 33, 5.2.6 Other industrial sources:
- Research & development: Analytical chemistry tests (including Nitrosamine drug substance-related impurities (NDSRIs), standards). Many NDSRIs are less potent (or negative in genotoxicity studies) and handled sporadically. Additionally, NDMA is used in hepatic fibrosis model as an inducing agent.
Comment 6
p. 51, 7.1.2.1 Absorption and distribution
Dermal absorption in animals is missing. It is notable that in dermal studies in rodents, cancer in various organs, mainly liver and lungs, was observed, while no skin cancers were reported.

Comment 7
p.52, 7.1.2.2 Metabolism
Besides carcinogenic adducts that are formed in activation process, formaldehyde or acetaldehyde are also produced as by-products. These substances could contribute not only to the damage of hepatic tissues but also to tumors at the point of entry; importantly for occupational exposure – they are nasal carcinogens at higher doses (Schroeter et al., 2014). Also, adducts that are formed display various potencies to cause cancer.

Comment 8
p. 54 Acute toxicity – human data
Poisoning cases are missing. Two fatalities involving exposure to unknown concentrations of NDMA fumes, as well as three deaths after ingestion, liver was a target organ. (WHO, 2002). Hepatotoxicity is the most prominent and characteristic systemic effect of nitrosamines, resulting in centrilobular necrosis, hemorrhage, fibrosis, cirrhosis, and ascites, which have been observed in humans exposed by inhalation or ingestion.

Comment 9

p. 83, 7.7.2.1 Carcinogenic potency ranking
It is worth mentioning, that TD50 values for NMEA, NDPA and NDBA are based on poor quality, short studies (30 week). Depending on the used dose descriptor (TD50, T25 or BMDL or BMD), slightly different potency ranking can be obtained.

Comment 10
a) first calculation based on inhalation study
9.1.2.1.1 Klein et al. (1991): in this 2-year inhalation study in female rats, there was a significant increase in nasal cavity tumours and kidney cancer at a NDMA dose of 0.12 mg/m3. Nasal cavity tumours were identified as the most sensitive findings. Calculated T25 = 50 µg/m3. T25 / 25 000 = to extrapolate to 1:100000 = 0.002 µg/m3.
Proposal: To remove this approach from final calculations, since performed inhalation studies are poor quality (low number of animals, dose levels, high mortality at the highest dose etc) and derive nonreliable PoDs. To be included as a part of the discussion, but not to derive additional cancer risk calculations due to mentioned limitations.
In a similar study, performed by Moiseev and Benemansky, 1975, an exposure to a lower dose of 0.002 ppm (=5 µg/m3) did not produce significantly increased incidences in any tumour type, compared to controls (as reported in ATSDR 2019).
Furthermore, it is recommended to discuss the different outcomes of the Klein et al. (1991) and the Moiseev and Benemansky (1975) and take into consideration the shortcomings of the studies. It is important to make the readers aware that published studies for nitrosamines are often of poor quality. A ECHA document will serve also as a guidance how to derive health-based safety limits also for other nitrosamines, therefore, that makes the discussions of shortcomings of studies even more important.
Comment 11
P. 104: The cancer risk values were estimated for 4:1000 and 4:100.000 (according to DECOS). There are also differences in cancer risk levels between countries, organisations etc.
Current draft, ECHA: The excess life-timer cancer risk was calculated for XY cases per 100.000 (Table 35, 36, 37).
According to the EU draft "opinion on limit value setting for non-threshold carcinogens, a risk-based approach" a risk level between 4:1000 and 4:10.000 is also appropriate, however, needs priority action (see section 6 of the attached draft opinion). The OEL shall be as protective as possible whilst taking into account feasibility aspects.

Comment 12
- include NMor since it was detected in various occupational settings, and sufficient data exists to derive BMD based on oral study. Supporting inhalation study is also available (poor quality).
Comment 13
p. 23, 3.2 Other legislations: limits for nitrosamine impurities in medicinal products (EMA: EMA/369136/2020, EMA/409815/2020 Rev.15)
Comment 14
9.1.1.3 EFSA: BMD analysis on rat liver tumour incidence data and obtained BMDL10 values of 35 µg/kg bw/day for NDMA, 10 µg/kg bw/day for NDEA, 14 µg/kg bw/day for NMor, 62 µg/kg bw/day for NPip, and 127 µg/kg bw/day for NPyr. These BMDs are based on pooled malignant and benign tumours.
Comment 15
- p. 82: ‘’Tumours of the respiratory tract, including the nasal cavity, were frequently reported in mice and hamsters even via parenteral administration of the substances:’’
Proposal: remove ‘’frequent’’, or provide more information on type of tumours, incidences etc. if possible.

Comment 16

Proposal to adjust the concentrations for nitrosamines handled intermittently, in concordance to ICH M7's less than lifetime (LTL) approach.

References:

Akagi, J., Toyoda, T., Cho, Y.M., Mizuta, Y., Nohmi, T., Nishikawa, A. et al. (2015) Validation study of the combined repeated-dose toxicity and genotoxicity assay using gpt delta rats. Cancer Science, 106(5), 529–541.

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Johnson, G. E., Dobo, K., Gollapudi, B., Harvey, J., Kenny, J., Kenyon, M., … Zeller, A. (2021). Permitted daily exposure limits for noteworthy N-nitrosamines. Environmental and Molecular Mutagenesis, 62(5), 293– 305. https://doi.org/10.1002/em.22446

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Souliotis, V. L., Henneman, R. H., Reed, C. D., Chhabra, S. K., Diwan, B. A., Anderson, L. M., & Kyrtopoulos, S. A. (2002). DNA adducts and liver DNA replication in rats during chronic exposure to N-nitrosodimethylamine (NDMA) and their relationships to the dosedependence of NDMA hepatocarcinogenesis. Mutation Research, Fundamental and Molecular Mechanisms of Mutagenesis, 500(1–2), 75–87. https://doi.org/10.1016/S0027-5107(01)00301-3

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ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 08.3_Draft Opinion on Risk Based Approach agreed_by_WPC_28-09-2022.docx
ECHA/RAC Response
Your detailed comments have been considered and several corrections or editorial changes have been implemented and details have been specified in the in the Opinion and/or Annex 1. The possibility for a threshold for genotoxicity at low dose levels has been captured in the Opinion and/or Annex 1 and was acknowledged by RAC. The RAC plenary concluded that the use of a non-threshold approach is justified for nitrosamines. The ERRs have been updated. NMor is now included in the opinion. The different toxicological studies on NDMA were assessed by RAC in detail. A detailed discussion on uncertainties in the inhalation studies, and basis for ERR calculations, are presented in the Opinion.

PUBLIC ATTACHMENTS
1. OEL nitrosamine.zip [Please refer to comment No. 4]
2. NEG comments on nitrosamines 15 June 2023.pdf [Please refer to comment No. 5]
3. PL0749_AT523589A2.pdf [Please refer to comment No. 1]

CONFIDENTIAL ATTACHMENTS
1. 08.3_Draft Opinion on Risk Based Approach agreed_by_WPC_28-09-2022.docx [Please refer to comment No. 6]