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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Substance name: 1,4-dioxane
EC number: 204-661-8
CAS number: 123-91-1

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
23.11.2021	Sweden	Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG)	International NGO	1
Comment received				
See attached file "NEG comments on ECHA 14-dioxane November 2021" ECHA note – An attachment was submitted with the comment above. Refer to public attachment NEG comments on ECHA 14-dioxane November 2021.pdf				
ECHA/RAC Response				
Thank you for the detailed comments. Suggestions presented in your comments are mostly implemented as proposed (see revisions in Annex 1 to the RAC opinion). Please find below explanation for some suggestions not taken on board. Overall comments: The recommendations are given as mg/m^3, with ppm in brackets. Where data in publications are referred, the units are shown as in the source (with the corresponding mg/m^3/ppm value in brackets). Preferred value approach: Values are not rounded at this stage. Minor editorial comments: Abbreviations have been checked: the documents do not currently include an abbreviations list, however tis is under review for future ECHA documents. Comment 'page 7': details on sampling time are included in Section 9.2.4. Comment 'page 16': text reflects now that the indicator is in urine. The half life provided was absolute for HEEA. Text slightly modified to avoid this confusion.				

Comment ‘page 16’: still found useful to briefly explain in Section 6.2.1. the sources of background exposure to 1,4 dioxane (to make clear why we could potentially look for biomarkers).

Tables 8-10: Although LD50 values are not crucial for the OEL setting, the tables give an overview of the acute toxicity.

Comment Section 7.4.1.

Date	Country	Organisation	Type of Organisation	Comment number
25.11.2021	Germany	Division 4 - Hazardous Substances and Biological Agents of the Federal Institute of Occupational Safety and Health	National Authority	2

Comment received

Division 4 - Hazardous Substances and Biological Agents of the Federal Institute of Occupational Safety and Health prepared the following comment on the draft of the OEL-report for the sub-stance 1,4-Dioxan (EC: 204-661-8, CAS: 123-91-1).

General remarks
ECHA refers in its OEL-report to some US worker exposure data and some information in an old risk assessment report. But ECHA does not refer to a recent risk management option analysis (RMOA) that was prepared and submitted by Germany in 2020 (https://echa.europa.eu/documents/10162/010b37a1-9d0d-a69e-a703-df8626102fae) . A refer-ence to this RMOA would be beneficial as the RMOA compared and analysed several regulatory measurement options, such as the authorisation procedure, and finally came to the conclusion that an OEL would be the most appropriate option to protect workers.
The paragraphs in the report about Tonnage, Uses and Exposure are in line with the results we derived during the evaluation and drafting of the RMOA.
We suggest that the OEL report is supplemented with an assessment based on systemic effects addressing all relevant tumour types, and double-checked for inconsistencies with the RAC Opinion for harmonised classification. Deviations should be explained and justified.
Rationale
The ECHA scientific report (ECHA 2021) basically relies on the same studies as described in the RAC opinion on the harmonised classification of 1,4-dioxane (ECHA 2019). The OEL derivation further leans on previous cancer risk assessments and/or OEL proposals of other bodies, namely SCOEL (2004), DECOS (2011) and DFG (Hartwig 2020).
All Committees give special weight to the latest 2-year inhalation study in male rats (Kaisai 2009; see incidence table below). There are, however, differences/inconsistencies in the interpretation of results and MoA considerations.

Source ECHA (2019)

Point of departure

RAC considers the peritoneal mesothelioma observed in this study as the most sensitive endpoint. In contrast, according to ECHA (2021), DECOS (2011) considers nasal lesions, and DFG (Hartwig 2020) nasal toxicity and carcinogenic effects in the nose, liver and kidney as critical effects. ECHA (2021) is less clear regarding the critical effect and uses nasal lesions as reference for OEL calcula-tion while not mentioning peritoneal mesothelioma at all.

MoA
• Genotoxicity: There seems to be agreement that genotoxicity most likely is not the driving MoA for carcinogenicity of 1,4-dioxane, as it only occurs in vivo at very high doses and/or in the presence of cytotoxicity. Remaining uncertainty is acknowledged but not quantified.

• (non-genotoxic) regenerative hyperplasia MoA: RAC considered this MoA, which was sug-gested by Dourson et al. (2017) during the public consultation of the CLH process, as poten-tially plausible cause for the induction of liver tumours, but states:

"For the induction of the other tumour types reported following exposure to 1,4-dioxane, peritoneal mesothelioma and nasal cavity squamous cell carcinoma, no clear MoA has been postulated. There is also information showing that 1,4-dioxane could be considered as a genotoxic substance at higher dose levels, and toxicity of metabolites cannot be ex-cluded. Therefore, it is considered that no definite conclusions can be made about the MoA for the induction of tumours following exposure to 1,4-dioxane."

In contrast, ECHA (2021) concludes "…although there is some uncertainty on the mode of ac-tion, the carcinogenicity of 1,4-dioxane is considered to be related to non-genotoxic mecha-nisms, involving saturation of the metabolic capacity and irritation at high exposure levels." This statement seems to imply that the mechanism is not limited to liver tumours but pos-tulated for other cancer types as well.

• Local irritation: There seems to be agreement that the mechanism for nasal tumours is linked to local irritation of the nasal epithelia, followed by inflammation, regenerative cell proliferation and hyperplasia.

[SCOEL (2004), DECOS (2011), DFG (Hartwig 2020) and ECHA (2021) consider local irritation as starting point for OEL derivation resulting in 8 h TWA OELs of 20 ppm, 6 ppm, 10 ppm and 6 ppm, respectively.]

OEL calculation
In section 9.2.2, ECHA (2021) states that "An 8 h TWA is recommended to protect workers against local and systemic effects of 1,4-dioxane." The calculation, however, is only based on local effects in the chronic toxicity study by Kasai et al. (2009) and sensory irritation in humans after short term (2 h) exposure (Ernstgaard et al. 2006). A calculation based on the systemic effects is not done.
ECHA recommends an OEL (8h TWA) of 6 ppm on the basis of local effects in the nasal epithelium of rats after chronic inhalation at the lowest concentration of 50 ppm. The OEL is supported by a study with volunteers showing no sensory irritation at an exposure concentration of 20 ppm for 2 hours. Since at the LOAEC of 50 ppm almost all animals showed local irritation in the nose it is questionable whether an extrapolation factor of 3 is sufficient to extrapolate to a NAEC. However on the other hand, there have been no signs of sensory irritation in a study with volunteers exposed to 20 ppm.
Concerning systemic effects, in the 2-year-inhalation study (Kasai 2009) with male rats liver necrosis occurred at the lowest concentration of 50 ppm in 3 out of 50 animals (control 1/50; 50 ppm: 3/50; 250 ppm: 6/50; 1250 ppm: 12/50)). Therefore, ECHA is

asked whether the proposed OEL of 6 ppm is also protective against systemic effects, for which a LOAEC of 50 ppm can be derived from the chronic inhalation study.
The difference might not be large, as not the nasal tumours but pre-neoplastic events observed at the lowest dose are used as starting point (increased incidences of nuclear enlargement of the res-piratory epithelium, and nuclear enlargement, atrophy, and respiratory metaplasia of the olfactory epithelium). On the other hand, an assessment based on systemic effects would have required the use of additional assessment factors. Thus, even if one could assume that the outcome is likely to be in the same order of magnitude, the BfR suggests that the assessment should be performed.
Editorial remarks:
In table 4 on page 11 (Existing OELs from the Gestis database), an OEL from Germany (DFG) of 20 ppm is referred to. However, the MAK value of the German MAK commission of the DFG has been lowered to 10 ppm in 2018, which is correctly mentioned in chapter 9.2.1.3.
Chapter 6.1 „External exposure" should be renamed to „Monitoring of inhalation exposure"
Paragraph in Chapter 6.1: "available validated methods for measurement 1,4-dioxane air" should be changed to "available validated methods for the measurement of 1,4-dioxane in air"

References

DECOS (2011). 1,4-Dioxane. Health-based recommended occupational exposure limit. Health Council of the Netherlands.

Dourson, M. L., Higginbotham J., Crum J., Burleigh-Flayer H., Nance P., Forsberg N. D., Lafranconi M., and Reichard J. (2017). 'Update: Mode of action (MOA) for liver tumors induced by oral expo-sure to 1,4-dioxane', Regulatory Toxicology and Pharmacology, 88: 45-55.

ECHA (2019). RAC Opinion proposing harmonised classification and labelling at EU level of 1,4-dioxane, EC Number: 204-661-8, CAS Number: 123-91-1, CLH-O-0000001412-86-264/F Adopted 15 March 2019 https://echa.europa.eu/documents/10162/024a7c7e-eb2a-827d-0d88-5ef4a48e932e

ECHA (2021). ECHA Scientific report for evaluation of limit values for 1,4-dioxane at the workplace. Prepared by the European Chemicals Agency. 27 September 2021

Ernstgard L., Iregren A., Sjogren B., and Johanson G. (2006). 'Acute effects of exposure to vapours of dioxane in humans', Human & Experimental Toxicology, 25: 723-29.

Hartwig A. (2020). '1,4-Dioxane – Addendum for re-evaluation of the BAT value. Assessment Values in Biological Material. Translation of the German version from 2020.' in, The MAK Collection for Occupational Health and Safety, volume 5.

Kasai T., Kano H., Umeda Y., Sasaki T., Ikawa N., Nishizawa T., Nagano K., Arito H., Nagashima H., and Fukushima S. (2009). 'Two-year inhalation study of carcinogenicity and chronic toxicity of 1,4-dioxane in male rats', Inhalation Toxicology, 21: 889-97.

SCOEL (2004). "Recommendation from Scientific Committee on Occupational Exposure Limits for 1,4-Dioxane. European Commission."

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 211125_Comm_FB4_BAuA_OEL_Report_1,4-Dioxan_final.pdf

ECHA/RAC Response

Thank you for your detailed comments.

1) General remarks
A description of the RMOA outcome has been added.
Details on systemic effects have been further assessed and considered in the OEL derivation.

2) Point of departure
In addition to nasal effects, considerations on systemic effects as point of departure have been included.

3) MoA
Thank you for noticing general agreement on genotoxicity (not being the main reason for carcinogenicity) and on the mechanisms behind nasal tumours.

4) OEL calculation
The section on the derivation of the OEL has been significantly revised and covers now also calculations based on systemic effects.

5) Editorial changes
Implemented based on proposals. However, the title of Section 6.1 ('External exposure') is a standard title in the template of the Annex and was therefore not changed.

Date	Country	Organisation	Type of Organisation	Comment number
24.11.2021	Netherlands	Health Council of the Netherlands	Academic Institution	3

Comment received

Dear madam/sir,

On behalf of the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council of the Netherlands, I would like to thank you for the opportunity to comment on ECHA's public draft report on 1,4-dioxane, which was made available by the ECHA for public consultation in September 2021. The DECOS has previously recommended on an occupational exposure limit for 1,4-dioxane in 2011. The DECOS appreciates the fact that this recommendation has been referenced in the draft report. The DECOS has the following comments:

Carcinogenicity
The ECHA concludes that 1,4-dioxane is carcinogenic in animals and should be classified in category 1B, based on neoplastic lesions in the liver and in the nasal cavity of rodents observed both after exposure via inhalation and in drinking water. Furthermore, the ECHA concludes that 1,4-dioxane is carcinogenic by a non-genotoxic mode of action.
The DECOS supports these conclusions, as is outlined in the DECOS report of 2011.

Recommended OEL
The ECHA derives an 8h-TWA OEL, based on adverse effects at 50 ppm (183 mg/m3) in the nose of rats (increased incidences of nuclear enlargement of the respiratory epithelium) observed in a study by Kasai et al. (2009). An assessment factor of 3 is applied since a LOAEC is used as a starting point. Further, an additional assessment

factor of 3 is applied for the uncertainty regarding differences in sensitivity to nasal irritation within the population. With an overall assessment factor of 9, ECHA derives a recommended OEL of 6 ppm (22 mg/m3). The ECHA notes that this recommended OEL is supported by the fact that in a study with human volunteers, no sensory irritation effects were observed at 20 ppm for 2 h.
The DECOS supports this recommendation, which is in line with the OEL proposed by DECOS previously.

Short-term exposure limit
In contrast to DECOS, the ECHA derives a short-term exposure limit (STEL). The DECOS supports a STEL of 20 ppm as described in section 9.2.3, and proposes to add a reference to this section.

Skin notation
The ECHA recommends a skin notation for 1,4-dioxane. This recommendation appears to be based on a study by Dennerlein et al. (2015), in which an estimated amount of 984 mg of 1,4-dioxane is absorbed when 2000 cm2 surface area of skin is exposed for 1 hour (this value is extrapolated from a measured absorption value of 315 µg by a surface area of 0.64 cm2). The DECOS previously estimated an amount of 6 mg 1,4-dioxane to be absorbed by a surface area of 2000 cm2 during a working day (based on absorption data reported by the ATSDR). Following the strategy for assigning a "Skin Notation" as proposed by ECETOC (Document No. 31), the DECOS did not recommend a skin notation for 1,4-dioxane.
The DECOS notes that a large difference exists between the dermal absorption estimates by the ECHA and the DECOS in 2011. The DECOS recommends to evaluate both approaches, substantiate the approach preferred and clarify the criteria that are used to conclude on the necessity of a skin notation.

Kind regards, on behalf of the DECOS,

S.R. Vink
Scientific secretary

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Health Council Netherlands - Commentary letter RAC 14-dioxane -ECHA-November 2021.pdf

ECHA/RAC Response

Thank you for the support on carcinogenicity, OEL and STEL.
Regarding skin notation, the section has been modified.

PUBLIC ATTACHMENTS
1. 211125_Comm_FB4_BAuA_OEL_Report_1,4-Dioxan_final.pdf [Please refer to comment No. 2]
2. Health Council Netherlands - Commentary letter RAC 14-dioxane -ECHA-November 2021.pdf [Please refer to comment No. 3]
3. NEG comments on ECHA 14-dioxane November 2021.pdf [Please refer to comment No. 1]