

Evaluation from the Danish Working Environment Authority's (AT) Occupational exposure limit quality committee of the report: Maleic acid anhydride. Scientific basis for setting a health-based occupational exposure limit. The report is from 2022.

Members of the quality committee: Nellie Anne Martin (Environmental Protection Agency - Division of Chemicals and Biocides); Anoop Kumar Sharma (Technical University of Denmark-National Food Institute); Zara Ann Stokholm (Aarhus University - Department of Clinical Medicine); Lisbeth E Knudsen (University of Copenhagen - Department of Public Health)

This evaluation is based on a meeting 4th June 2024 arranged by The Danish Working Environment Authority, where the results from the report were discussed after the authors from the working group at NRCWE (Pernille Høgh Danielsen and Ulla Vogel) presented the content of the report. After the presentation, the members of the quality committee asked questions to the authors.

The report reviews data relevant to assessing the hazards of maleic acid anhydride in humans and in animals. Toxicokinetics and genotoxicity are briefly described, and previous risk assessments of maleic acid anhydride are summarized. The scientific basis for setting an occupational exposure limit (OEL) are presented. The current Danish OEL (TWA 8h) for maleic acid anhydride is 400 µg/m³. In the report, it is described that the working group considers local irritative effects and respiratory sensitization as critical effects, as these effects were observed in human observational studies. The proposed OEL is based on a 6-month inhalation study in rats, hamsters and monkeys. Irritation was observed at all dose levels in all three assessed animal species and the LOAEL was defined at 1.1 mg/m³. Based on this LOAEL value, the working group calculated two DNEL values 2 and 7 µg/m³, depending on the choice of LOAEL to NOAEL assessment factor. The working group recommends using the DNEL value of 2 µg/m³, because of gross signs of effects was observed in all 3 animal species, and furthermore allergic sensitization observed in workers is a potential forerunner for severe outcome. Raw data from the critical study are not available.

General comments:

Use either µg/m³ or mg/m³ throughout the report.

Most information about toxicity was secondhand information from published reviews and reports and it is recommended to clearly state when text is quotations from these studies to distinguish quotes and the assessment of NFA. Often it is not clear if quotations are from other studies or formulations of NFA.

Tables providing an overview of studies with essential information would be beneficial of *in vivo* studies, epi studies and other countries OELs.

Systemic effects of kidney damage and some reproductive disturbances are reported and should be mentioned and discussed in more detail in the report, even though these studies used oral gavage as the administration route. There should be more elaboration of why systemic effects of kidney and reproductive effects are disregarded in the hazard characterization.

The authors recommend using the lowest DNEL value, and the quality committee suggests more elaboration of this choice including the quality of the data. The Danish EPA document and ECHA documents could be used and the precautionary principle may be mentioned, because of unavailability of raw data of the critical study, which is a huge limitation.

More justification for the use of a threshold value of the critical effects.

Mechanisms of action are described in the literature and may be included (MAK and the Danish EPA document from 2013 could be used).

Literature: Literature search was done in PubMed and Web of Science and governmental databases. The committee suggests that a Danish evaluation of health hazards by exposure to maleic anhydride is included in the revised revision (The Danish Environmental Protection Agency: Evaluation of health hazards by exposure to Maleic anhydride and proposal of a health-based quality criterion for ambient air, Environmental Project No 1497, 2013).

The following ECHA documents should be included. ECHA CLH report (CLH report. Proposal for Harmonized Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2, Substance Name: Maleic anhydride). Furthermore, the ECHA registration dossier (<https://echa.europa.eu/da/registration-dossier/-/registered-dossier/15798/7/9/1>).

The committee also suggests including a QSAR prediction performed in the database (<https://qsar.food.dtu.dk>) The QSAR prediction may support genotoxicity and cancer data.

Human observations:

We recommend either a brief introduction to the human studies, followed by facts from the studies presented systematically in the text including type of study, number of persons included, type of industry, exposure levels (if reported), are workers exposed to maleic acid anhydride only or a combination of substances and the outcome of the studies. Another possibility is a table with the essential information of the studies. Table 2 should be clearer in relation to %. A brief summary of the human data would be helpful.

These papers may be included:

1. Guerin JC, Deschamps O, Guillot YL, Chavaillon JM, Kalb JC. [A case of asthma due to maleic anhydride (author's transl)]. *Poumon Coeur* 1980;36:393-395.
2. Hansen MR, Lander F, Skjold T, Kolstad HA, Hoffmann HJ, Schlünssen V. [Occupational asthma caused by maleic anhydride]. *Ugeskr Laeger*. 2014 Sep 8;176(37):V04140237. Danish. PMID: 25294039.

Genotoxicity:

It should be mentioned that only one *in vivo* study is available and there is no information about gene mutations *in vivo*. In the Danish EPA document at table of *in vitro* studies is provided and these studies may be included.

Previous evaluations:

A table would be very helpful including the essential information including the critical studies and the outcome. This table could also include the OELs. Furthermore, it should be clear if the evaluations are based on human data or animal data. More elaboration on why NFA agrees with the MAK evaluation and not with DECOS evaluation.

The MAK Commission (1992/2018): More elaboration on the last sentence: "Damage to the embryo or fetus is unlikely when the MAK value is not exceeded (MAK, 2018).

Specific comments:

In the foreword, consumption of 5,063,000 kg – change it to tons/year.

The first paragraph, last sentence in the foreword – fumes referring to gasses or aerosols or both?

Predominant effects is mentioned on page 5 – we recommend to use critical effect or another known risk assessment term.

Setting an occupational exposure limit

The committee supports the decision to use local irritative effects and respiratory sensitization as critical effects.

The current working group emphasizes that gross signs of nasal and ocular irritation was present in all species and all exposure levels in the animal inhalation study, and that allergic sensitization seen in workers is a forerunner for severe adverse health effects.

The committee supports the NRCWEs recommendation: **to use the calculation with the highest LOAEL- to NOAEL assessment factor which results in the DNEL of 2 µg/m³.**

References:

ECHA documents:

<https://echa.europa.eu/da/registration-dossier/-/registered-dossier/15798>

ECHA CLH report (CLH report. Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2, Substance Name: Maleic anhydride)

The Danish Environmental Protection Agency: Evaluation of health hazards by exposure to Maleic anhydride and proposal of a health-based quality criterion for ambient air, Environmental Project No 1497, 2013

Guerin JC, Deschamps O, Guillot YL, Chavaillon JM, Kalb JC. [A case of asthma due to maleic anhydride (author's transl)]. *Poumon Coeur* 1980;36:393-395.

Hansen MR, Lander F, Skjold T, Kolstad HA, Hoffmann HJ, Schlünssen V. [Occupational asthma caused by maleic anhydride]. *Ugeskr Laeger*. 2014 Sep 8;176(37):V04140237. Danish. PMID: 25294039.