National Research Centre
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Maleic acid anhydride

Scientific basis for setting a health-based occupational exposure limit

(Maleinsyreanhydrid:

Videnskabelig dokumentation for helbredsbaserede risikoestimater)

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Rapport

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Foreword

Maleic acid anhydride (CAS 108-31-6) is widely used in the chemical industry manufacturing of lacquers, lubricants, polymers, polyesters, plasticizers, pharmaceuticals or alkyd resins. In Denmark, maleic acid anhydride is mostly used in the production of pesticides and other agrochemicals according to Produktregisteret, where the total consumption is noted to be 5,500 tons/year (2022). Workers can be exposed to powders or crystals of maleic anhydride during manufacturing processes, but also to fumes from hot processes.

In 2018, the German Research Foundation (DFG) Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, better known as the MAK Commission, evaluated the scientific data and suggested a lowering of the national MAK value for maleic anhydride to 0.081 mg/m^3. An occupational exposure limit (OEL) which is ~5 times lower than the existing Danish OEL (TWA 8h) for maleic anhydride of 0.4 mg/m^3.

At the request of the Danish Working Environment Authority, a working group at the National Research Centre for the Working Environment (NFA) reviewed data relevant to assess the hazard of maleic anhydride and calculate a health-based OEL.

The working group wishes to thank toxicologist Poul Bo Larsen, DHI, Denmark for reviewing the report.

Copenhagen, December 2022

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Executive summary

Maleic anhydride is widely used in the chemical industry and comes in white crystals/flakes or powders. Workers can potentially be exposed at industrial sites where maleic anhydride is manufactured, where it is used as an intermediate in chemical synthesis or where it is used as monomer. Occupational exposure is likely to occur by inhalation or dermal routes.

In humans, the most frequently reported effects after inhalation are local irritation such as rhinitis and conjunctivitis, but also asthma, and allergy caused by IgE-mediated sensitisation are evident. Additionally, exposure to maleic acid anhydride by skin contact is associated with allergic contact dermatitis.

In animal experiments, the predominant effects are kidney toxicity following oral exposure and nasal/ ocular /airway irritation following exposure by inhalation. Generally, limited data are available in animals.

The current working group considers local irritative effects and respiratory sensitisation as critical effects, as these effects were observed in human observational studies. In long-term inhalation studies in animals, irritation were observed at all dose levels in all three assessed animal species. On the other hand, hyperplastic and metaplastic changes were only observed in the rodent species, which, in contrast to monkeys, are obligatory nasal breathers. There are no available human data on exposure-response relationships that can be used to derive a health-based OEL.

The current Danish OEL (TWA 8h) for maleic acid anhydride is 0.4 mg/m^3, which corresponds to the MAK-value from 1992. However, the MAK commission re-evaluated the data on maleic acid anhydride in 2018. No new experimental data were available, but due to a change in approach the MAK-value were lowered 5-fold, from 0.4 mg/m^3 to 0.081 mg/m^3. This was based on animal data.

The current working group is of the opinion that maleic acid anhydride operates by threshold mechanisms related to the critical effects. Because of lack of human quantitative exposure-response data, animal toxicity data were used as scientific basis for calculating a health-based DNEL for toxicological effects.

The calculation of DNELs results in 0.007 or 0.002 mg/m^3, depending on the choice of LOAEL-to-NOAEL assessment factor for inhalation studies. These values are ~11-fold and ~37-fold lower than the MAK value from 2018 (0.081 mg/m^3), respectively.

The current working group emphasises that 'gross signs of nasal and ocular irritation was present in all species and all exposure levels' in the inhalation study in animals, and that the allergic sensitisation observed in workers, is a potential forerunner for severe outcomes. Based on this, the current working group recommends to use the calculation with the highest LOAEL-to-NOAEL assessment factor, which results in the DNEL of 0.002 mg/m^3.

Dansk sammenfatning

Maleinsyreanhydrid er meget udbredt til brug i kemiske industri og kommer i hvide krystaller/flager eller pulvere. Arbejdere kan potentielt blive eksponeret på industrianlæg, hvor maleinsyreanhydrid fremstilles, hvor det anvendes som mellemprodukt i kemisk syntese, eller hvor det anvendes som monomer. Erhvervsmæssig eksponering vil sandsynligvis forekomme ved indånding eller ved hudkontakt.

Hos mennesker er de fremherskende helbredseffekter efter indånding lokal irritation såsom rhinitis og konjunktivitis, men også astma og allergi forårsaget af IgE-medieret sensibilisering er rapporteret. Derudover er eksponering for maleinsyreanhydrid ved hudkontakt forbundet med allergisk kontakteksem.

I dyreforsøg ses de fleste toksiske effekter i nyrerne efter oral eksponering og næse-, øjen-, luftvejsirritation er de største effekter efter eksponering ved inhalation. Generelt findes der begrænsede data fra dyr.

Den nuværende arbejdsgruppe anser lokale irritative effekter og respiratorisk sensibilisering som kritiske effekter, da disse blev observeret i humane observationsstudier. I langvarige inhalationsstudier på dyr blev luftvejsirritation observeret ved den laveste dosis i både, rotter, hamstere og aber. Til gengæld blev der kun observeret hyper- og metaplastiske ændringer hos gnaverarterne, som i modsætning til aber, kun ånder via næsen. Der er ingen tilgængelige humane data om eksponering-respons-forhold, der kan bruges til at udlede en helbredsbaseret OEL.

Den nuværende danske OEL (TWA 8h) for maleinsyreanhydrid er 0,4 mg/m^3, hvilket svarer til MAK-værdien fra 1992. MAK-kommissionen revurderede dog den videnskabelige evidens for maleinsyreanhydrid i 2018. Der blev ikke fundet nye forsøgsdata, men en ændret brug af usikkerhedsfaktorer resulterede i at MAK-værdien sænket fra 0,4 mg/m^3 til 0,081 mg/m^3. Dette var baseret på dyredata.

Den nuværende arbejdsgruppe er af den opfattelse, at mekanismen for de kritiske effekter ved eksponering med maleinsyreanhydrid er en tærskeleffekt. På grund af manglen på humane kvantitative eksponerings-responsdata blev dyretoksicitetsdata brugt som videnskabeligt grundlag for at beregne en helbredsbaseret Derived No-Effect Level (DNEL) for de toksikologiske effekter.

Beregningen af DNEL resulterer i 0.007 eller 0.002 mg/m^3, afhængig af valget af LOAEL-til-NOAEL usikkerhedsfaktoren. Disse værdier er henholdsvis ~11 gange og ~37 gange lavere end MAK-værdien fra 2018 (0,081 mg/m^3).

Den nuværende arbejdsgruppe understreger, at der var udtalte tegn på næse- og øjenirritation hos både rotter, hamstere og aber ved alle eksponeringsniveauer i inhalationsundersøgelsen hos dyr, samt at allergisk sensibilisering observeret hos arbejdere er en potentiel forløber for alvorlige helbredseffekter. På baggrund af dette anbefaler den nuværende arbejdsgruppe at anvende

beregningen med den højeste LOAEL-til-NOAEL usikkerhedsfaktor, hvilket resulterer i en DNEL på 0.002 mg/m^3.

Abbreviations

ACGIH	The American Conference of Governmental Industrial Hygienists
AF	Assessment Factor
ATSDR	The Agency for Toxic Substances and Disease Registry
DECOS	The Dutch Expert Committee on Occupational Safety
DFG	German Research Foundation
DNEL	Derived No-Effect Level
ECHA	European Chemicals Agency
EU	European Union
HSA	Human Serum Albumin
NEG	Nordic Expert Group
NOAEL	No Observed Adverse Effect Level
LOAEL	Lowest Observed Adverse Effect Level
MAK	Maximale Arbeitsplatzkonzentration (maximum workplace concentration)
NFA	National Research Centre for the Working Environment
NIOSH	The National Institute of Occupational Safety and Health
OEL	Occupational Exposure Limit
OSHA	Occupational Safety and Health Administration
RAC	The Committee for Risk Assessment
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SCOEL	Scientific Committee on Occupational Exposure Limit Values
TWA	Time Weighted Average

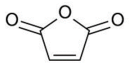
Introduction

The chemical formula of maleic anhydride is $C_4H_2O_3$ (CAS No: 108-31-6).

Maleic anhydride is manufactured by catalytic oxidation of butane, or to a lesser extent, of benzene. Maleic anhydride is rapidly hydrolysed to maleic acid under aqueous conditions (NEG, 2004).

Maleic anhydride comes in colourless or white crystals/flakes or powders with a pungent odor. Selected physicochemical properties are provided in Table 1.

Table 1. Physicochemical properties (OECD SIDS, 2004)

Property	Value
Chemical Formula	 Maleic anhydride: $C_4H_2O_3$
Molecular Weight	98.06
Physical Form	White solid at 20 °C (molten at 60 °C)
Melting Point	51.2 to 53.1 °C
Boiling Point	185 ± 3.8 °C
Vapor Pressure	15.1 Pa (0.114 torr) at 22 °C 37.7 Pa (0.283 torr) at 30 °C 108 Pa (0.814 torr) at 40 °C
Water Solubility	Rapidly hydrolyses to maleic acid
Synonyms	2,5-furandione Toxilic anhydride Cis-butenedioic anhydride Maleic acid anhydride
Classification[a]	Acute Tox. 4 Skin Corr. 1B Eye Dam. 1 Skin Sens. 1A Resp. Sens. 1 STOT RE 1

[a] https://echa.europa.eu/da/information-on-chemicals/cl-inventory-database/-/discli/details/42130

The current Danish OEL (TWA 8h) for maleic anhydride is 0.4 mg/m^3. OELs from various countries are presented in Table 2.

Table 2. Occupational exposure limits (8-hour TWAs) for maleic anhydride in various countries according to the GESTIS database.

Country	OEL (mg/m³)
Australia, Latvia, Romania, USA, UK, China, Singapore	1
Norway	0.8
Poland	0.5
Denmark, Austria, Finland, Japan, Spain, Switzerland, South Korea	0.4
Sweden	0.2
Germany, Hungary	0.08
Belgium, Canada, New Zealand	0.01

Workers can potentially be exposed to maleic anhydride at industrial sites where maleic anhydride is manufactured, where it is used as an intermediate in chemical synthesis or where it is used as monomer in polymerization reactions. Maleic anhydride is widely used in the chemical industry manufacturing of lacquers, lubricants, polymers, polyesters, plastics, pharmaceuticals, resins or pesticides/agrochemicals. Occupational exposure is likely to occur by inhalation or dermal routes. In humans, the predominant effects after inhalation are rhinitis, conjunctivitis and asthma. The airway and respiratory symptoms can be caused by irritation, allergic hypersensitivity, or a combination of both. Exposure to maleic acid anhydride by skin contact is associated with allergic contact dermatitis.

In animal experiments, the predominant effects are kidney toxicity when exposed orally to high concentrations and nasal/ ocular /airway irritation when exposed by inhalation.

Our literature search strategy follows the guidance suggested by DECOS (DECOS, 2021). The search starts with the search for chemical hazard and risk assessment reports that were published by other scientific organizations, such as e.g. DECOS, DFG, SCOEL, IARC, ATSDR, NIOSH and RAC of the European Chemicals Agency (EU). If such reports are available, the literature search starts at the last date of the search mentioned in the relevant assessment report.

Original peer-reviewed literature was retrieved using the databases PubMed and Web of Science, and through screening of reference lists in original studies and reports. The current working group conducted a literature search, identifying the publications on maleic acid anhydride published between 2017 and 2022, as the MAK Commission published an evaluation of maleic acid anhydride in year 2018. A search in PubMed in December 2022 using the following search string ("Maleic acid anhydride*"[Text Word] OR "Maleic anhydride*"[Text Word]) AND “toxicity”[Text Word] resulted in 48 publications. However, all publications were excluded based on a review of the titles and/or abstracts. Performing the same search string in Web of Science resulted in 0 publications. The current working group concludes that no new literature of relevance has been published since the most recent MAK evaluation (MAK, 2018).

The documentation in this report is mainly based on the two latest evaluations of maleic anhydride by the MAK Commission (MAK, 1992, 2018) and an evaluation of a large panel of cyclic acid anhydrides, including maleic anhydride, completed by DECOS in cooperation with the

Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (DECOS, 2010; NEG, 2004).
A report by The Danish Environmental Protection Agency (The Danish EPA, 2013) was identified in the literature search. However, it mainly references or quotes a 1996 report by the UK Health and Safety Executive (HSE), which is publicly unavailable. Additionally, although the report was published in 2013, the work was actually completed in 2006 as noted in the preface. More detailed information was found in both the DECOS report and in the two MAK reports.

The OEL derivation and risk assessment methodology of this report will follow the guidelines outlined by REACH guidance documents (ECHA, 2012, 2019).

Mechanisms and toxicokinetics

A general feature for cyclic anhydrides including maleic acid anhydride, is that the substances are readily hydrolysed to acid on mucous membranes and on damp skin, and can cause irritation, reddening, corneal damage, dermatitis and burns.

Maleic acid anhydride exposure might cause allergic sensitisation in the airways caused by specific IgE antibodies. At repeated exposure, IgE antibodies can trigger immune responses, which result in inflammation of the mucous membranes of the respiratory tract. The allergic hypersensitivity is generally irreversible and incurable (DECOS, 2010)

According to the DECOS/NEG report, no data is available regarding the toxicokinetics of maleic acid anhydride (DECOS, 2010; NEG, 2004).

Human data

Human exposure

Often, several cyclic anhydrides are included in the same industrial work processes, which makes exposure assessment difficult. Only few studies have measured maleic anhydride in workplace air.

In the most recent study, exposure measurements of maleic anhydride were carried out in a factory during the production of resins. The mean exposure levels, measured during different processing methods/job tasks, ranged between 0.0014 and 0.0286 mg/m^3 for average sampling times of 13 to 84 min. The calculated time-weighted average (TWA-8) exposure over 8 h for maleic anhydride ranged between 0.0004-0.0009 mg/m^3 depending on the job task. The exposure levels of maleic anhydride were quite low compared to those of two other cyclic anhydrides measured at the same factory. It is noted in the study that the use of maleic anhydride was very infrequent, which could explain the low exposure levels (van Tongeren et al., 1995).

Higher exposure levels of maleic anhydride have been reported in an older study. Dust concentrations of maleic anhydride were 0.83 mg/m^3 for inhalable and 0.17 mg/m^3 for respirable particulate mass measured at a resin factory while workers were batching the powdered chemical into the reactor (Lee et al., 1991).

Human observations

Few observational studies on human exposure to maleic acid anhydride exist in the literature. Most often, workers are exposed to a combination of different anhydrides. Observations are limited to effects in skin, eyes, airways and lungs. No data are available on other organ systems. We have included human studies that clearly state the use of maleic acid anhydride (alone or in combination) or report human effects specifically attributed to exposure to maleic acid anhydride. An overview of the studies is presented in Table 3.

Table 3. Overview of the human studies

Study type	No. of subjects	Industry	Exposure	Observations	Reference
Cross-sectional	92	Two chemical plants, Germany	No exposure measurements. One worker exposed to MA alone, 41 to MA in combination with another anhydride	The specific MA workers cannot be identified. 56/92 subjects report work-related symptoms, 7 had elevated IgE specific for MA	Baur et al. 1995
Clinical	190	5 ceramics factories, Italy	No exposure measurements, but MA was reported used	2 subjects showed sensitization to MA	Motolese et al., 1993

Patient case	1	Polyester resin factory, Finland	Pouring MA from sacks to vessels using fresh-air helmet	IgE-mediated rhinoconjunctivitis and contact urticarial specific for MA	Kanerva & Alanko, 2000
Clinical	9	Occupations were storeman and batch weigher	No exposure measurements. Two workers exposed to MA	Bronchial challenge testing with positive asthmatic reactions specific for MA	Durham et al., 1987
Clinical	4	Workers	All exposed to MA	Three had an asthmatic reaction after challenge to MA. One of the three had MA-specific IgE	Graneek et al., 1987
Patient case	1	Factory manufacturing alkyd and polyester resins	MA: inhalable particle concentration 0.83 mg/m^3 and respirable particle concentration 0.09 mg/m^3	Acute asthmatic response.	Lee et al., 1991
Retrospective cohort	401 (152 previous workers)	Four industrial sites (alkyd resins)	Present exposure measurement of MA: 1.8 and 2.8 µg/m^3 (factory 1 and 3). Past exposure measurements up to 5.4 and 4.9 µg/m^3 (factory 1 and 3)	34 subjects reported respiratory symptoms and 12 was positive for sensitization. Not specific for MA	Barker et al., 1998; van Tongeren et al., 1995 (on the exposure levels)
Patient case	1	Pesticide producing factory	No exposure measurements. Exposed to MA by daily handling	Respiratory symptoms, work-related asthma and elevated MA-specific IgE	Hansen et al. 2014
Patient case	1	Pilot plant producing MA	No exposure measurements	Wheeze, breathlessness, haemolytic anaemia	Gannon et al.

MA: maleic acid anhydride

Genotoxicity and carcinogenesis
There are no data available on carcinogenesis, genotoxicity, reproductive or developmental toxicity in humans exposed to maleic acid anhydride.

Irritation and sensitisation
Cyclic anhydrides are hydrolysed to acids after direct contact with skin or mucous membranes and can cause irritation, reddening, corneal damage, dermatitis and burns (DECOS, 2010).

In a study including 92 workers occupationally exposed to anhydrides, 56 reported work-related complaints, mainly of the upper respiratory tract. The reported symptoms included rhinitis (44 x), cough (24 x), conjunctivitis (22 x), dyspnea (18 x), hemorrhagic rhinitis (11 x) and phlegm (9 x). Only one worker in the study was exposed to maleic acid anhydride alone, however the worker cannot be individually identified from the study description. Individual exposure levels were not estimated due to the lack of air concentration measurements. Enzyme-allergosorbant tests were performed and 7 of the workers (6 symptomatic and 1 asymptomatic) had elevated IgE antibody concentrations specific to maleic acid anhydride–human serum albumin (HSA)-conjugates suggesting immunological cross-reactivity. Overall, one-fourth of the workers with symptoms had elevated IgE antibody concentrations specific to anhydride-HSA-conjugates (Baur et al., 1995).

Allergic dermatitis

Allergic contact dermatitis (type IV) due to cyclic acid anhydride exposure is rare, whereas contact urticaria (type I) is more common (DECOS, 2010).

In a cross-sectional dermatological examination, 190 workers at 5 ceramics factories were investigated. The patch test series included maleic acid anhydride (1% in ether). Two workers had a positive patch test reaction to maleic acid anhydride (Motolese et al., 1993).

Maleic acid anhydride has caused IgE-mediated rhinoconjunctivitis and contact urticaria in a process operator exposed to maleic acid anhydride dust in a factory manufacturing polyester resin. The conclusion was based on anamnestic data, skin prick test, enzyme-allergosorbant and provocation tests (Kanerva & Alanko, 2000).

Respiratory allergy and asthma

Allergic respiratory manifestations are well known effects of occupational exposure to cyclic acid anhydrides. Respiratory diseases that could be related to allergy include rhinitis, rhinoconjuctivitis and occupational asthma. Allergic rhinitis and asthma are associated with IgE-mediated immune responses (DECOS, 2010).

In a challenge test of two maleic acid anhydride-exposed workers, asthma reactions were verified by bronchial challenge testing whereas control tests were negative. Both subjects were described as atopic (Durham et al., 1987).

Four cases of asthma in workers exposed to maleic acid anhydride was reported. Three of the workers showed a late asthmatic reaction and an increase in airway responsiveness to inhaled histamine following bronchial challenge to maleic acid anhydride. One of the three had specific IgE antibodies in serum (Graneek et al., 1987).

A worker at a facility manufacturing pesticides developed work-related symptoms such as dry, irritative cough, breathing problems, chest tightness, and rhinoconjunctivitis. Exposure occurred during regular inspections and sampling from the production facility, and during filling the system 1-2 times daily. Elevated specific IgE for maleic acid anhydride was measured, indicating an IgE-mediated allergic reaction (Hansen et al. 2014).

A case study described a worker who developed cough, rhinitis, breathlessness and wheezing after one month of co-exposure to maleic acid anhydride and phthalic anhydride. He developed symptoms within minutes of exposure and had an acute asthmatic attack. He was transferred to another job and had complete relief of symptoms. Later, he was again exposed during work and immediately developed an acute asthmatic attack. The worker was a smoker, and no atopic tendency was identified. In a bronchial provocation test with maleic acid anhydride crystals, the worker experienced a dual (i.e. immediate and late) asthmatic response, whereas the test with phthalic anhydride was negative. For maleic anhydride, the inhalable particle concentration was 0.83 mg/m^3 and the respirable particle concentration 0.09 mg/m^3 (Lee et al., 1991).

A worker in maleic acid anhydride production who had exposure-related asthmatic symptoms developed severe haemolytic anaemia. He relapsed two weeks after the return to work the following year. Afterwards, he remained stable as long he avoided exposure to maleic acid anhydride. IgE antibodies specific for maleic acid anhydride were detected in the radio-allergosorbent test (RAST). Tests for IgG antibodies produced negative results (Gannon et al., 1992). However, it was questioned whether the haemolytic anaemia was causally related to maleic anhydride exposure (Jackson & Jones, 1993).

A retrospective cohort study by Barker et al. (1998) aimed to clarify risk factors for sensitisation and respiratory symptoms among workers exposed to different acid anhydrides in resin production. From a cohort with 401 workers, 46 out of 359 (12%) had work related respiratory symptoms that occurred for the first time while working with acid anhydrides. 12 out of 401 workers (3 %) were found positive for sensitisation with a skin prick test to acid anhydride human serum albumin. Sensitisation to acid anhydrides was associated with work related respiratory symptoms and with smoking at the time of exposure to acid anhydride. The workers were not only exposed to maleic anhydride but also to phthalic and trimellitic anhydride. Therefore, it is not possible to clarify the potential for skin and respiratory sensitisation of maleic anhydride exposure alone (Barker et al., 1998).

Summary

The current working group notes the limited human data related to health effects following occupational exposure to maleic acid anhydride. There are, however, sufficient evidence that maleic acid anhydride can cause irritation and, in addition, respiratory allergies caused by IgE-

mediated sensitisation, similar to most other cyclic acid anhydrides. However, there are no available human data on exposure-response relationships that can be used to derive a health-based OEL.

Animal data

Full-text publications and reports of animal studies conducted by industrial companies are often publicly unavailable. Consequently, we had to rely on the evaluation by MAK 1992. Direct quotations from MAK 1992 are shown in italics in the following subsections. An overview of the identified animal studies is presented in Table 4.

Table 4. Overview of the animal studies

Species (sex)	Route	Duration	Results[a]	NOAEL	Reference[b]
Rat (M/F)	Inhalation	6 hours	No chromosomal aberrations	-	Monsanto Co. 1984a
Rat (M/F)	Oral (diet)	2 years	No tumours	-	Procter & Gamble Co. 1984
Rat (M/F)	Oral (diet)	90 days	+ Kidney changes	40 mg/kg/day	Dow Chemical C. 1984a
Rat (M/F)	Oral (diet)	183 days	+ Kidney changes	250 mg/kg/day	Dow Chemical C. 1984b
Rat (M/F)	Inhalation	30 days	+ Irritation (respiratory organs) + Inflammation (upper airways) + Hyperplasia (upper airways)	12 mg/m^3 (LOAEL for inflammation and hyperplasia)	Monsanto Co. 1984b
Rat, Hamster, Monkey (M/F)	Inhalation	6 months	+ Irritation (nasal, ocular, airways) + Inflammation (nasal) + Hyperplasia (nasal, not monkeys)	1.1. mg/kg/ day (LOAEL for nasal/ocular irritation)	Short et al. 1988 affiliated to Monsanto Co.
Rat (F, pregnant)	Oral (gavage)	Day 6 to day 15 of gestation	No change in viable fetuses, number of resorptions, implantation sites or corpora lutea	128 mg/kg/day (Mortality in the pregnant rats)	Monsanto Co. 1984c
Rat (F, pregnant)	Oral (gavage)	Day 6 to day 15 of gestation	No treatment-related effects on fetal development. + Kidney toxicity	20 mg/kg (kidney weight in F1 mice); 55 mg/kg (kidney toxicity)	Short et al. 1986 affiliated to Monsanto Co.

[a]For more details see the individual sections below.

[b]Original reports. Information in the table are mostly limited to the statements obtained from MAK 1992.

Genotoxicity and carcinogenesis

The current working group notes that only one study investigating chromosomal aberrations *in vivo* after inhalation exposure to maleic acid anhydride and one 2-year carcinogenicity study involving oral exposure were identified as described below. No *in vivo* studies on mutagenic effects and the few *in vitro* studies show negative results in Ames tests were identifed (The Danish EPA, 2013).

No increase in chromosomal aberrations was found in the bone marrow of rats exposed to maleic anhydride concentrations of 1, 10, 100 mg/m³ for 6 hours by inhalation. Groups of 5 animals per dose and sex were killed after 6, 24 and 48 hours (Monsanto Co. 1984a – quoted from MAK 1992).

Male and female rats were exposed to 0, 10, 32, or 100 mg/kg/day maleic anhydride in the diet, seven days a week for two years. There was only marginal toxicity, which was evidenced by a small (<6%), but dose-related, decrease in body weights of male rats fed 32 and 100 mg/kg/day compared to the controls. The tumour incidences in the treated group were not increased relative to the control group (Procter & Gamble Co. 1984 - quoted from MAK 1992).

Long-term exposure (oral)

Male and female rats were fed in the diet 0, 20, 40, 100, 250, or 600 mg/kg/day of maleic anhydride, seven days a week for 90 days. Macroscopic changes were observed in the kidney and histological examination revealed necrosis associated with tubule dilation, hypertrophy and degeneration and regeneration processes in the tubules. The NOAEL for this study is 40 mg/kg/day (Dow Chemical Co. 1984a - quoted from MAK 1992).

In male rats fed 0, 250, or 600 mg/kg/day maleic anhydride in the diet for 183 days, there was a significant increase in the relative weights of liver, heart and kidney. Decreased body weights for rats exposed to 600 mg/kg/day were observed. Treatment-related changes were present in the kidneys of rats terminated at 90 and 183 days. Both tubular and glomerular changes in treated animals were more severe than in controls, and much more severe in the treated rats at 183 days compared to 90 days. The LOAEL for this study is 250 mg/kg/day (Dow Chemical Co. 1984b - quoted from MAK 1992).

Short-term exposure (inhalation)

Rats (groups of 10 of each sex) exposed to maleic anhydride concentrations of 0.012, 0.032 and 0.086 mg/l, 6 hours daily, 5 days per week for 1 month caused irritation of the respiratory organs. Inflammation and hyperplasia in the epithelium of the upper airways were found in all treated animals. The severity of the findings was dose dependent. Equivalent changes in the lungs developed only in the medium and high dose groups. In these two dose groups, body weight gain was reduced in both sexes, but food consumption was reduced only in the females (Monsanto Co. 1984b – quoted from MAK 1992).

Long-term exposure (inhalation)

In a study by Short et al., rats, hamsters and monkeys were exposed to 1.1, 3.3, 9.8 mg/m^3 maleic acid anhydride 6 hours/day, 5 days/week for 6 months by inhalation (Short et al., 1988).

The authors are affiliated to Monsanto Co. and in addition to the peer-reviewed scientific publication, the (MAK, 1992) refers to the original report. The original report is not publicly available, and according to MAK, it seems not to include more informative data than the Short et al. 1988 publication. The current working group therefore refers to the scientific publication by Short et al., 1988, and quotations from that study are shown in italics below.

General observations: *"Nasal and ocular irritations were observed in rats, hamsters and monkeys at all test levels during this study. In the high-dose group,* ***rats*** *exhibited a red-tinged nasal discharge, isolated cases of ocular discharge, and sneezing;* ***hamsters*** *exhibited nasal discharge and several animals demonstrated marked dyspnea or gasping;* ***monkeys*** *had nasal discharge, ocular irritation, and slight dyspnea with coughing and sneezing. These effects were less severe in animals from the low- and mid-dose groups".*

Nasal histopathology: *"The nasal tissue from all species were evaluated for histopathological changes. The changes were categorized as being hyperplastic, or inflammatory in nature. All changes were judged to be reversible. The hyperplastic and metaplastic changes were noted in the rodent species, but not in monkeys".* These histopathological observations are presented in Table 5.

Inflammatory changes: *"Inflammatory changes were observed in the nasal tissue* ***of all species****.* ***Rats*** *at all exposure levels exhibited a focal to multifocal infiltration of the nasal epithelium with neutrophils and eosinophils, which was generally graded as trace to mild. A luminal exudate was present in only one and three males from the mid- and high dose groups, respectively. In* ***hamsters*** *a trace focal, multifocal, diffuse submucosal infiltration of neutrophils was often associated with a luminal exudate. The luminal exudate occurred more frequently in hamsters than in rats. Its incidence ranged from about 30 to 70% in treated groups but also occurred in about 35% of the control hamsters.* ***Monkeys*** *exhibited a trace focal to multifocal and/or submucosal infiltration of neutrophils into the nasal tissue at all exposure levels".* (Note: quantitative data are not presented in the Short et al. 1988 publication).

Other effects: Body weights of rats from the mid- and especially the high dose group were reduced. No effect on body weight of hamsters and monkeys. An increased amount of hemosiderin deposits was observed in the spleens of high-dose female rats, but this was considered by the authors to be of doubtful toxicological significance. The clinical and haematological investigations in all species and the lung function test in monkeys revealed no difference from the control groups.

A no observed effect level (NOAEL) could not be determined as the lowest concentration used (1.1 mg maleic anhydride/m^3) showed local irritative effects in nose and eyes for all three species. The LOAEL for this study is 1.1 mg/m^3 for all species. In the discussion, Short et al state *'During the exposure period, gross signs of nasal and ocular irritation were present in all species at all exposure levels'*.

Thus, the current working group notes that gross signs of nasal and ocular irritation was present in all three species at the identified LOAEL.

Table 5. Histopathological observations in nasal tissue (Short et al., 1988)

	Total maleic acid anhydride (mg/m³)			
Observation	0	1.1	3.3	9.8
Mucosa, epithelial hyperplasia				
Rat	Percentage trace/percentage mild grade **(a)**			
Male (n=15)	0/0	13/40	7/93	0/80
Female (n=15)	0/0	40/33	27/67	0/93
Hamster	Percentages trace/percentage mild grade **(a)**			
Male (n=15)	0/0	0/0	0/33	0/53
Female (n=15)	0/0	0/0	27/27	7/27
Monkey	Percentages trace/percentage mild grade **(a)**			
Male (n=3)	0/0	0/0	0/0	0/0
Female (n=3)	0/0	0/0	0/0	0/0
Mucosa, squamos metaplasia				
Rat	Percentage **(b)**			
Male (n=15)	0	13	13	73
Female (n=15)	0	0	13	87
Hamster	Percentage **(b)**			
Male (n=15)	0	13	7	53
Female (n=15)	0	13	7	60
Monkey	Percentage **(b)**			
Male (n=3)	0	0	0	0
Female (n=3)	0	0	0	0

(a) Percentage of animals with trace grade/percentage of animals with mild grade
(b) Percentage of animals with observation

Reproductive and developmental toxicity

Pregnant female rats (n=5) were administred maleic acid anhydride by oral gavage of maleic acid anhydride of 8, 16, 32, 128, 192 or 256 mg maleic acid anhydride/kg by oral gavage from day 6 to day 15 of gestation. The two highest dose levels were lethal for 3 of 5 and 5 of 5 animals, respectively. The lethal dose of 192 mg/kg did not cause any changes in the number of viable fetuses, number of resorptions, implantation sites or corpora lutea (Monsanto Co. 1984c - quoted from MAK 1992).

In a combined multi-generation and teratogenesis study, pregnant rats (n= 19-23) were given daily doses of 30, 90 or 140 mg/ kg of maleic anhydride by oral gavage from day 6 to day 15 of gestation. Dams in the treated groups showed reduced weight gain or weight loss between days 6-15 of

gestation. Malformations were observed in one fetus from the control group, two fetuses from the low-dose group and three fetuses from the high-dose group. The authors argued that since each malformation was a single occurrence and differed among the various groups, there was no evidence of a dose-related increase in malformation. The authors concluded that no treatment-related effects on fetal development were observed (Short et al. 1986).

In the multi-generation study, daily doses of 20, 55 or 150 mg/kg of maleic anhydride by oral gavage were given to the parent generation for 80 days. The highest dose level of 150 mg/kg caused treatment-related mortality of all generations due to renal toxicity, amounting to 60% (F0 males), 65% (F0 females), 58% (F1 males) and 14% mortality in F1 females, and the second generation of adult rats had to be discontinued. Kidney necrosis occurred in high-dose F_0 males and females. Increased kidney weights were observed in low- and mid-dose groups of adult F_1 females (108 and 111% at 20 and 55 mg/kg, respectively). The authors furthermore report a number of deaths attributed to gavage-related injuries, especially in the F1 female group with 100% mortality of which 14% were accounted to be treatment-related. The authors concluded that dose levels of up to 55 mg/kg did not cause loss of fertility, changes in litter size or reduced survival in any generation and no teratogenic effects were observed (Short et al., 1986). As F1 females were exposed both during fetal life and after birth (from postnatal day 22), the increase in kidney weights in F1 females could indicate that the prenatal exposure increased sensitivity towards exposure.

Summary

The current working group notes the limited animal data related to maleic acid anhydride. Additionally, the two key-study publications by Short et al. are to some extent written in vague terms with less focus on quantitative data.

Systemic effects
Based on the two identified animal studies and supported by negative in vitro results, there is no evidence of maleic acid anhydride genotoxicity or carcinogenicity the current working group concludes that there is no evidence of genotoxic or carcinogenic effects of maleic acid anhydride in animals. However, the current working group notes that the data is insufficient to draw a definitive conclusion. The feeding studies generally showed dose-dependent increased kidney toxicity, and a NOAEL of 40 mg/kg/day was reported. There is no evidence of reproductive and developmental effects of maleic anhydride in the available studies, but a LOAEL of 20 mg/kg bw/day can be determined in orally exposed adult F_1 females (based on increased kidney weight).

Local effects
Long-term inhalation studies showed dose-related local irritative effects in nose and eyes, and inflammatory changes in nasal tissue for rats, hamsters and monkeys at all assessed dose levels. Hyperplasia and metaplasia of the nasal mucosa were evident in rodents, but not in monkeys. A LOAEL of 1.1 mg/m^3 can be determined, based on the long-term inhalation animal study by Short et al. 1988, with irritative effects as the critical effect regarding airborne exposure to maleic acid anhydride.

Previous evaluations

DECOS/NEG (2010/2004)

In 2010, The Dutch expert Committee on Occupational Safety (DECOS) evaluated the consequences of exposure to fourteen different cyclic acid anhydrides including maleic anhydride. This was a cooperation with the Nordic Expert Group (NEG) for Criteria Documentation of Health Risks from Chemicals (NEG, 2004). DECOS retrieved additional literature published until end of 2009.

DECOS considered induction of allergic sensitisation as the critical health effect for ten of the fourteen cyclic acid anhydrides (including maleic anhydride), because it is an irreversible change associated with a higher risk of developing allergic reactions.

Related to whether a threshold level exists, DECOS relies on a Health Council advisory report on work-related respiratory allergies concluding that a threshold level does exist for allergic sensitization and that a health based recommended OEL can be calculated, using the same procedures and methods as for other non-carcinogenic substances (Health Council, 2008).

DECOS was concerned that only for two of the cyclic acid anhydrides, sufficient data on exposure levels were available to derive OELs. Furthermore, data on chemical composition and reactivity, immunological reactivity, and cross-reactivity were insufficient. Therefore, DECOS could not predict whether an OEL for one cyclic acid anhydride would also protect against the sensitising properties of other cyclic acid anhydrides.

However, DECOS states: "*it would be prudent to avoid respiratory exposure to cyclic anhydrides as much as possible, in particular in those conditions where exposure exceeds concentrations in which the better studied anhydrides, such as trimellitic anhydride (TMA) and hexahydrophtalic anhydride (HHPA), are known to cause sensitisation*".

Based on human epidemiological data, DECOS determined exposure levels at which 10% of the occupationally exposed population would be sensitized to be 18 and 0.73 μg/m^3 for TMA and HHPA, respectively. The current working group notes that this implies that according to DECOS, threshold-based OELs for the two better studied anhydrides TMA and HHPA should be lower than 18 and 0.73 μg/m^3, respectively. However, the current working group also notes that according to the GESTIS database, the Netherlands does not currently have OELs for TMA nor HHPA.

DECOS abstained from making a recommendation on maleic anhydride, because of the lack of adequate human data on exposure and response to derive a health-based recommended OEL.

According to the GESTIS database, the Netherlands does not currently have an OEL for maleic anhydride.

Environment Agency Austria under the REACH Regulation (2013)

In 2013, the Environment Agency Austria evaluated maleic anhydride under REACH Regulation as part of the Community rolling action plan (CoRAP) (Environment Agency Austria, 2013). Maleic anhydride was selected for substance evaluation in order to clarify suspected risks about: human health/sensitisation, exposure/ high risk characterization ratio and the aggregated tonnage of the chemical.

The main reasons for concern were the potential for exposure during work tasks and processes, where maleic anhydride is used in ways where high exposure levels may occur and the possibility, that the sensitizing effects were not covered by the proposed hazard reference value at that time, which was based on the German DNEL (0.41 mg/m^3 (1992 MAK value), which is also the current Danish OEL).

In the evaluation report, Environment Agency Austria questioned the derivation of the DNEL/MAK value because 1) the sensitizing effects of maleic anhydride were not covered by the DNEL and 2) the applied assessment factors were not in line with the REACH guidance and were not adequately justified.
However, the Environment Agency Austria did not propose a more appropriate DNEL.
Notably, the MAK value has been re-evaluated and reduced 5-fold in 2018 as described in the next section of the present report.

The Environment Agency Austria evaluation report concludes that further harmonized classifications are needed: Eye damage 1 (causes serious eye damage), STOT RE 1 (causes damage to the respiratory tract through prolonged or repeated exposure), STOT RE 2 (may cause damage to the kidneys through prolonged or repeated exposure) and Skin Sens. 1A (may cause an allergic skin reaction) (ECHA CLH report, 2015).
The current working group notes that STOT RE 2 is not included in the present harmonized classification (https://echa.europa.eu/da/information-on-chemicals/cl-inventory-database/-/discli/details/42130).

The MAK Commission (1992/2018)

The German Research Foundation (DFG) Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, better known as the MAK Commission, has in 2018 re-evaluated maleic anhydride (MAK, 2018). The previous evaluation was made in 1992 (MAK, 1992) and was based on the previously described 6-month inhalation study in rats, hamsters and monkeys were a LOAEL of 0.27 ml/m^3 (1.1 mg/m^3) for nasal/ ocular irritation and metaplasia in nasal epithelium was identified (Short et al., 1988).

No new studies were identified for the 2018 re-evaluation, but the MAK Commission uses a new empirical approach to set the maximum concentration at the workplace (MAK value) based on a publication by Brüning et al. 2014. The latter describes how local irritation data should be taken into account in risk assessment procedures. The authors of the Brüning publication are all experts

from regulatory bodies in Germany (Bruning et al., 2014). The authors suggest that an assessment factor of 3 should be applied for extrapolation from animal data for all substances with indication of local irritating effects as the most sensitive response ("leading health effect") in animal studies but without reliable human data; unless individual data argue against this approach. In such cases, a substance-specific approach should be applied (Bruning et al., 2014).

Quoted from the MAK report 2018 (freely translated from German):

"No conclusions could be made on health effects caused specifically by maleic acid anhydride from a study on workers exposed to different anhydrides in resin production (Barker et al. 1998). Animal experiments are therefore used to derive a MAK value. In a 6-month inhalation study on rats, hamsters and monkeys, the lowest concentration used (1.1 mg maleic anhydride/m³) showed irritative effects in nose and eyes for all three species (Short et al. 1988)".

"There are no new data, but according to Brüning et al. (2014), uncertainties should be taken into account which results in a significantly lower MAK value. From the LOAEC [Lowest Observed Adverse Effect Concentration] *of approx. 0.27 ml/m³ (1.1 mg/m³) a NAEC* [No Adverse Effect Concentration] *of 0.09 ml/m³ can be extrapolated (1:3). Taking into account the approach suggested by Brüning et al. (2014), using (1:3) for irritating effects animal-to-humans and since there is no increase in effect with chronic exposure, the MAK value derived is 0.02 ml/m³ (0.081 mg/m³)".*

The new 2018 MAK value for maleic anhydride was therefore set at 0.02 ml/m³ (0.081 mg/m³), which is a 5-fold reduction from the former MAK value of 0.41 mg/m³.

The MAK Commission also concludes: Maleic anhydride is not genotoxic *in vitro* and *in vivo*. No increased tumour incidences was observed in a chronic feeding study in rats. Skin contact is not expected to contribute significantly to systemic toxicity. In humans, airway sensitization is observed. There are positive results of contact sensitization in mice and guinea pigs. Workers are protected against reprotoxicity as long as the MAK value is not exceeded (MAK, 2018).

Other regulatory values

The Division of Occupational Safety and Health (Cal/OSHA) is the main government agency authorized to inspect California workplaces for occupational safety and health violations. Their permissible exposure limit is 0.4 mg/m³.

The American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) is 0.01 mg/m³. TLVs are health-based values established by committees that review existing published and peer-reviewed literature. Since TLVs based solely on health factors, there is no consideration given to economic or technical feasibility. TLVs are not standards, but guidelines designed for use by decision makers regarding safe levels of exposure. The documentation from ACGIH is not publicly available.

Occupational Safety and Health Administration (OSHA) has a permissible exposure limit (PEL) for maleic anhydride at 1 mg/m^3.

Summary

The current working group notes that the MAK value are based on an animal study due to the lack of human quantitative exposure-response data, and that DECOS abstained from making a recommendation on maleic anhydride due to insufficient human data.
In line with the Environment Agency Austria, the current working group notes that assessment factors used to calculate the 1992 MAK value were not documented in the evaluation report and the value at 0.41 mg/m^3 were therefore not adequately justified (MAK, 1992). The current Danish OEL (TWA 8h) for maleic anhydride is the same as the 1992 MAK value (0.4 mg/m^3). The MAK value derivations from 1992 and 2018 were based on the LOAEL of 1.1 mg/m^3, but the assessment factors for deriving the 2018 MAK value was justified, in contrast to the 1992 MAK value, where the choice of assessment factors was not justified in the evaluation report (MAK, 2018). The 2018 MAK value for maleic anhydride was reduced to 0.081 mg/m^3.

Scientific basis for setting an occupational exposure limit

The current working group considers local irritation and respiratory allergic sensitisation as the critical effects, as these effects were observed in human observational studies. The current working group acknowledges that systemic effects in the kidney have been observed after oral exposure in animals, with NOAELs being relatively higher than the LOAEL in the inhalation study by Short et al. 1988. Thus, the NOAEL for systemic effects in the kidneys in the gavage study was 40 mg/kg day ((Dow Chemical Co. 1984a - quoted from MAK 1992). The LOAEL of 1.1 mg/m^3 in the inhalation study in rats (Short et al., 1988) would correspond to a daily dose of 1.1 mg/m^3 x 0.8 L/min/kg x 1/1000 m^3/L x 6 h/day x 60 min/h = 0.32 mg/kg day assuming 100% absorption of maleic acid anhydride in the lung and a rat ventilation rate of 0.8 L/min/kg, which is the default value recommended by ECHA. Thus, the LOAEL for respiratory allergic sensitization is much lower that the NOAEL for systemic effects in the kidneys. Notably, the systemic effects observed from oral exposure were not supported by similar findings of kidney toxicity in the inhalation study. Based on this, the current working group does not consider the systemic effects in the kidney following oral exposure as a critical effect. Generally, we consider inhalation to be a more relevant exposure route in occupational settings. In long-term inhalation studies in animals, airway irritation were observed at all dose levels in all three assessed animal species. On the other hand, hyperplastic and metaplastic changes were only observed in the rodent species, which, in contrast to monkeys, are obligatory nasal breathers. Because of the lack of human quantitative exposure-response data, the current working group decided to use the animal data as scientific basis for calculating an OEL. According to DECOS, a threshold level exists for allergic sensitisation from inhaled allergens. This suggests that a health-based recommended OEL can be calculated using methodologies similar to those used for non-carcinogenic substances. The current working group agrees with DECOS and therefore calculates the Derived No-Effect Level (DNEL) for toxicological effects having a threshold.

Health-based exposure limit based on inhalation studies in rodents and monkeys

The current working group calculates the health-based exposure limit based on the 6-month inhalation study in animals for threshold mechanisms (nasal/ ocular irritation in rodents and monkeys and hyperplasia/metaplasia in nasal epithelium in rats) (Short et al., 1988). In the current report, we calculate the DNEL as recommended by ECHA for toxicological effects having thresholds (ECHA, 2012, 2019).

A LOAEL of 1.1 mg/m^3 is identified in rats, hamsters and monkeys exposed to maleic acid anhydride for 6 hours/day, 5 days/week for 6 months by inhalation.

First, the LOAEL is modified to correct for an 8-hour working day and to correct for a higher breathing rate in workers at light work (10 m^3/day) compared to at rest (6.7 m^3/day):

$LOAEL_{corr}$ = 1.1 mg/m^3 * 6 hour/8 hour * 6.7 m^3/10 m^3 = 0.55 mg/m^3

Secondly, the corrected LOAEL is adjusted by assessment factors (default values suggested by ECHA).

The following default assessment factors (AF) are used:

- When a LOAEL is the starting point for the DNEL calculation, it is suggested to use an assessment factor between 3 and 10 (ECHA). The current working group therefore performs calculations for both assessment factors 3 and 10.
- Interspecies extrapolation (ECHA default factor): 2.5
- Intraspecies interpolation (ECHA default factor for workers): 5
- Extrapolation from sub-chronic to chronic (ECHA default factor): 2

The overall assessment factor, $AF_{overall\ min} = 3 * 2.5 * 5 * 2 = 75$
The overall assessment factor, $AF_{overall\ max} = 10 * 2.5 * 5 * 2 = 250$

This results in DNELs:
$DNEL_{min} = NOAEL_{corr}/AF_{overall\ min} = 0.55\ mg/m^3 / 75 = 0.007\ mg/m^3$
$DNEL_{max} = NOAEL_{corr}/AF_{overall\ max} = 0.55\ mg/m^3 / 250 = 0.002\ mg/m^3$

Summary

Our calculation of DNELs results in 0.007 or 0.002 mg/m³, depending on the choice of assessment factors. The resulting health-based OEL is ~11-fold and ~37-fold lower than the MAK value from 2018 (0.081 mg/m³).

The current working group emphasises 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 sensitisation seen in workers is a forerunner for severe adverse health effects.
Based on this and from a precautionary point of view, the current working group recommends using the calculation with the highest LOAEL-to-NOAEL assessment factor, which results in the DNEL at 0.002 mg/m³.

Conclusion

The current working group considers local irritative effects and respiratory sensitisation as critical effects, as these effects were observed human observational studies. In long-term inhalation studies in animals local irritation as well as hyper- /metaplasia formation were reported.

DECOS considers the induction of allergic sensitisation as the critical effect and abstains from setting a health-based recommended OEL or reference value due to the lack of human data on exposure and response. DECOS considers the biological mechanism of action as a threshold effect.

The current working group notes that there are no available data on genotoxicity and carcinogenesis or reproductive and developmental toxicity in humans. Furthermore, maleic acid anhydride is an allergic sensitizer, with limited data on immunological reactivity and cross-reactivity. Limited data are available in animals.

The present Danish OEL (TWA 8h) for maleic acid anhydride is 0.4 mg/m^3, which corresponds to the MAK-value from 1992. However, the MAK commission re-evaluated the data on maleic acid anhydride in 2018. No new experimental data were available, but due to a change in approach the MAK-value was lowered 5-fold from 0.4 mg/m^3 to 0.081 mg/m^3. This was based on an animal study from 1988.

Because of lack of human quantitative exposure-response data, the current working group uses animal data as scientific basis for calculating a health-based DNEL for toxicological effects having thresholds based on animal toxicity data.

The calculation of DNELs results in 0.007 or 0.002 mg/m^3, depending on the choice of LOAEL-to-NOAEL assessment factor. These values are ~11-fold and ~37-fold lower than the MAK value from 2018 (0.081mg/m^3), respectively.

The current working group emphasises that '*gross signs of nasal and ocular irritation was present in all species and all exposure levels*' in the inhalation study in animals, and that allergic sensitisation seen in workers, is a forerunner for severe adverse health outcomes.
The current working group recommends to use the calculation with the highest LOAEL-to-NOAEL assessment factor which results in the DNEL of 0.002 mg/m^3.

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