
***m*-Phthalodinitrile**

(CAS reg no: 626-17-5)

Health-based Reassessment of Administrative
Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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
1 Introduction

The present document contains the assessment of the health hazard of *m*-phthalodinitrile by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft document was prepared by MA Maclaine Pont, M.Sc. (Wageningen University, Wageningen, the Netherlands).

The evaluation of the toxicity of *m*-phthalodinitrile has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the data bases Toxline, Medline, and Chemical Abstracts, covering the period 1981 until July 1999, 1966 until November 1999, and 1937 until September 1999, respectively, and using the following key words: benzenedicarbonitrile, isoftalodinitrile, isoftalonitrile, isophthalodinitrile, isophthalonitrile, 1,3-benzenedicarbonitrile, dicyanobenzene, or 626-17-5. The final literature search has been carried out in November 1999.

In April 2001, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identity

name	:	<i>m</i> -phthalodinitrile
synonyms	:	1,3-benzenedicarbonitrile; <i>m</i> -dicyanobenzene; 1,3-dicyanobenzene; dinitrile of isophthalic acid; isophthalodinitrile; isophthalonitrile; <i>m</i> -PDN; IPN
molecular formula	:	C ₈ H ₄ N ₂
structural formula	:	
CAS reg no	:	626-17-5

Data from How92.

Pure *m*-phthalodinitrile is a crystalline powder (BUA88), forming when recrystallized from alcohol (ACG99). The industrial product is stated to be at least 98% pure, containing 4-methylbenzotrile (max 1.5%), *m*-benzenedicarbonitrile (max 0.5%), and benzotrile (max 0.5%) as impurities (BUA88).

3 Physical and chemical properties

molecular weight	:	128.1
boiling point	:	288°C (sublimes)
melting point	:	162°C
flash point	:	-
vapour pressure	:	at 25°C: 0.8 Pa
solubility in water	:	slightly soluble in (hot) water
Log P _{octanol/water}	:	0.8 (experimental); 1.09 (estimated)
conversion factors (20°C, 101.3 kPa)	:	not applicable

Data from ACG99, BUA88, <http://esc.syrres.com>.

4 Uses

m-Phthalodinitrile is used as an intermediate in the manufacture of polyurethane paints and varnishes, pharmaceuticals, and agricultural chemicals, such as chlorothalonil (the 2,4,5,6-tetrachloro derivative of *m*-phthalodinitrile) (ACG99, BUA88).

5 Biotransformation and kinetics

No data have been found.

6 Effects and mechanism of action

Human data

No data have been found. In a 15-year review of industrial experience with *m*-phthalodinitrile, published in 1969, no adverse effects were reported (ACG99).

Animal data

m-Phthalodinitrile was not a skin irritant in rabbits. No evidence of irritation (erythema, oedema) was observed at levels of 2000 mg/kg or 500 mg total dose (ACG99) or when a 50% aqueous paste of *m*-phthalodinitrile was applied under occlusion for 15 minutes (followed by wash-off procedure) or 20 hours (no wash off) (Zel69). No irritation was observed in the eyes of rabbits after single instillation of 50 mg into the conjunctival sac for 5 minutes (ACG99). However, in a separate experiment, a 50% aqueous paste induced marked intravascular injections (exposure period unknown; observation period: >8 days) (Zel69).

None of a group of rats (number, strain, and sex unknown) subjected to 1-hour inhalation exposures of concentrations of *m*-phthalodinitrile up to 8970 mg/m³ showed any treatment-related effects. Particle size was over 2.2 µm (*i.e.*, particles passed an 18-mesh screen (1/18 inch)), but particle size distribution and what portion of the stated air concentrations were respirable were not known (ACG99).

The following oral LD₅₀s have been found: rat: >5000 mg/kg bw, guinea pig: 370 mg/kg, rabbit: 350 mg/kg, and mouse: 178 mg/kg (Lew92).

Rats survived an 8-hour exposure to air saturated with *m*-phthalodinitrile (*i.e.*, air saturated with volatile parts of the test substance at 20°C*); observation time: 7 days) (Zel69).

In subacute inhalation studies, groups of rats (number, strain, sex not known) were exposed to actual aerosol concentrations of *m*-phthalodinitrile of 190 or 1250 mg/m³, 6 hours/day, 5 days/week, for 2 weeks. No deaths occurred in the control or experimental groups. Both experimental groups showed decreased food consumption and reduced body weight. After 7 days, half the rats in the low exposure group exhibited alopecia. Rhinorrhea was evident after the first exposure at 1250 mg/m³ and it continued throughout the study. Diarrhoea occurred on day 2 in the low-concentration group; diarrhoea continued throughout the rest of the exposure period in the high-concentration group. Histological examination of lungs, trachea, and liver and kidneys of control and treated animals did not reveal any exposure-related alterations. Pulmonary changes such as inflammation of alveoli and bronchioles were present in both control and exposed groups, and the incidence of pulmonary inflammation did not follow a dose-response relationship. Thus, the pulmonary inflammation was not considered compound/exposure related (unpublished study from 1972, cited

* The (theoretic) concentration in saturated air can be calculated using the formula: (vapour pressure in Pa x 10⁶ ppm)/10⁵ Pa. Using a vapour pressure of 0.8 Pa (at 25°C), the committee estimates that these animals could have been exposed to, at most, 8 ppm or (roughly) 40 mg/m³.

in ACG99). Since the original study as well as details, such as, for instance, particle size and particle size distribution, were not available, the committee could not evaluate this study properly.

Dermal toxicity studies were performed in rabbits by applying doses of 500, 1000, or 2000 mg/kg bw to the intact or abraded skin during 6 hours/day, 5 days/week, for 3 weeks. Occasional, slight local skin reactions were observed. Systemic toxicity was limited to increased organ size (but without histological change) at the two high dose levels and reduced body weight in females at the highest dose. Otherwise, body weight changes were comparable in control and treated groups. There were no compound-related changes in haematology, blood chemistry, and urinalysis parameters and at post-mortem macroscopic and microscopic examination (unpublished study from 1972 cited in ACG99). Since it was not clear which organs were affected and which animals (with abraded or intact skin), the committee is not able to draw conclusions from this study.

The committee did not find data on the potential carcinogenicity, mutagenicity/genotoxicity, or reproduction toxicity of *m*-phthalodinitrile.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for *m*-phthalodinitrile in the Netherlands is 5 mg/m³, 8-hour TWA.

Existing occupational exposure limits for *m*-phthalodinitrile in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

m-Phthalodinitrile was not irritating to the skin of rabbits. No eye irritation was seen after single instillation of 50 mg for 5 minutes while marked vascular injection was induced by a 50% aqueous paste.

Species differences were observed after acute oral dosing of *m*-phthalodinitrile, with LD₅₀-values ranging from approximately 180 mg/kg bw in mice and approximately 350 mg/kg bw in guinea pigs and rabbits to higher than 5000 mg/kg bw in rats. Based on these data, the committee concludes that *m*-phthalodinitrile should be considered as 'toxic if swallowed'.

Unpublished inhalation and dermal toxicity studies which were not available to the committee showed that inhalation exposure of rats to aerosol concentrations of unknown particle sizes and particle size distributions of 190

and 1250 mg/m³, 6 hours/days, 5 days/week, for 2 weeks, caused occasional diarrhoea (on day 2) and rhinorrhoea and diarrhoea, respectively. No other treatment-related effects were observed. Dermal application of 1000 or 2000 mg/kg bw, 6 hours/day, 5 days/week, for 3 weeks, to the intact or abraded skin of rabbits caused increased organ sizes (not specified) at both levels and reduced female body weight at 2000 mg/kg bw. No effects were seen at 500 mg/kg bw.

The committee did not find data on the potential carcinogenicity, mutagenicity/genotoxicity, or reproduction toxicity of *m*-phthalodinitrile.

The committee considers the toxicological data base on *m*-phthalodinitrile too poor to justify recommendation of a health-based occupational exposure limit.

The committee concludes that there is insufficient information to comment on the present MAC-value.

References

- ACG99 American Conference of Governmental Industrial Hygienists (ACGIH). *m*-Phthalodinitrile. In: TLVs[®] and other occupational exposure values - 1999. [CD-ROM]. Cincinnati OH, USA; ACGIH[®], Inc, 1999.
- ACG00 American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2000. Cincinnati OH, USA: ACGIH[®], Inc, 2000: 100.
- ACG01 American Conference of Governmental Industrial Hygienists (ACGIH). 2001 TLVs[®] and BEIs[®]. Threshold Limit Values for chemical substances and physical agents. Biological Exposure Indices. Cincinnati OH, USA: ACGIH[®], Inc, 2001: 48.
- Arb00a Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2000; At-vejledning C.0.1.
- Arb00b Arbetskyddstyrelsen. Hygieniska gränsvärden och åtgärder mot luftföroreningar. Solna, Sweden: National Board of Occupational Safety and Health, 2000; Ordinance AFS 2000/3.
- BUA88 Beratergremium für Umweltrelevante Altstoffe (BUA) (CDCh-Advisory Committee on Existing Chemicals of Environmental Relevance). Benzenedicarbonitriles. Weinheim, FRG: VCH Verlagsgesellschaft mbH, 1988; BUA rep no 32.
- CEC00 Commission of the European Communities (CEC). Commission Directive 2000/39/EC of 8 June 2000 establishing a first list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work. Official Journal of the European Communities 2000; L142 (16/06/2000): 47-50.
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- DFG01 Deutsche Forschungsgemeinschaft (DFG): Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. List of MAK and BAT values 2001. Maximum concentrations and biological tolerance values at the workplace. Weinheim, FRG: Wiley-VCH, 2001; rep no 37.
- Gai74 Gaidamaka VV. Extent of the hazard and the hygienic standardization of isophthalonitrile in a reservoir. Russian. [Stepen' opasnosti i gigenicheskoe normirovanie izoftalonitrila pri postuplenii ego v vodoem.] Gig Sanit 1974; 11: 17-20. cited from Chem Abstr 83:158624e.
- How92 Howard PH, Neil M, ed. Dictionary of chemical names and synonyms. Chelsea, USA: Lewis Publishers, 1992.
- HSE01 Health and Safety Executive (HSE). EH40/2001. Occupational exposure limits 2001. Sudbury (Suffolk), England: HSE Books, 2001.
- Lew92 Lewis RJ Sr, ed. Sax's dangerous properties of industrial materials. 8th ed. New York, USA: Van Nostrand Reinhold, 1992; 2799-800.
- SZW01 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2001. The Hague, the Netherlands: Sdu, Servicecentrum Uitgevers, 2001: 28.
- TRG00 TRGS 900. Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. BArbBl 2000; 2.
- Zel69 Zeller H, Hofman HTH, Thiess AM, *et al.* Zur Toxizität der Nitrile (Tierexperimentelle Untersuchungsergebnisse und werksärztliche Erfahrungen in 15 Jahren). Zentralbl Arbeitsmed 1969; 19: 226-38.
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Annex

Occupational exposure limits for *m*-phthalodinitrile in various countries.

country -organisation	occupational exposure limit		time-weighted average	type of exposure limit	note ^a	lit ref ^b
	ppm	mg/m ³				
the Netherlands						
- Ministry	-	5	8 h	administrative		SZW01
Germany						
- AGS	-	5 ^c				TRG00
- DFG MAK-Kom.	-	-				DFG01
Great Britain						
- HSE	-	-				HSE01
Sweden	-	-				Arb00b
Denmark	-	5	8 h			Arb00a
USA						
- ACGIH	-	5	8 h	TLV		ACG01
- OSHA	-	-				ACG00
- NIOSH	-	5	10 h	STEL		ACG00
European Union						
- SCOEL	-	-				CEC00

^a S = skin notation, which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation

^b Reference to the most recent official publication of occupational exposure limits

^c Measured as the respirable fraction