1,3-Dichloro-5,5-dimethylhydantoin

(CAS No: 118-52-5)

Health-based Reassessment of Administrative Occupational Exposure Limit

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

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1 Introduction

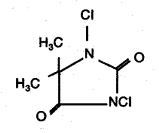
The present document contains the assessment of the health hazard of 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by RN Hooftman, M.Sc. and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of DCDMH has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the on-line databases Medline, Toxline, and Chemical Abstracts covering the period 1966 to 24 October, 1997 (19971024/UP), 1965 to 20 October 1997 (19971020/ED), and 1967 to 28 October, 1997 (971028/ED); vol 127 iss 18), respectively, and using the following key words: 1,3-dichloro-5,5-dimethylhydantoin and 118-52-5. HSDB (no record) and RTECS, databases available from CD-ROM, were consulted as well (NIO97, NLM97). The final search was carried out in October 1997.

In December 1998, the President of the Health Council released a draft of the document for public review. Comments were received by the following individuals and organisations: P Wardenbach, Ph.D. (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund, Germany). These comments were taken into account in deciding on the final version of the document.

An additional literature search in May 2002 did not result in information changing the committee's conclusions.

2 Identity

name	:	1,3-dichloro-5,5-dimethylhydantoin
synonyms	:	hydantoin, 1,3-dichloro-5,5-dimethyl-; 1,3-dichloro-5,5-dimethyl-2,4-imidazolidinedione; 2,4-imidazolidinedione, 1,3-dichloro-5,5-dimethyl-; dichlorodimethylhydantoin; Dactin; Daktin; Dantoin; Dichlorantin; Halane; Hydan; Hydantoin; Omchlor
molecular formula	:	$C_5H_6Cl_2N_2O_2$
structure	:	
CAS number	:	118-52-5

Data from ACG91, NLM97.

3 Physical and chemical properties

molecular weight	:	197.03
boiling point	:	-
melting point	:	132ºC
flash point	:	-
vapour pressure	:	-
solubility in water	:	at 20ºC: 0.05 g/100 mL
Log $P_{octanol/water}$	:	-0.94 (estimated)
conversion factors (20ºC, 101.3 kPa)	:	-

Data from ACG91, NLM97, http://esc.syrres.com.

DCDMH forms white crystals with mild chlorine odour, containing a minimum of 66% 'available chlorine' by weight. After melting at 132ºC, it turns brown and conflagrates with evolution of chlorine at 210ºC. It sublimes at 100ºC. In contact with water and, in particular, hot water, hypochlorous acid is liberated. At pH = 9, the compound decomposes completely forming nitrogen chloride.

4 Uses

The compound is used as a chlorinating agent, as a disinfectant, a household laundry bleach, an industrial deodorant, and in water treatment, as a chemical intermediate for amino acids, drugs, and insecticides, as a stabiliser for vinyl chloride polymers, and as a catalyst.

5 Biotransformation and kinetics

The commitee did not find data on biotransformation and kinetics of DCDMH.

6 Effects and mechanics of action

Human data

An operator at a reactor station of a chemical company, exposed to a time-weighted average concentration exceeding 0.2 mg/m^3, experienced cough and chest discomfort (ACG91).

Animal data

Irritation and sensitisation

DCDMH (dosis: 0.5 g) applied to the intact and abraded clipped skin of 2 rabbits was concluded to be severely irritating (sites covered for 24 hours; readings at 24 and 72 hours; scoring according to Draize: combined scores: 6.0, maximum possible score: 8.0). Aqueous solutions (adjusted to 600 ppm 'available chlorine'), applied in 0.5 mL quantities in a similar way, resulted in slight irritation (combined average score: 0.56). A similar result was obtained for sodium hypochlorite (adjusted to 600 ppm 'available chlorine') (Gly81).

The committee did not find data on the potential sensitisation of DCDMH.

When aqueous solutions (0.1 mL) of DCDMH and sodium hypochlorite (600 ppm 'available chlorine') were instilled into the eyes of rabbits (n=5/group), both solutions were rated as mildly irritating using the Draize scoring system. The tables summarising scores and ratings were lacking in the copy which was at the committee's disposal (Gly81).

Acute toxicity

Five out of 10 rats (n=5/sex; sex of dead animals not reported) died within 2 days following a 1-hour exposure to 20.5 g/m^3 of DCDMH dust (observation period: 14 days). Signs observed during and/or shortly after ending exposure were, amongst others, excessive lachrymation and salivation, mucoid nasal discharge, red nasal discharge, gasping, decreased activity, partially closed eyes, and yellow staining of the ano-genital fur. Upon necropsy, discoloration of lungs and liver and distention of the stomach with gas were seen. Weight gains were slower than what was considered normal (Gly81).

A dermal LD_{50} exceeding 20,000 mg/kg bw has been reported for rabbits (NIO97).

Following oral administration as a 10% (w/v) aqueous suspension, an LD_{50} of 542 mg/kg bw was estimated in rats (observation time: 14 days). No effects were seen in animals receiving approximately 270 mg/kg bw. In rats receiving doses of 400-900 mg/kg bw, generalised tremors, salivation, hyperpnoea, cyclic running, and coma (in moribund rats) were observed. These signs occurred approximately 10 minutes after dosing, and their severity was roughly dose related; deaths occurred within 18 hours. Upon necropsy, there were no gross pathological alterations other than haemorrhages in the gastrointestinal tract (Gly81). Other oral LD_{50} values reported are: 550 mg/kg bw in rats, 1520 and > 20,000 mg/kg bw in rabbits, and 1350 mg/kg bw in guinea pigs (NIO97). In pregnant mice, daily oral (gavage) doses of 500 mg/kg bw on gestational days 6 through 13 caused mortality in 18% of the animals (Har87a, Har87b).

Repeated-dose toxicity

In a subacute oral study, groups of 20 rats (n=10/sex) received DCDMH or sodium hypochlorite in their drinking water at a concentration corresponding to 20 ppm of 'available chlorine' for 30 days. During these days, the rats received a total amount of approximately 165 mg DCDMH/rat (i.e., 5.5 mg/day per rat; body weights were not given). In neither of these groups, effects were found on body weights, water consumption, clinical signs, haematological and urinalysis parameters, and gross and microscopic examination when compared with untreated controls (Gly81).

Carcinogenicity

According to the ACGIH, a long-term toxicity/carcinogenicity study has been performed under auspices of the National Toxicology Program (NTP), but since the data were considered to be inadequate, no technical report was issued (ACG91).

Mutagenicity and genotoxicity

DCDMH was negative when adequately tested at a sufficiently high dose range (0.1-100 µg/plate) in *S. typhimurium* strains TA100, TA1535, TA1536, and TA98 with and without metabolic activation by hamster and rat liver S9 fraction (Haw83).

In Chinese hamster ovary cells, DCDMH did neither induce chromosome aberrations nor increase the frequency of sister chromatic exchanges (SCEs) when tested up to toxic doses (dose ranges: 1.6-16 µg/mL and 0.5-16 µg/mL, respectively), with and without exogenous metabolic activation (Gal87). DCDMH was reported to be positive in a mouse lymphoma assay conducted under the auspices of the NTP (ACG91), but since no reference was presented, the committee could not verify this statement.

In validating an *in vitro* transformation assay using Rauscher leukaemia virus-infected rat embryo cells which was developed to detect mutagens/carcinogens by measuring the acquisition of attachment independence (recognised as being characteristic of transformed cells), DCDMH was positive (doses: 6.3 and 12.2 µg/5.2 x 10^{-4} cells) (Tra81).

When DCDMH was tested in the sex-linked recessive lethal mutation assay in *D. melanogaster*, negative results were obtained after larval or adult feeding (doses: 950 and 1000 ppm, respectively); upon injecting adults (dose: 250 ppm), a positive result was observed (Woo85, Zim89).

Reproduction toxicity

In a preliminary developmental toxicity test in which CD-1 mice were given daily doses of 500 mg/kg bw/day in corn oil by gavage on gestational days 6 through 13, 9 out of 50 maternal animals died. However, treatment did not affect the number of viable litters (24/24) or neonatal response parameters (number of liveborn per litter, the percentage survival, pup birth weight, pup weight gain) (Har87a, Har87b).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for DCDMH in the Netherlands is 0.2 mg/m^3, 8-hour TWA.

Existing occupational limits for DCDMH in some European countries and the USA are summarised in the annex.

8 Assessment of health hazard

No adequate human data were available to the committee.

Pure DCDMH was severely irritating to the skin of rabbits. Aqueous solutions (adjusted to 600 ppm 'available chlorine') were only slightly or mildly irritating to the skin and eyes of rabbits. From a 1-hour inhalation study in which 5 out of 10 rats died following exposure to approximately 20 g/m^3 of DCDMH dust, it can be concluded that the compound is not very toxic under these exposure conditions. Most prominent effects observed were irritation of the eyes and the respiratory tract and effects on lungs and liver (discolouration).

From a dermal LD_{50} value in rabbits (exceeding 20 g/kg bw), DCDMH is not considered to be toxic upon dermal exposure; from oral LD_{50}s, DCDMH can be considered as harmful by the oral route. No effects were observed in rats receiving a relatively low dose of 5.5 mg/rat for 30 days. There were no data available from studies in which animals were repeatedly exposed by inhalation to DCDMH.

A positive result in a cell transformation test may indicate a carcinogenic potential, but data from a long-term toxicity/carcinogenicity study of DCDMH were stated to be inadequate for preparing a report.

DCDMH did not induce mutations in *S. typhimurium* strains. When tested in mammalian cell systems, the compound was stated to induce mutations in the mouse lymphoma assay; it did not have clastogenic effects in Chinese hamster ovary cells; it was negative in the sex-linked recessive lethal test with *D. melanogaster* after larval and adult feeding, but a positive result was obtained upon injecting adults. There were no data available from genotoxicity studies in intact animals.

In a preliminary developmental toxicity test, there were no indications for possible effects on the offspring of mice treated with daily oral doses (500 mg/kg bw/day, gestational day 6-13) sufficiently high to cause maternal toxicity (i.e., 18% mortality).

The committee considers the toxicological database on 1,3-dichloro-5,5-dimethylhydantoin too poor to justify recommendation of a health-based occupational exposure limit.

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

References

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ACG02a American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values -2002. Cincinnati OH, USA: ACGIH®, Inc, 2002: 40.

ACG02b American Conference of Governmental Industrial Hygienists (ACGIH). 2002 TLVs® and BEIs®. Threshold Limit Values for chemical substances and fysical agents. Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, Inc, 2002: 26.

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Arb00b Arbetarskyddsstyrelsen. Hygieniska gränsvärden och åtgärder mot luftföroreningar. Solna, Sweden: Arbetarskyddsstyrelsen, 2000; Ordinance AFS 2000:3.

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Gal87 Galloway SM, Armstrong MJ, Reuben C, et al. Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluation of 108 chemicals. Environ Mol Mutagen 1987; 10 (suppl 10): 1-175.

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Har87a Hardin BD, Schuler RL, Burg JR, et al. Evaluation of 60 chemicals in a preliminary developmental toxicity test. Teratog Carcinog Mutagen 1987; 7: 29-48.

Har87b Hardin BD. A recommended protocol for the Chernoff/Kavlock preliminary developmental toxicity test and a proposed method for assigning priority scores based on results of that test. Teratog Carcinog Mutagen 1987; 7: 85-94.

Haw83 Haworth S, Lawlor T, Mortelmans K, et al. Salmonella mutagenicity test results for 250 chemicals. Environ Mutagen 1983; 5 (suppl 1): 3-142.

HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational exposure limits 2002. Sudbury (Suffolk), England: HSE Books, 2002: 16.

NIO97 US National Institute of Occupational Safety and Health (NIOSH), ed. Registry of Toxic Effects of Chemical Substances (RTECS) [CD-ROM], issue October 1997. SilverPlatter International, 1997 (last update 1,3-dichloro-5,5-dimethylhydantoin file: October 1997).

NLM97 US National Library of Medicine (NLM), ed. Hazardous Substances Data Bank (HSDB) [CD-ROM], issue March 1997. SilverPlatter International, 1997 (last update 1,3-dichloro-5,5-dimethylhydantoin file: October 1996).

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Tra81 Traul KA, Takayama K, Kachevsky V, et al. A rapid in vitro assay for carcinogenicity of chemical substances in mammalian cells utilizing an attachment-independence endpoint. J Appl Toxicol 1981; 1: 190-5.

TRG00 TRGS 900: Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. BArBl 2000; 2.

Woo85 Woodruff RC, Mason JM, Valencia R, et al. Chemical mutagenesis testing in Drosophila. V. Results of 53 coded compounds tested for the National Toxicology program. Environ Mol Mutagen 1985; 7: 677-702.

Zim89 Zimmering, S, Mason, JM, Valencia, R. Chemical mutagenesis testing in Drosophila. VII. Results of 22 coded compounds tested in larval feeding experiments. Environ Mol Mutagen 1989; 14: 245-51.

Annex

Occupational exposure limits for 1,3-dichloro-5,5-dimethylhydantoin in various countries.

country -organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
-Ministry of Social Affairs and Employment	-	0.2	8 h	administrative		SZW02
Germany						
-AGS	-	0.2[c]				TRG00
-DFG MAK-Kommission	-	-				DFG02
Great-Britain						
-HSE	-	0.2	8 h	OES		HSE02
	-	0.4	15 min			
Sweden	-	-				Arb00b
Denmark	-	0.2	8 h			Arb00a
USA						
-ACGIH	-	0.2	8 h	TLV		ACG02b
	-	0.4	15 min	STEL		
-OSHA	-	0.2	8 h	PEL		ACG02a
	-	0.2	10 h	REL		ACG02a
-NIOSH	-	0.4	15 min	STEL		
European Union						
-SCOEL	-	-				CEC00

[a] S = skin notation; this means that skin absorption may contribute considerably to the body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] As inhalable fraction of the aerosol.