Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding adviezen herevaluatie bestuurlijke MAC-waarden
Uw kenmerk : ARBO/AMIL/97/00648
Ons kenmerk : U 2706/CB/MP/563-O3
Bijlagen : 18
Datum : 14 december 2000

Mijnheer de staatssecretaris,

Op verzoek van uw ambtsvoorganger bied ik u hierbij de eerste adviezen aan van een reeks over de gezondheidskundige basis van uit het buitenland overgenomen grenswaarden voor beroepsmatige blootstelling aan stoffen. Het verzoek om deze adviezen is in algemene zin vervat in brief nr ARBO/AMIL/97/00648 en in latere stadia door uw departement toegespitst op afzonderlijke stoffen. De adviezen zijn opgesteld door een daartoe door mij geformeerde internationale commissie van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

De beoogde reeks van in het Engels gestelde adviezen zal losbladig worden gepubliceerd onder ons publicatienummer 2000/15OSH en, conform de aan de Gezondheidsraad voorgelegde toespitsingen van de adviesaanvraag, betrekking hebben op 168 stoffen. Het u thans aangeboden eerste pakket bestaat uit een Algemene Inleiding (publicatienummer 2000/15OSH/000) en uit de adviezen genummerd 2000/15OSH/001 tot en met 2000/15OSH/017, respectievelijk betrekking hebbend op:
cesiumhydroxide, cyclopentaan, diboraan, dimethoxymethaan, dipropylketon, fenylfosfine, germaniumtetrahydride, hexachloornaftaleen, methaanthiol, methylcyclohexanol, methylisopropylketon, mica, natriumhydroxide, octachloornaftaleen, silaan, tetrachloornaftaleen, en yttrium en yttriumverbindingen.

Bij afronding van de werkzaamheden van de hierboven bedoelde commissie ontvangt u een Nederlandstalige samenvatting van de in de gehele reeks van adviezen neergelegde bevindingen.

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
Telefoon (070) 340 75 20
email: GR@gr.nl

Postadres
Postbus 16052
2500 BB Den Haag
Telefax (070) 340 75 23

Gezondheidsraad
Health Council of the Netherlands

Onderwerp : Herevaluatie uit het buitenland overgenomen grenswaarden
Ons kenmerk : U
Pagina : 2
Datum : 14 december 2000

De u thans aangeboden adviezen heb ik vandaag ter informatie doen toekomen aan de Minister van Volksgezondheid, Welzijn en Sport en aan de Minister van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer.

Hoogachtend,

prof. dr JJ Sixma

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
Telefoon (070) 340 75 20
email: GR@gr.nl

Postadres
Postbus 16052
2500 BB Den Haag
Telefax (070) 340 75 23

Diborane

(CAS Reg. nr: 19287-45-7)

Health-based Reassessment of Administrative Occupational Exposure Limits

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

No. 2000/15OSH/003, The Hague, 14 December 2000

Preferred citation:
Health Council of the Netherlands: Committee on Updating of Occupational Exposure Limits. Diborane; Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands, 2000; 2000/15OSH/003.

1 Introduction

The present document contains the assessment of the health hazard of diborane 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 AAE Wibowo, Ph.D. (Coronel Institute of the Academic Medical Centre, Amsterdam, the Netherlands).

Literature was retrieved from the data bases Medline, Embase, Toxline and Chemical Abstracts, starting from 1966, 1988, 1967 and 1970, respectively, and using the substance name as a key word. Also Current Contents (from 1997 backwards) and the CD-roms HSEline, Cisdoc, Mhidas and NIOSHtic were consulted (from 1997 backwards). Data considered to be critical were evaluated by reviewing the original publications. The final literature search has been carried out in October 1997.

In March 2000, the President of the Health Council released a draft of the document for public review. Comments were received by the following individuals and organizations: L Whitford (Health & Safety Executive, London, United Kingdom), dr P Wardenbach (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund, Germany). These comments were taken into account in deciding on the final version of the document.

2 Identity

name	:	diborane
synonyms	:	diboraan (Dutch) boroethane diboron hexahydride
molecular formula	:	B_2H_6
structural formula	:	H_3BBH_3
CAS reg nr	:	19287 - 45 - 7

3 Physical and chemical properties

molecular weight	:	27.7
boiling point	:	-92.5^0C
melting point	:	-165^0C
relative vapour density (air=1)	:	0.96
solubility in water	:	hydrolizes to hydrogen and boric acid
log $P_{oct/water}$	:	-
conversion factors (20^oC, 101.3 kPa)		1 mg/m^3 = 0.87 ppm 1 ppm = 1.15 mg/m^3

Data from IPC93.

Diborane is a flammable gas with a repulsive, sickly-sweet odour. It is also described as having an odour of 'rotten eggs'. The median odour threshold was 3.7 mg/m^3 (range 3.3 - 4.2 mg/m^3) (Com53). The American Industrial Hygiene Association reported a range of 2.1 - 4.0 mg/m^3 (1.8 - 3.5 ppm) for the odour threshold (AIH89).

4 Uses

Diborane is used as a selective reducing agent, initiator of rubber vulcanization, bactericide, fungicide, initiator of ethylene, vinyl, styrene and acrylic polymerization (Rou59), high energy rocket propellant (Uem95) and as a boron source in the production of integrated circuits in the semiconductor industry (Nom96).

5 Biotransformation and kinetics

The International Programme on Chemical Safety (IPCS) of the World Health Organisation reported that occupational exposure may occur by inhalation (IPC93).

Diborane is a very reactive gas. In contact with air, a small quantity of diborane is converted to higher hydrides, pentaborane and decaborane (Rou59). In an aquaous environment, diborane hydrolizes to form boric acid and hydrogen. Due to its chemical and physical characteristics, the upper

respiratory tract and the lungs are the target organs of occupational exposure to diborane.

There is no data on absorption, distribution, metabolism and excretion of the compound. It is conceivable that some diborane may be absorbed (Rou59).

6 Effects and mechanism of data

Human data

There is no data on irritation and sensitization nor epidemiological data available on exposure to diborane. Only a few case-reports have been described.

Rousch Jr. reported that men working with diborane had similar complaints as cough, tightness in the chest and occassionally also headache (Rou59). The symptoms concerned the respiratory tract and were non-specific.

In health risk assessment of diborane, concomitant exposure to pentaborane and decaborane should be taken into account. Penta- and decaborane differ from diborane in that they affect the central nervous system rather than the pulmonary system (Wil85), giving rise to dizziness, drowsiness and headache as early symptoms (Low57). Decaborane has also been found to cause damage to the liver and kidneys (Sch58).

Lowe and Freeman (Low57) reported a case of accidental exposure to diborane. Five and a half hours after the accident the worker developed light-headedness and hiccups, followed by nausea and drawsiness. The following day the drawsiness persisted and the muscles of both thighs became painful and began to shake. On admission to hospital, diaphoresis was profuse and photophobia was evident. Neurological examination revealed no abnormalities. On the following days his condition improved and he was discharged seven days after exposure.

Cordasco *et al*. (Cor68) described a patient who was acutely exposed to diborane fumes through an unprovoked explosion. He developed shortness of breath, vertigo and dry cough. After being given oxygen (by mask) he obtained relief 20 minutes later. Six days later, the dry cough recurred after the patient was again exposed to diborane and he developed concomitant generalized chest tightness. Chest x-ray examination demonstrated a pneumonitis at both bases.

Animal data

No data on irritation or sensitization of diborane were found.

Schechter (Sch58) reported an LC_{50} of diborane in rats of 92 mg/m^3 (80 ppm) after a 4 hour exposure period. Pentaborane and decaborane were more toxic than diborane, having LC_{50}s of 6.8 and 45.5 ppm respectively. More recently, Uemura *et al*. (Uem95) reported an LC_{50} of 36.2 mg/m^3 (31.5 ppm) for diborane in mice after 4 hour exposure and observation during 2 weeks.

Uemura *et al*. (Uem95) performed an experiment in which groups (n=10) of male ICR mice were exposed by inhalation to 17.3 mg/m^3 (15 ppm) diborane for 1, 2, 4 or 8 hours, and observed during 3 days. In the 8-hour exposure group the reaction of the mice to noise was decreased. Ruffled fur and systemic tremors were observed in some of the animals. Body weights were significantly decreased 1 and 2 days after exposure, and significant increases in absolute lung and trachea weights were found. No changes were observed on hematological and biochemical parameters. Severe inflammatory changes were found in the lungs of the exposed groups in an exposure duration-related manner. The lesions were similar to diffuse panbronchiolitis in human cases.

Nomiyama *et al*. (Nom95a) exposed groups (n=10) of male ICR mice to 1.2 mg/m^3 (1 ppm) or 5.8 mg/m^3 (5 ppm) diborane by inhalation during 1, 2, 4 or 8 hours. Within the group exposed to 5.8 mg/m^3 lung weights (both absolute and relative) were increased. However, lung weights were significantly decreased in the group exposed to 1.2 mg/m^3. Diffuse panbronchiolitis-like obstructive changes were observed in the lungs of the mice exposed to 5.8 mg/m^3, and this response was dose- and exposure duration-related. In this experiment a no-observed adverse effect level (NOAEL) in mice of 1.2 mg/m^3 (1 ppm) diborane (for an 8-hour exposure) was found.

Nomiyama *et al*. (Nom95b) also exposed groups (n=8) of male Wistar rats to 23 mg/m^3 (20 ppm) diborane for 4 hours and they evaluated time-course changes up to 14 days post exposure. Examination of the bronchoalveolar lavage fluid (BALF) showed increases of neutrophils on the day of exposure, followed by gradual decreases for the next three days. Rapid marked increases of α_1-antitrypsin and superoxide dismutase activities were detected in the BALF on the day of exposure, and phospholipids had sharply increased on day 3. After 14 days these parameters returned to their background levels. The authors also studied groups (n=12) of rats exposed to 1.2 or 11.5 mg/m^3 (1 or 10 ppm) diborane for 4 hours to assess the dose-effect relationship after 3 days. In this study total protein, α_1-antitrypsin and phospholipids in the BALF were dose-dependently increased. Also serum α_1-antitrypsin activity was significantly increased. Superoxide dismutase activity in the BALF, albumin and creatinine content were significantly increased in the lower dose group

only. On histopathology of the lungs, diffuse panbronchiolitis-like obstructive changes were observed in the group exposed to 11.5 mg/m^3. The authors concluded that no NOAEL was found in this study.

Uemura *et al*. (Uem95) exposed groups (n=10) of male ICR mice to 5.8 mg/m^3 (5 ppm) diborane for 6 hours/day, 5 daysweek for 2 and 4 weeks. The mice were killed on the day after final exposure. In this study the authors observed lymphoid hyperplasia in the perivascular and peribronchial areas, and infiltration of macrophage and plasma cells into the alveoli. In the mice exposed for 4 weeks, the lesions were more severe than in those exposed for 2 weeks. The lesions consisted of hyperplasia and desquamation of Clara cells in the lungs. In the nasal cavity, the authors observed mucous exudate and inflammatory cells. No significant changes were seen in hematological (RBC and diff count of WBC) and serum biochemical (CPK, Ch-E, GOT, GPT, Al-p, BUN, Na and K) parameters. In this study, hepatic congestion was more frequent observed in the exposed groups. There were no histo-pathological changes in the brain, thyroid gland, thymus, heart, spleen and kidney.

Nomiyama *et al*. (Nom95a) also exposed groups (n=10) of male ICR mice to diborane concentrations of 0.2 mg/m^3 (0.2 ppm) or 0.8 mg/m^3 (0.7 ppm) for 6 hours/day, 5 days/week, for 2 or 4 weeks. No significant differences in behavior or external appearance between the control and exposed mice were seen. Lung weight was significantly greater in mice exposed to 0.8 mg/m^3 during 2 weeks. A slight dose-related infiltration of polymorphous neutrophils, mainly in the peribronchiolar region, was observed in mice exposed to 0.2 or 0.8 mg/m^3 diborane for 2 or 4 weeks. The authors concluded that for subacute exposure of mice 0.2 mg/m^3 diborane was no longer a NOAEL. The committee suggests to appoint this level as the lowest observed adverse effect level (LOAEL) in mice.

Nomiyama *et al*. (Nom96) again studied the effects of inhalation of diborane in groups of male Wistar rats (n=12) at levels of 0.13 or 1.1 mg/m^3 (0.11 and 0.96 ppm, respectively), 6 hours/day, 5 days/week, for 8 weeks. No significant differences were found between the exposed groups and control group in behavior, external appearance, body weight and histopathology of the lung. Examination of the BALF revealed that the percentage of neutrophils increased in a dose-dependent manner, whereas the percentage of macrophages was decreased in rats exposed to 1.1 mg/m^3. Total and individual phospholipids in BALF was increased in rats exposed to 1.1 mg/m^3. Also dose-dependent increases were found on the α_1-AT and SOD activities in serum. The results of this study indicate a LOAEL of 0.13 mg/m^3 in rats for effects on the lung.

Krakow (Kra53) reported that rats exposed to an average concentration of 2.3 mg/m^3 (2 ppm) for a period of 1 to 4 days (6 hours/day), showed no significant changes in the organs examined. But exposure to 6 mg/m^3 (5.2 ppm) diborane, 6 hours/day, 5 days/week, for 2 to 3 weeks showed pulmonary damage. The number of animals studied was not reported. Pathological pulmonary changes already occurred in rats exposed to an average of 2.5 mg/m^3 (2.2 ppm) after one to four weeks of exposure.

No data on long-term exposure, mutagenicity, genotoxicity and carcinogenicity have been found.

Reproduction toxicity

Nomiyama *et al*. (Nom96) reported no effects on the testes (sperm counts and sperm head abnormalities) after groups of rats (n=12) inhaled 0.13 or 1.10 mg/m^3 diborane, 6 hours/day, 5 days/week, for 8 weeks.

No other data on reproduction toxicity have been found.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) of diborane in the Netherlands is 0.1 mg/m^3 (0.1 ppm), 8 h TWA.

Existing occupational exposure limits for diborane in some European countries and in the USA are summarized in the annex.

8 Assessment of health hazard

The target organs of occupational exposure to diborane are the upper respiratory tract and the lungs as observed from human data and in animal experiments. Effects on the central nervous system (CNS) as reported in human case-reports are probably due to contamination with other boron hydrides like pentaborane and decaborane that are known for CNS effects (Loe57, Sch58). The human data do not allow the establishment of an health-based occupational exposure limit.

The available animal data only concern acute and subacute studies. From these studies the following no observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs) for effects of diborane on the respiratory tract of rodents have been found:

- NOAEL in mice of 1.2 mg/m^3 after 8 h exposure period (Nom95a);

- LOAEL in rats of 1.2 mg/m^3 after 4 h exposure period (Nom95b);
- LOAEL in mice of 0.2 mg/m^3 after exposure for 6 hours a day, 5 days a week, for 4 weeks (Nom95a);
- LOAEL in rats of 0.13 mg/m^3 after exposure for 6 hours a day, 5 days a week, for 8 weeks (Nom96).

In a single subacute inhalation study in rats no effect of diborane on the testes was reported (Nom96). No further data on reproduction toxicity of diborane have been found.

No data on long-term exposure, mutagenicity, genotoxicity and carcinogenicity of diborane were found.

The committee takes the LOAEL of 0.13 mg/m^3 for lung effects in the subacute rat study (Nom96) as a starting point. Since the effects induced by diborane are local rather than systemic, the committee considers an assessment factor for interspecies variation unneccessary. Application of an overall assessment factor of 9 to account for starting from a LOAEL and for intraspecies variation, results in a preferred value of 0.01 mg/m^3.

The committee recommends a health-based occupational exposure limit for diborane of 0.01 mg/m^3 (0.01 ppm), as an 8 h time weighted average (TWA).

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Annex

Occupational exposure standards for diborane 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	0.1	0.1	8 h	administrative		SZW00
Germany						
-AGS	0.1	0.1	8 h			TRG00
-DFG MAK-Kom.	-	-				DFG99
Great-Britain						
-HSE	0.1	0.12	8 h	OES		HSE99
Sweden	-	-				NBO96
Denmark	0.1	0.1	8 h			Arb96
USA						
-ACGIH	0.1	0.11	8 h	TLV		ACG00
-OSHA	0.1	0.1	8 h	PEL		
-NIOSH	0.1	0.1	10 h	REL		
European Union						
-SCOEL						

[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