Azobisisobutyronitrile

Health-based recommended occupational exposure limit

Gezondheidsraad

Health Council of the Netherlands

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding advies over azobisisobutyronitril
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Mijnheer de Staatssecretaris,

Bij brief van 3 december 1993, nr DGV/MBO/U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid de Gezondheidsraad om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen. In dat kader bied ik u hierbij een advies aan over azobisisobutyronitril. Het is opgesteld door de Commissie WGD van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

Ik heb dit advies vandaag ter kennisname toegezonden aan de Minister van Volksgezondheid, Welzijn en Sport, de Minister van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer en de Minister van Sociale Zaken en Werkgelegenheid.

Hoogachtend,

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Azobisisobutyronitrile

Health-based recommended occupational exposure limit

Dutch expert committee on occupational standards
a committee of the Health Council of the Netherlands

to

the Minister and State Secretary of Social Affairs and Employment

No. 2002/01OSH, The Hague, 12 March 2002

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues..." (Section 21, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature Preservation & Fisheries. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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Samenvatting en advieswaarde

Vraagstelling

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid leidt de Commissie WGD van de Gezondheidsraad gezondheidskundige advieswaarden af voor stoffen in de lucht op de werkplek waaraan beroepsmatige blootstelling kan plaatsvinden. Deze aanbevelingen vormen de eerste stap in een drietrapsprocedure die moet leiden tot wettelijke grenswaarden (MAC-waarden).

In het voorliggende rapport bespreekt de commissie de gevolgen van blootstelling aan azobisisobutyronitril (AIBN) en presenteert zij, indien mogelijk, een gezondheidskundige advieswaarde voor die stof. De conclusie van de commissie is gebaseerd op wetenschappelijke publicaties die vóór november 2000 zijn verschenen.

Fysische en chemische eigenschappen

Azobisisobutyronitril is een zeer brandbaar wit poeder. Bij verhitting (107°C) kan AIBN ontleden in tetramethylsuccinonitril (TMSN). Dit is een relevant gegeven, omdat AIBN in de beroepsfeer gebruikt wordt bij temperaturen tussen de 105 en 180°C. AIBN kan exploderen als het wordt opgelost in aceton en heptaan.

De stof wordt gebruikt voor de polymerisatie van vinylmonomeren en onverzadigde polyesters, en verder bij de productie van vinylschuim.

Monitoring

Vanwege de lage dampdruk bij kamertemperatuur is het aannemelijk dat AIBN alleen in de vorm van stofdeeltjes voorkomt op de werkplek. In dat geval kan de algemene methode voor het bepalen van inhaleerbare stof worden gebruikt om AIBN in de lucht te meten. Het AIBN-gehalte in stof kan analytisch-chemisch worden bepaald, bijvoorbeeld door middel van gaschromatografische en polarografische methoden, na extractie met een geschikt oplosmiddel.

Grenswaarden

Noch in Nederland noch in andere landen zijn grenswaarden voor AIBN vastgesteld. Voor TMSN, het ontleedproduct van AIBN, is in verscheidene landen, waaronder Nederland, een grenswaarde voor beroepsmatige blootstelling voor- of vastgesteld van 3 mg/m^3 (0,5 ppm), gemiddeld over een achturige werkdag, en gekenmerkt met een huidnotatie.

Kinetiek

Er zijn geen gegevens gevonden over de absorptie, distributie, stofwisseling en uitscheiding van AIBN.

Wel zijn er beperkte gegevens beschikbaar die erop duiden dat in ratten cyaanwaterstof (HCN) wordt gevormd na intraveneuze, intratracheale en intraperitoneale toediening van AIBN.

Effecten

Bij werknemers werkzaam bij de productie van polyvinylchlorideschuim zijn bewusteloosheid, spasmen, hoofdpijn en misselijkheid gerapporteerd. De onderzoekers wijten echter deze klachten aan het ontleedproduct, TMSN, een stof met een neurotoxische werking. Uit de literatuur komen sterke aanwijzingen naar voren dat de aan AIBN toegeschreven gezondheidseffecten bij de mens in werkelijkheid worden veroorzaakt door zijn ontleedproduct TMSN, dat ontstaat bij verhitting van AIBN. Op de werkplek wordt AIBN namelijk in het algemeen verhit.

In dierexperimenteel onderzoek zijn geen aanwijzingen gevonden dat AIBN irriterend is voor ogen en huid of dat het overgevoeligheidsreacties in de huid kan veroorzaken. Na ingestie zijn bij dieren LD_{50}-waarden gevonden tussen de 50 en 400

mg per kg lichaamsgewicht. De LD_{50}-waarde is die dosis waarbij de helft van de blootgestelde dieren sterft.

De commissie heeft geen betrouwbare dierexperimentele gegevens gevonden over effecten van AIBN na eenmalige of herhaalde blootstelling, via inademing of ingestie. Ook heeft de commissie geen betrouwbare dierexperimentele gegevens gevonden over effecten op de reproductie of aanwijzingen gevonden voor een kankerverwekkende werking van AIBN. Verder zijn in de literatuur geen aanwijzingen gevonden dat AIBN DNA-mutaties of -schade kan veroorzaken in bacteriën.

Evaluatie en advies

Wegens gebrek aan wetenschappelijke gegevens kan de commissie geen gezondheidskundige advieswaarde voor de beroepsmatige blootstelling aan azobisisobutyronitril (AIBN) aanbevelen.

Dit advies bevat een aanvullende overweging van de commissie over het gebruik van de gezondheidskundige advieswaarde van TMSN voor het afleiden van een grenswaarde voor AIBN bij beroepsmatige blootstelling.

Executive Summary

Scope

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands recommends health-based occupational exposure limits for the concentration of toxic substances in air at the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards. They constitute the first step in a three-step procedure that leads to legally-binding limit values.

In the present report, the committee discusses the consequences of occupational exposure to azobisisobutyronitrile (AIBN) and recommends, if possible, a health-based occupational exposure limit. The committee's conclusions are based on scientific publications prior to November 2000.

Physical and chemical properties

Azobisisobutyronitrile is an extremely flammable, white powder. When heated (to 107°C), it decomposes with the liberation of free nitrogen into two free radicals, which can react to tetramethyl succinonitrile (TMSN). The formation of TMSN is relevant in an occupational context, because AIBN is generally used at temperatures between 105° and 180°C. Furthermore, it can explode when dissolved in acetone or heptane.

AIBN is used in the polymerisation of all common vinyl monomers and of unsaturated polyesters, and is used as a blowing agent in the production of vinyl foam.

Monitoring

In view of the low vapour pressure at room temperature, it is likely that AIBN will only occur as dust at the workplace. A general method for measuring inhalable dust should than be suitable for measuring AIBN. The AIBN content in dust may be assessed by analytical-chemical methods after extraction with a suitable solvent and applying gas chromatographical and polarographical methods.

Current limit values

No occupational exposure limits were found for AIBN. For TMSN, the decomposition product, the occupational exposure limit is 3 mg/m^3 (0.5 ppm) in most countries, including the Netherlands, with a skin notation added.

Kinetics

There were no data available on the absorption, distribution, metabolism, or excretion of AIBN.

Limited information indicates that free hydrogen cyanide may be formed in rats following intravenous, intratracheal, and intraperitoneal administration.

Effects

Unconsciousness, spasms, headaches, and nausea were reported in workers involved in polyvinyl chloride foam production. These effects were attributed to the AIBN's decomposition product TMSN, which is a potent neurotoxic agent. In the literature, there is strong evidence that AIBN-related health effects in humans are caused by its decomposition product TMSN, which is formed upon heating AIBN. At the workplace, it is general practice to heat AIBN.

Experimental animal data do not indicate an eye or skin irritating or a skin sensitising potential. Oral LD_{50}-values in rodents ranged between 50 and 400 mg AIBN per kg bw.

The committee did not find reliable animal data from single or repeated inhalation or repeated oral toxicity studies, including those on reproduction toxicity or carcinogenicity. In the literature, no evidence was found that AIBN induces mutations or primary DNA damage in bacteria. However, further data from *in vitro* mammalian cell systems and *in vivo* tests are lacking.

Evaluation and recommendation

The committee considers the toxicological data base on azobisisobutyronitrile to be too poor to derive a health-based recommended occupational exposure limit (HBR-OEL).

This report contains an additional consideration of the committee about the use of the OEL of TMSN for setting an occupational exposure limit for AIBN.

Hoofdstuk **1**

Scope

1.1 Background

In the Netherlands, occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, at the request of the Minister of Social Affairs and Employment (Annex A). This evaluation should lead to a health-based recommended exposure limit for the concentration of the substance in air. Such an exposure limit cannot be derived if sufficient data are not available or if the toxic action cannot be evaluated using a threshold model. In the latter case, an exposure-response relationship is recommended for use in regulatory standard setting.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister on the feasibility of using the health-based value as a regulatory Occupational Exposure Limit (OEL) or recommends a different OEL. In the final step of the procedure, the Minister of Social Affairs and Employment sets the official Occupational Exposure Limit.

1.2 Committee and procedure

This document contains the assessment of DECOS, hereafter called the committee, of the health hazard of azobisisobutyronitrile (AIBN). The members of DECOS are listed in Annex B. The first draft of this report was prepared by Dr Ir AA Rutten, IA van de

Gevel, Msc, and F de Vrijer, at TNO Nutrition and Food Research, Zeist, the Netherlands, by contract with the Ministry of Social Affairs and Employment.

In 1995, the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex C. DECOS has taken these comments into account in deciding on the final version of the report.

1.3 Data

For the preparation of this document, literature has been retrieved from several on-line data bases (last update on-line search: 1995).

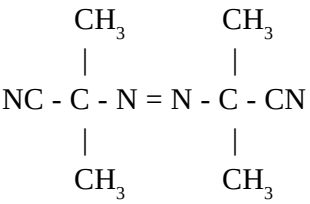
Before finalising the document, the committee performed an additional literature search in SilverPlatter® CD-ROM versions of Medline (January 1995 - November 2000) and Toxline (January 1995 - September 2000), of which relevant studies are included in this report. The results of this search were no reason for the committee to alter the recommendations based on the older literature search.

Hoofdstuk **2**

Identity, properties and monitoring

2.1 Identity

Structure



Chemical names and synonyms/registry numbers

Name	azobisisobutyronitrile
CAS registry number	78-67-1
CAS index name	2,2'-azobis[2-methylpropanenitrile]
Synonyms	azobisisobutylonitrile; 2,2'-azobisisobutylonitrile; 2,2'-azodi-isobutyronitrile; 2,2'-azobis(2-methylpropionitrile); α,α'-azobis-isobutyronitrile; α,α'-azodiisobutyronitrile; 2,2'-dimethyl-2,2'-azopropionitrile; 2,2'-dicyano-2,2'-azopropane
EINECS number	201-132-3
EEC number	608-019-00-1
RTECS number	UG0800000

2.2 Physical and chemical properties (Che99, NLM00)

Molecular formula	$C_8H_{12}N_4$
Molecular weight	164.24 g/mol
Melting point	105°C
Auto-ignition temperature	64°C
Relative density (water=1)	1.1
Solubility in water (20°C)	insoluble
Solubility in organic solvents	methanol: 1.8, 5.0, and 16.1 g/100 mL, at 0, 20, 40°C, resp; ethanol: 0.6, 2.0, and 7.2 g/100 mL, at 0, 20 and 40°C, resp; in vinyl monomers

AIBN is a white powder that decomposes at 107°C. It is extremely flammable, and may ignite itself if the decomposition temperature is exceeded. It can explode when dissolved in acetone or heptane (Che99, Smi81).

In solution, AIBN decomposes on heating to form two free radicals with the liberation of nitrogen (see equation below). The two free radicals that are initially formed, can react to the important decomposition product TMSN. The thermal decomposition half-life time of AIBN in toluene solution is described by (Smi81):

$$\log (t_{1/2}) = 7142\ (1/T) - 18.355\ T \quad [T \text{ in Kelvin; } t=\text{min}]$$

For example, the half-life time of AIBN is 100,000 min. (ca. 70 days) at ca. 30°C, whereas at 105°C, the melting point of AIBN, the half-life time is only 4 min. In

industrial processes AIBN is used at temperatures ranging between 100°C and 150°C. This shows that at a relatively mild temperature of 30°C only small amounts of the decomposition TMSN product are formed. In contrast, upon heating TMSN may be formed in larger quantities.

$$\underset{\text{(AIBN)}}{NC\text{-}C(CH_3)_2\text{-}N{=}N\text{-}C(CH_3)_2\text{-}CN} \longrightarrow 2\ NC\text{-}C\text{-}(CH_3)_2 + N_2\uparrow$$

$$2\ NC\text{-}C\text{-}(CH_3)_2 \longrightarrow \underset{\text{TMSN*}}{NC\text{-}C(CH_3)_2\text{-}C(CH_3)_2\text{-}CN}$$

2.3 EU classification and labelling (Ano00)

According to the 25th Amendment to Annex 1 of Directive 67/548/EEC, AIBN is, amongst others, classified as "risk of explosion by shock, friction, fire or other sources of ignition", "highly flammable", "harmful by inhalation and if swallowed ", and labelled as follows:

Symbols	explosive harmful
Risk phases	R2 : risk of explosion by shock, friction, fire or other sources of ignation R11: highly flammable R20/22: harmful by inhalation and if swallowed
Safety phrases	S39: wear eye/face protection S41: in case of fire and/or explosion do not breathe fumes S47: keep at temperature not exceeding .. °C (to be specified by the manufacturer)

2.4 Validated analytical methods

2.4.1 Environmental monitoring

No method for monitoring AIBN in air has been published. However, since AIBN does hardly vaporise at room temperature (Che99), general dust methods should be applicable (for overview see Bol95). The AIBN content in the dust may be assessed by analytical-chemical methods after extraction with a suitable solvent and applying gas chromatographic and polarographic methods (see section 2.4.2).

* Some chemical and physical properties of TMSN: Mw is 136.2, specific gravity is 1.070, melting point is 170.5°C [sublimes], insoluble in water and soluble in alcohol (CAS reg. no. 3333-52-6).

2.4.2 *Biological monitoring*

No specific method for the determination of AIBN in biological samples could be found.

Benzene-polarographic and gas-chromatographic methods for detection of AIBN in water have been described (Dmi75, Num79).

Hoofdstuk **3**

Sources

3.1 Natural occurrence

AIBN is not found in nature.

3.2 Man-made sources

3.2.1 Production

AIBN is produced by the following routes: hypochlorite (NaOCl) oxidation of 2-aminoisobutyronitrile (British patent, 1952 to Rohm & Haas; US patent, 1955 to DuPont), from 2,2'-dichloro-2,2'-azopropane (British patent, 1963 to Monsanto), and by oxidation of α,α-hydrazobutyric acid dinitrile (NLM00).

3.2.2 Uses

Azobisisobutyronitrile (AIBN) is an efficient source of free radicals for vinyl polymerisations and chain reactions, *e.g.*, chlorination. It is widely applied as a blowing agent in the production of vinyl foam. In the production process, AIBN is used at temperatures ranging from 105° to 180°C. At these temperatures, the compound decomposes in a variety of solvents at nearly first order rates, giving free radicals with no evidence for induced chain decomposition (Smi81).

AIBN can be used in bulk, solution and suspension polymerisations and, because no oxygenated residues are produced, it is suitable for use in pigmented or dyed systems that may be susceptible to oxidative degradation (Smi81). Furthermore, AIBN is used for curing unsaturated polyester resins (NLM00).

Hoofdstuk **4**

Exposure

4.1 General population

Since AIBN is primarily used in industry as a raw material for the vinyl production, it is unlikely that the general population will be exposed to this compound.

No data were found on exposure of the general population via air, food or food products.

In the former Soviet Union, small amounts (0.2-10 mg/L) of AIBN were detected in polymer production effluent waters (Dmi75).

4.2 Working population

At room temperature, AIBN is an hardly vaporising solid (Che99). Therefore, occupational exposure will be via inhalation of particles and via the skin, e.g. while mixing AIBN prior to its use.

When utilised as a vinyl polymerisation initiator in a closed system, average exposure levels for manufacturing and processing were stated to be 0.3 (range: 0.13-0.56 mg/m^3; 12-h TWA) and <0.5 mg/m^3 (8-h TWA), respectively. Exposure duration was reported to be 33 and 2 days/year, respectively (DuP84).

Hoofdstuk **5**

Kinetics

5.1 Absorption

Rusin (Rus62b) reported that AIBN is not absorbed through the skin. Since no experimental data were listed, this finding is not considered to be adequate. No further data were found in the literature with respect to the uptake of AIBN. TMSN, a decomposition product of AIBN, is reported to be absorbed via the skin in rabbits (EPA81).

5.2 Distribution

No data were found.

5.3 Biotransformation

Some information of biotransformation is reported after intraperitoneal, intravenous, and intratracheal injection of AIBN in rats. Free hydrogen cyanide (HCN) was found in the blood, the liver, the brain, and the lungs and was regarded as the basic cause of toxicity. The HCN antidotes, $NaNO_2$ and $Na_2S_2O_3$, counteracted the fatal effects of lethal dose levels of AIBN (Rus62a/b). No details are reported and, therefore, the study is considered to be inadequate for evaluation.

In metabolic studies in rats, TMSN was shown to give rise to little or no blood HCN levels or blood and urine isothiocyanate concentrations, indicating that TMSN is probably metabolised in the rat by a pathway that does not involve inorganic cyanide (EPA81).

5.4 Elimination

No data were found.

5.5 Possibility for biological monitoring

No data were found.

Hoofdstuk **6**

Effects

6.1 Observations in man

Sixteen workers (9 males, 7 females) of a German factory, where AIBN and polyvinyl chloride powder were utilised in making vinyl foam products, were examined after 5 cases of unconsciousness showing spasms had been occurred. Symptoms reported included, amongst others, headaches (n=12), nausea (n=7), frothing at the mouth (n=7), vomiting (n=5), balance disturbances (n=5), breathing difficulties (n=4), and tremors (n=3). Although exposures were not characterised, the author attributed these findings to TMSN (Rei57). In its documentation on the TLV of TMSN, ACGIH reported that several workers making polyvinyl chloride foam in one plant in Ontario experienced complaints of headaches and nausea (ACG00).

Since no detailed information was given on the compounds involved and their concentrations, DECOS can not draw conclusions concerning the potential toxicity of AIBN in humans from this information. The effects observed in these foam workers are most likely related to TMSN since this compound is known to be a potent neurotoxic agent (convulsant) (ACG00).

6.2 Animal Experiments

6.2.1 Irritation and sensitisation

Eye

Treatment of the eyes of male albino rabbits (number not indicated), for 20 seconds, with 10 mg AIBN powder or with 0.1 mL of a 10% suspension in propylene glycol, caused mild conjunctival inflammation observed at the day of treatment and through 4 days, respectively (observation period: 7 days). There were no effects on iris or cornea (Has62).

When 100 mg of finely ground powder was instilled in the eyes of 6 New Zealand albino rabbits, slight conjunctival erythema and discharge (mean conjunctival score: 4) was observed at the observation time of 1 hour, while there were no effects on cornea and iris. At the subsequent observation times (24 through 168 h), all scores were zero (You74).

Skin

In a summarising table, AIBN was reported to cause slight oedema and slight to moderate redness when doses of 5-20 mL/kg bw of a 20% solution (the kind of solvent was not identified) were applied to the skin (rubber cuff and gauze pads) of guinea pigs (n=3). Application of 2 or 5 g/kg bw as a solid, moistened with acetone, induced very slight redness but no oedema (n=2 guinea pigs). When moistened with water, amounts of 0.5-1.0 g/kg bw resulted in slight oedema and, in one of the 2 animals, erythema. Both animals appeared normal at week 1 and 2 (Eas60).

Dermal application of a 25% ointment in Carbowax 1500 to the intact skin of albino guinea pigs caused occasional mild erythema (1/10). No irritation was observed after treatment with a 10% ointment (in Carbowax) or with 10 and 25% suspensions in dimethyl phthalate. There was no evidence of sensitisation after a series of 9 exposures to the abraded skin of 10 guinea pigs, followed by a 2-week exposure-free period and challenge test (no more details presented) (Has62).

6.2.2 Toxicity due to acute exposure

In an unpublished, acute inhalation study, rats were exposed to calculated (nominal) concentrations of AIBN of 8, 9, and 12 g/m^3, for 4 hours. During exposure, deep breathing, eye irritation, discomfort, and pallor were observed while animals showed

nervousness, ruffled fur and weight loss up to 4 days after exposure. At post-mortem examination, at post-treatment day 14, there were mild hyaline granular degeneration in the kidneys of all exposed rats and slight hypotrophy of the thymic medulla in the animals of the high-concentration group. The lungs were normal. Actual concentrations and particle size (distributions) were not presented (Has62). In a range-finding study preceding a 2-week inhalation study, performed in the same laboratory, the 4-hour "Approximate Lethal Concentration" was determined to be 0.95 g/m^3. No additional information was given. It was not clear whether this concentration was calculated or actually measured, nor was the particle size distribution given (Nas81) (see also Section 6.2.3). In view of lack of relevant information on exposure data (concentration, particle size), the committee is of the opinion that no conclusions can be drawn from this study regarding the toxicity of AIBN following acute inhalation exposure.

Referring to an unpublished study performed in 1944, it was reported that inhalatory exposure to unknown concentrations of AIBN for 8 hours, once or 2-3 times, caused mortality, preceded by spasms, in all exposed mice (n=16). Post-mortem examination showed liver changes (fatty degeneration, necrosis, haemorrhage). No effects were seen in rats and rabbits. No additional data were given (Rei57).

One male New Zealand albino rabbit survived a single dermal dose of 5.0 g/kg bw, while a female animal died after treatment with a single dose of 7.9 g/kg bw. Signs of intoxication included reduced appetite and activity, increasing weakness, and collapse. Upon necropsy, haemorrhagic areas in the lungs, liver hyperaemia, enlarged gall bladder, discoloured kidneys, and gastrointestinal inflammation were seen in the deceased female rabbit. The viscera of the male animal were normal (sacrifice at post-treatment day 14) (You74).

No mortality was reported in the skin irritation experiments discussed in Section 6.2.1.

Other acute lethal toxicity data of AIBN are summarised in Table 1.

Lethal oral doses were reported to cause clinical signs such as discomfort, irritability, inactivity, convulsions, tremors, and weight loss, as well as liver, lung, brain, and kidney damage. At non-lethal doses, discomfort, irritability, and weight loss were observed, but no gross organ lesions at post-mortem examinations (She62).

Table 1 Acute effects on experimental animals after single exposure to AIBN.

animal species	*route*	*effects*	*remarks*	*ref.*
rat (male)	oral	ALD 670 mg/kg bw	as 10-20% suspension in acetone/peanut oil (1:0); doses, 130-2,250 mg/kg bw, n=1/dose	She62
rat (female)	oral	ALD 450 mg/kg bw	as 3-5% suspensions; doses, 200-670 mg/kg bw, n=1/dose	She62
rat	oral	LD_{50} 100-200 mg/kg bw	as 5% in corn oil (used warm); doses, 50-1,600 mg/kg bw, n=6	Eas60*
rat	oral	LD_{50} 50-100 mg/kg bw	as 2% in corn oil; doses, 50-100 mg/kg bw, n=2	Eas60
rat	oral	LD_{50} 50-400 mg/kg bw	as 10% in 2% NaSC; doses, 50-3,200 mg/kg bw, n=3	Eas60
rat (male/females)	oral	LD_{50} 360 mg/kg bw	as 10% in corn oil; doses, 250-500 mg/kg bw, n=2 males/3 females or 3 males/2 females	You74
mouse	oral	LD_{50} 700 mg/kg bw	-	Rus62b
mouse	oral	LD_{50} 200-400 mg/kg bw	as 2% in corn oil; doses, 50-800 mg/kg bw, n=5	Eas60
rat	ip	LD_{50} 25-50 mg/kg bw	as 5% in corn oil (used warm); doses, 10-400 mg/kg bw, n=6	Eas60
mouse	ip	LD_{50} 100-200 mg/kg bw	as 2% in corn oil; doses, 10-200 mg/kg bw, n=5	Eas60
rat	sc	LDLo 30 mg/kg bw	no more data presented	Rei57
mouse	sc	LDLo 40 mg/kg bw	no more data presented	Rei57
rabbit	sc	LDLo 50 mg/kg bw	no more data presented	Rei57
guinea pig	sc	LDLo 50 mg/kg bw	no more data presented	Rei57

ALD, approximate lethal dose; LDLo, lowest dose inducing mortality; ip, intraperitoneal; sc, subcutaneous. * Data in Eas60 were presented as approximate values.

In Table 2, the acute toxicity data of TMSN are shown. TMSN is more toxic than AIBN after oral administration in rats.

Table 2 Acute effects on experimental animals after single exposure to TMSN, a decomposition product of AIBN.

animal species	*route*	*effects (LD_{50}s)*	*reference*
rat	oral	30 mg/kg bw	NIO78
rat	ip	17.5 mg/kg bw	NIO78
rat	sc	30 mg/kg bw	NIO78
rabbit	ip	20 mg/kg bw	NIO78
guinea pig	oral	17.5-25 mg/kg bw	NIO78

ip, intraperitoneal; iv, intravenous; sc, subcutaneous

6.2.3 *Toxicity due to short-term exposure*

In an unpublished study with limited data, male rats (n=10/group) were exposed by inhalation to AIBN dust concentrations (mass median aerodynamic diameter of the particles: 7.8-11.5 µm) of 0, 9.8±3.7 and 79.5±17.9 mg/m^3, 6 hours/day, 5 days/week, for 2 weeks. Five rats per group were randomly selected for sacrifice after the 10th exposure, while the remaining five rats per group were killed after a 14-day recovery-observation period. During exposure, no clinical signs of toxicity were seen in any of the exposed animals, apart from lung problems in one rat of the high-exposure group. In the high-exposure group, mean body weight was significantly lower than that of controls on exposure day 2 through 4, but not in the other exposure groups. Serum total protein tended to be higher and urine osmolality was lower then corresponding values in control animals. Post-mortem examinations showed effects on the liver, such as increased liver weights and cytoplasmic basophilia of hepatocytes, which were not seen in the recovered animals. In the low-exposure group, effects observed were limited to increases in serum total protein and in absolute and relative liver weights in the animals sacrificed immediately after the last exposure (Nas81). The committee is of the opinion that no firm conclusions can be drawn from this study regarding the effects of AIBN following short-term inhalation exposure. In view of the large particle sizes, the compound probably did not reach the lungs in sufficient quantities and exposure has been probably by the oral route via secondary ingestion, as is suggested by the presence of histological and weight changes of the liver and the absence of effects in the lungs. In fact, the mass median aerodynamic diameter should have been between 1-3 µm, as is been recommended by current EPA guidelines for repeated inhalation exposure (EPA98).

No other short-term toxicity data were reported. In a long-term oral toxicity study (8 months), an interim kill was carried out at 3 months (ca. 90 days) (Mot71). However no data were shown and findings are poorly described (see also 6.2.4).

6.2.4 *Toxicity due to long-term exposure and carcinogenicity*

Albino rats (n=50) were treated orally (by gavage) with AIBN (25 mg, 2 times/week) up to 8 months (interim kill at 3 and 5 months). Biochemical characteristics in plasma were affected (data not presented in the publication). Furthermore, the liver, the kidneys, and other organs were affected (data not shown) (Mot71). Since no data were presented, the committee considers this study not adequate to evaluate the long-term (oral) toxicity of AIBN. However, the results allow the conclusion that the dose applied (ca. 110 mg/kg bw/day) is a toxic dose (Mot71).

No other data were found on long-term toxicity and carcinogenicity of AIBN.

6.2.5 Genotoxicity

AIBN did not induce a significant increase in mutation frequency when tested in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, both in the presence and absence of a rat liver metabolic activation system at concentrations of 10 to 2,500 (+S9) or 5,000 (-S9) µg/plate (Bar76).

In the SOS Chromotest, using 3 different *E. coli* strains (PQ37, PM21, GC4798), no clear genotoxicity (borderline activity in strain PQ37) was observed for AIBN (Ede89).

6.2.6 Reproduction toxicity

No data were found on the reproduction toxicity of AIBN.

6.3 Summary

Unconsciousness, spasms, headaches, and nausea were reported in workers involved in polyvinyl chloride foam production. These effects were attributed to the AIBN's decomposition product TMSN, which is considered a potent neurotoxic agent.

The experimental animal data available do not indicate that AIBN is an eye or skin irritating or a skin sensitising compound. Oral LD_{50}-values in rodents ranged between 50 and 400 mg AIBN per kg bw. The dermal and oral acute lethal toxicity studies do not meet current OECD or EC requirements.

The committee did not find data from valid single or repeated inhalation or repeated oral toxicity studies, including those on reproduction toxicity or carcinogenicity. The committee concludes that there is no evidence that AIBN induces mutations or primary DNA damage in bacteria. However, in view of the lack of further data from *in vitro* mammalian cell systems and *in vivo* tests, the committee can not draw definite conclusions regarding the possible mutagenicity and genotoxicity of AIBN.

Hoofdstuk **7**

Existing guidelines, standards and evaluations

7.1 General population

No guidelines or standards for the general population were found.

7.2 Working population

For AIBN, no occupational guidelines or standards were found. However, for the decomposition product of AIBN formed upon heating, tetramethyl succinonitrile (TMSN), occupational exposure limits of 3 mg/m^3 (0.5 ppm) (8-h TWA) have been established or recommended in the Netherlands (DECOS, administrative), Germany, UK, and by the ACGIH (USA). A skin notation for TMSN has been added (ACG00, DFG00, HSE00, SZW99). Recently, the committee on Updating of Occupational Exposure Limits of the Health Council of the Netherlands has recommended a HBR-OEL for TMSN of 0.2 mg/m^3 (8-hour TWA) (see Annex D).

In its documentation, ACGIH states that TMSN is a potent convulsant. A TLV-TWA of 3 mg/m^3 is proposed, in order to minimise the potential for systemic toxicity manifested in workers as headache, nausea, and convulsions. A skin notation was considered appropriate, because structurally related dinitriles were reported to cause mortality in dermally treated animals (ACG99).

Hoofdstuk **8**

Hazard assessment

8.1 Assessment of health hazard

At room temperature, AIBN is a solid having a low vapour pressure. Therefore, in occupational settings exposure will be mainly to dust, the respiratory tract and the skin being the main exposure routes. At the workplace it is general practice to heat AIBN. Upon heating, a decomposition product tetramethyl succinonitrile (TMSN) is formed, which is a known neurotoxic agent. The committee notices that TMSN may be responsible for the AIBN-induced effects described in this report.

The committee did not find reliable human data on the effects of AIBN through occupational exposure.

Experimental animal data do not indicate an eye or skin irritating or a skin sensitising potential. Oral LD_{50}-values in rodents ranged between 50 and 400 mg AIBN per kg bw. Further, there were no animal data from valid single or repeated inhalation or repeated oral toxicity studies, including those on reproduction toxicity or carcinogenicity. From *in vitro* mutagenicity and genotoxicity tests, the committee concludes that there is no evidence that AIBN induces mutations or primary DNA damage in bacteria. However, since further data from *in vitro* mammalian cell systems and *in vivo* tests are lacking, the committee is not able to draw a definite conclusion on the potential genotoxicity of AIBN.

8.2 Groups at extra risk

No specific groups at extra risk are identified in the literature.

8.3 Health-based recommended occupational exposure limit

The committee concludes that the toxicological data based on azobisisobutyronitrile is too poor to derive a health-based recommended occupational exposure limit (HBR-OEL), see however 8.4.

8.4 Additional consideration

The committee concluded that it is not possible to determine a health based occupational exposure limit for AIBN, because of a lack of scientific data.

However, the committee notices that tetramethyl succinonitrile (TMSN) may be responsible for the AIBN-induced effects described in this report and that the available data on the toxicity of TMSN can be used for the evaluation of the toxicity of AIBN. Based on well-performed subchronic animal studies, the Committee on Updating of Occupational Exposure Limits of the Health Council of the Netherlands, recommended a HBR-OEL for TMSN of 0.2 mg/m^3 (8-hour TWA) (see Annex D). Corrected for the difference in molecular weight, the committee is, therefore, of the opinion that applying an occupational exposure limit of 0.24 mg/m^3 for AIBN, as an 8-hour time-weighted average, is justifiable.

Hoofdstuk **9**

Recommendations for research

At room temperature, occupational exposure of AIBN will be via inhalation of particles. For this situation the following studies are recommended:

- toxicokinetic studies, investigating the possible formation of HCN in rodents, as was indicated in previous studies;
- short-term toxicity studies in rodents (28-day or 90-day toxicity studies by inhalation or by dermal exposure), including neurotoxicity;
- long-term toxicity and carcinogenicity (based on the results of genotoxicity studies);
- basic genotoxicity studies, such as chromosomal aberration assays.

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Annexes

Bijlage **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the

case of genotoxic carcinogens, a ‘exposure versus tumour incidence range’ and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

Bijlage **B**

The committee

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- P Boogaard
  toxicologist; Shell International Petroleum Maatschappij, The Hague
- PJ Borm
  toxicologist; Heinrich Heine Universität Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- DJJ Heederik
  epidemiologist; University of Utrecht, Utrecht
- LCMP Hontelez, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- TM Pal
  occupational physician; Nederlands Centrum voor Beroepsziekten, Amsterdam
- IM Rietjens
  professor of toxicology; Wageningen University, Wageningen.
- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, The Hague

- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- RA Woutersen
  pathologist; TNO Nutrition and Food Research, Zeist
- P Wulp
  occupational physician; Labour Inspectorate, Groningen
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, The Hague
- JM Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

The first draft of the present advisory report was prepared by A Rutten, IA van de Gevel and F de Vrijer, from TNO, Department of Occupational Toxicology, Zeist, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance: mw T van der Klugt.
Lay-out: J van Kan.

Bijlage **C**

Comments on the public review draft

A draft of the present report was released in 1995 for public review. The following person and organisation commented on the draft document:

- JI Delic, Health & Safety Executive, Merseyside, United Kingdom.

Bijlage **D**

Tetramethyl succinonitrile: (CAS reg no: 3333-52-6)

health-based reassessment of administrative occupational exposure limits

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

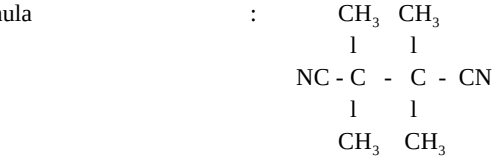
1 Introduction

The present document contains the assessment of the health hazard of tetramethyl succinonitrile 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 and Chemical Abstracts, starting from 1966, 1988 and 1970, respectively. Also Current contents and CD-ROM data bases from HSEline, Cisdoc, Mhidas and NIOSHtic, which cover the period up to and including 1997, were consulted. Another CD-ROM data base, from Poltox (Toxline, Cambridge Scient. Abstr. and FSTA), contained information on the period up to and including 1994. The following key words were used: tetramethyl succinonitrile, TMSN, and 333-52-6. The final literature search was carried out in May 1998.

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	:	tetramethyl succinonitrile
synonyms	:	tetramethyl succinyl acid dinitrile tetramethyl butanedinitrile
molecular formula	:	$C_8H_{12}N_2$
structural formula	:	
CAS reg no	:	3333-52-6

3 Physical and chemical properties

molecular weight	:	136.2
boiling point	:	-
melting point	:	170^0C (sublimes)
vapour pressure	:	-
solubility in water	:	insoluble
log $P_{octanol/water}$	:	1.11 (estimated)
conversion factors (20^oC, 101.3 kPa)	:	1 mg/m^3 = 0.18 ppm 1 ppm = 5.68 mg/m^3

Data from ACG99, http://esc.syres.com

Tetramethyl succinonitrile (TMSN) is an odourless and colourless crystalline solid material.

4 Uses

TMSN and nitrogen are released when the blowing agent, azo-bisisobutyronitrile, is heated and decomposes during the production of vinyl foam. TMSN is also the by-product of a polymerisation catalyst in photocopier toner (ACG99).

5 Biotransformation and kinetics

Hathaway *et al.* (Hat91) reported that uptake occurs after inhalation and through the skin, but no quantitative data are available. There is no specific information on the metabolism and excretion of this compound. Since tetramethyl succinonitrile belongs to the group of organic compounds that contain a cyanogroup as the characteristic functional group, it can be surmised that the compound will undergo biotransformation to cyanide, which is further metabolised to thiocyanate.

6 Effects and mechanism of action

Human data

Reinl (Rei57) reported five cases of acute accidental occupational exposure to tetramethyl succinonitrile. All cases showed about the same symptoms. After inhalation they got unconscious with convulsions. Further investigations on workers employed at the same factory displayed that some symptoms were prominent in the group: frequent headaches, excessive salivation and sense of taste, nausea, and vomiting. No exposure levels were reported.

Animal data

Harger and Hulpieu (Har49, abstract only), reported that experimental animals poisoned with tetramethyl succinonitrile exhibited violent convulsions, with asphyxial death between 1 minute and 5 hours after the first convulsion. The subcutaneous LD_{50} was 30 mg/kg bw in rats and 23 mg/kg bw in guinea pigs. The intravenous LD_{50} was 20 mg/kg bw in rabbits. A dose of 2.5 mg/kg bw caused convulsions. In rats, inhalation of 60 ppm (341 mg/m^3) of tetramethyl succinonitrile was fatal in 2 to 3 hours, and a concentration of 6 ppm (34 mg/m^3) was fatal in about 30 hours.

Reinl (Rei57) studied ten rats injected intraperitoneally with 5 mg/kg bw/day tetramethyl succinonitrile during 14 successive days. During the experiment and postexperimental observation the animals did not show any effects. However, the authors did not describe the clinical parameters they used in their experiment. They only reported that the body weights were even increased. No control group was used in this experiment.

Johannsen and Levinskas (Joh86) performed well conducted subchronic toxicity studies in rats and dogs. First, they performed a pilot study in which they found a single oral rat LD_{50} of TMSN of 38.9 (31.5 - 46.1) mg/kg bw. Next, they performed three subchronic gavage studies in rats. In the first study, groups of 15 male and 15 female rats were administered 0, 1, 3 or 10 mg/kg bw/day TMSN during 90 days. Clinical chemistry as well as pathological examinations of all organs of the exposed and control groups were performed. The authors found treatment-related morphological changes in the kidney of male, but not female rats at all dosage levels. These changes mainly consisted of degeneration of the proximal convoluted

tubules, also some of the distal convoluted tubules were affected. Hyaline droplet formation was observed in the cytoplasm of epithelial cells lining the tubules. Treatment-related liver changes were also seen in both male and female rats given 10 mg/kg bw/day TMSN. Microscopic changes consisted of enlarged hepatocytes in the centrilobular and midzonal regions of the liver. Absolute and relative liver weights were significantly increased in rats exposed to doses of 3 mg/kg bw/day TMSN or higher.

In the second study, groups of 15 male rats were administered 0, 0.1, 0.3 or 1.0 mg/kg bw/day TMSN for 90 days. Similar effects on the kidneys as in the first study were found. The renal changes were consistent with the definition of renal nephrosis. Again, numerous hyaline droplets were observed in the cytoplasm of epithelial cells of the tubules. No other toxicological effects were found.

The third gavage subchronic study was performed to determine the no-adverse effect level of renal tubular nephrosis in male rats. Groups of 15 male rats were administered 0, 0.001, 0.01 or 0.1 mg/kg bw/day TMSN during 90 days. At doses of 0.001 and 0.01, no microscopic changes were observed in the kidneys. The authors concluded that the no-observed-adverse-effect level (NOAEL) for effects on the kidney of male rats was 0.01 mg/kg bw/day TMSN.

A study on male rats using a dose of 0.3 mg/kg bw/day during 90 days and an observation period of 7 days showed that the effects on the kidney were reversible. The kidney as target organ in male rats was also found when TMSN was administered via drinking water.

The authors also performed a similar experiment in dogs (4 groups of 4 males and 4 females). TMSN was administered via gelatin capsules for 90 days. The doses were equivalent to 0, 0.3, 1.0 and 3.0 mg/kg bw/day. In the female dogs body weight gain was slightly suppressed. In 4 out of 8 dogs (3 female, one male) of the highest dose group relative liver weights were significantly increased at necropsy. No (microscopic) histological effects related to the treatment in either liver or kidney were found. Blood cyanide concentrations among the treated animals were comparable to the untreated controls, as well as haematological and urine analyses.

There is no data available on long-term exposure, carcinogenicity, mutagenicity, genotoxicity and reproduction toxicity.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for tetramethyl succinonitrile in the Netherlands is 3 mg/m^3 (0.5 ppm), 8-hour TWA, with a ‘skin’ notation (SZW99).

Existing occupational exposure limits for tetramethyl succinonitrile in various countries are summarized in the annex.

8 Assessment of health hazard

Accidental exposure of workers to tetramethyl succinonitrile caused acute systemic toxicity, with convulsions as the most prominent symptom. No data on exposure concentrations are available.

The committee considers the subchronic gavage experiment performed by Johanson and Levinkas (Joh86) as the key study. In this study, a no-observed- adverse-effect level (NOAEL) of 0.01 mg/kg bw per day TMSN was found for effects on the kidneys of male rats only (not in female rats, nor in male or female dogs). However, the committee considers the kidney effects, among which hyaline droplet formation, as not relevant to man because it is thought to be induced by the accumulation of the male rat-specific protein α-2u-globulin.

The committee considers the liver to be the target organ. Liver effects were found in male and female rats (increased relative liver weight and microscopic cellular changes) and dogs (increased relative liver weight) (Joh86). These effects were observed in rats (3 and 10 mg/kg bw/day) and in dogs (3 mg/kg bw/day). This means that the NOAEL for liver effects in both species is 1 mg/kg bw/day TMSN administered during 90 days.

The committee uses the NOAEL of 1 mg/kg bw/day in rats as a starting point for the assessment of a health-based recommended occupational exposure limit (HBROEL). Since workers are exposed for 5 days a week this NOAEL from a continuous feeding study (*i.e.*, 7 days/week) is adjusted by multiplying with a factor of 7/5, resulting in a no-adverse-effect level (NAEL) of 1.4 mg/kg bw/day. For differences in caloric demand between rats and humans the committee applies a scaling factor of 4. To account for inter- and intraspecies variation and the duration of exposure, the committee considers an overall assessment factor of 12 to be appropriate for the extrapolation of the subchronic oral NAEL in rats to a working lifetime exposed worker. A lower factor for interspecies variation is justified because the effects on the liver were found in two species and the effect levels were comparable. After applying the overall factor and assuming 100% absorption, an average body weight of a worker of 70 kg and a breathing volume of 10 m^3 per working day*, the committee recommends a preferred value of 0.2 mg/m^3, 8-hour TWA.

The committee recommends a health-based occupational exposure limit for tetramethyl succinonitrile of 0.2 mg/m^3 (0.036 ppm) as an 8-hour time-weighted average (TWA).

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* (1.4 mg/kg : (4 x 12)) x (70 kg : 10 m^3)

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Table 1 Occupational exposure limits for tetramethyl succinonitrile 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	0.5	3	8 h	administrative	S	SZW01
Germany						
-AGS	0.5	3	8 h		S	TRG00
	2	12	15 min			
-DFG MAK-Kom.	-	-[c]			S	DFG01
Great-Britain						
-HSE	0.5	2.8	8 h	OES	S	HSE01
	2	11	15 min			
Sweden	-	-				Arb00b
Denmark	0.5	3	8 h		S	Arb00a
USA						
-ACGIH	0.5	-	8 h	TLV	S	ACG01
-OSHA	0.5	3	8 h	PEL	S	
-NIOSH	0.5	3	10 h	REL	S	
European Union						
-SCOEL	-	-				CEC00

[a] S = skin notation; skin uptake can contribute substantially to the body burden; sens = substance can cause sensitisation.

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

[c] Listed among substances for which studies of the effects in man or in experimental animals have yielded insufficient information for the establishment of a MAK value

Bijlage **E**

Abbreviations

bp	boiling point
EC_{50}	concentration at which a described effect is found in 50% of the exposed animals or at which the effect is decreased up to 50% of the control value
HBR-OEL	health based recommended occupational exposure limit
h	hour
IC_{50}	concentration at wAbbreviationshich inhibition of a certain function is found up to 50% of the control value
LC_{50}	lethal concentration for 50% of the exposed animals
LC_{lo}	lowest lethal concentration
LD_{50}	lethal dose for 50% of the exposed animals
LD_{lo}	lowest lethal dose
LOAEL	lowest observed adverse effect level
MAC	maximaal aanvaarde concentratie (maximal accepted concentration)
MAEL	minimal adverse effect level
MAK	Maximale Arbeitsplatz Konzentration
MOAEL	minimal observed adverse effect level
MTD	maximum tolerated dose
NAEL	no adverse effect level
NEL	no effect level
NOAEL	no observed adverse effect level
OEL	occupational exposure limit
PEL	permissible exposure limit
ppb	parts per billion $(v/v)10^{-9}$
ppm	parts per million $(v/v)10^{-6}$
RD_{50}	concentration at which a 50% decrease of respiratory rate is observed
REL	recommended exposure limit

STEL	short term exposure limit
tgg	tijd gewogen gemiddelde
TLV	threshold limit value
TWA	time weighted average
V_{max}	maximal reaction velocity of an enzyme

Organisations

ACGIH	American Conference of Governmental Industrial Hygienists
CEC	Commission of the European Communities
DECOS	Dutch Expert Committee on Occupational Standards
DFG	Deutsche Forschungsgemeinschaft
EPA	Environmental Protection Agency (USA)
FDA	Food and Drug Administration (USA)
HSE	Health and Safety Executive (UK)
IARC	International Agency for Research on Cancer (WHO)
INRS	Institut National de Recherche et de Sécurité (France)
NIOSH	National Institute for Occupational Safety and Health (USA)
NTP	National Toxicology Programme (USA)
OECD	Organisation for Economic Cooperation and Development
OSHA	Occupational Safety and Health Association (USA)
RTECS	Registry of Toxic Effects of Chemical Substances
SER	Social and Economic Council (Sociaal-Economische Raad NL)
WATCH	Working Group on the Assessment of Toxic Chemicals (UK)
WHO	World Health Organisation

Toxicological terms

bid	*bis in diem* (twice per day)
bw	body weight
CARA	chronic non-specific respiratory diseases
CHD	coronary heart disease
CNS	central nervous system
ECG	electrocardiogram
EEG	electro encephalogram
FCA	Freunds Complete Adjuvans
FEV	forced expiratory volume
FSH	follicle stimulating hormone
GD	gestation day(s)
GPMT	guinea pig maximisation test
GSH	glutathione
HLiA	hamster liver activated
IHD	ischaemic heart disease
im	intramuscular
ip	intraperitoneal
ipl	intrapleural
it	intratracheal
iv	intravenous
LH	lutheinising hormone
MAC	minimal alveolar concentration

MFO	mixed function oxidase
NA	not activated
PNS	peripheral nervous system
po	*per os* (= oral)
RBC	red blood cells
RLiA	rat liver activated
SCE	sister chromatid exchange
sc	subcutaneous
UDS	unscheduled DNA-synthesis

Statistical terms

GM	geometric mean
OR	Odds Ratio
RR	relative risk
SD	standard deviation
SEM	standard error of mean
SMR	standard mortality ratio

Analytical methods

AAS	atomic absorption spectroscopy
BEEL	biological equivalent exposure limit
BEI	biological exposure index
BEM	biological effect monitoring
BM	biological monitoring
ECD	electron capture detector
EM	environmental monitoring
FID	flame ionisation detector
GC	gas chromatography
GLC	gas liquid chromatography
GSC	gas solid chromatography
HPLC	high performance liquid chromatography
IR	infrared
MS	mass spectrometry
NMR	nuclear magnetic resonance
PAS	personal air sampling
TLC	thin layer chromatography
UV	ultraviolet

Bijlage **F**

DECOS-documents

DECOS has produced documents on the following substances.

To be ordered from the Health Council of the Netherlands:

Aanpassing van grenswaarden bij flexibele werktijden	2001/06OSH
Acetone cyanohydrin	1995/05WGD
p-Aramid fibres	1997/07WGD
Azathioprine	1999/04OSH
Aziridine (ethyl imine)	2000/13OSH
1,2,3-Benzotriazole	2000/14OSH
Bisphenol A and its diglycidylether	1996/02WGD
Bromoethane	1998/10WGD
1,2-and t-Butanol	1994/10
n-, iso-, sec-, tert-Butylacetaten	2001/03OSH
β-Butyrolactone	1999/05OSH
Cadmium and inorganic cadmium compounds	1995/04WGD
Calculating cancer risk	1995/06WGD
Carbadox	1999/06OSH
Carbon disulphide	1994/08
Chlorine dioxide	1995/07WGD
p-Chloroaniline	1998/09WGD
4-Chloro-o-toluidine	1998/08WGD
Chlorotrimethylsilane	2001/05OSH
Chromium and its inorganic compounds	1998/01WGD
Cresols	1998/15WGD
1996-1997 WGD-rapporten/1996-1997 DECOS reports	1999/01WGD
1,2-Dichloroethane	1997/01WGD

Diethylsulphate	1999/08/OSH
Diglycidyl resorcinol ether	1999/09OSH
Diphenylamine	1997/05WGD
Epichlorohydrin (1-Chloro-2,3-epoxypropane)	2000/10OSH
1,2-Epoxybutane	1998/11WGD
1,2-Ethanediamine	1996/03WGD
Ethyleneglycol ethers	1996/01WGD
Ethylene thiourea	1999/03OSH
Formamide and dimethylformamide	1995/08WGD
Hydrazinoethanol, phenylhydrazine, isoniazid, maleic hydrazide	1997/03WGD
Isopropyl acetate	1997/04WGD
Lactate esters	2001/04OSH
Lindane	2001/07OSH
Man made mineral fibers	1995/02WGD
2-Meathylaziridine (propylene imine)	1999/10OSH
Methyl Methacrylate	1994/09
Methacrylates. Ethyl methacrylate, n-butyl methacrylate and isobutyl methacrylate	1994/11
Methyl-t-butylether	1994/23
Methyl chloride	1995/01WGD
4,4'-Methylene bis (2-Chloroaniline)	2000/09OSH
4,4'-Methylene dianiline	2000/11OSH
Metronidazole	1999/11OSH
2-Nitropropane	1999/13OSH
N-Nitrosodimethylamine (NDMA)	1999/12OSH
2-Nitrotoluene	1998/12WGD
Pentaerythritol	1997/06WGD
Phenol	1996/04WGD
o-Phenylenediamine	1998/06WGD
Piperidine	1997/08WGD
Procarbazine hydrochloride	1999/14OSH
1- and 2-Propanol	1994/24
Propylene oxide	1997/02WGD
Ronidazole	1998/05WGD
Styrene	1998/07WGD
Quartz	1998/02WGD
1,1,1-Trichloroethane	1995/03WGD
1,2,3-Trichloropropane	1994/25
1,2,3-Trichloropropane	1998/14WGD
Urethane (ethyl carbamate)	200012OSH
Vinylbromide	1999/15OSH
Wood dust	1998/13WGD