Indene

(CAS reg no: 95-13-6)

Health-based Reassessment of Administrative Occupational Exposure Limits

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

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1 Introduction

The present document contains the assessment of the health hazard of indene 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 C de Heer, Ph.D. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of indene 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 online data bases 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), and using the following key words: indene, inden, and 95-13-6. HSDB and RTECS, databases available from CD-ROM, were consulted as well (NIO98, NLM98). The final literature search has been carried out in October 1997, followed by an additional search in May 2001.

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

2 Identity

name	:	indene
synonyms	:	indonaphtene; inden; 1*H*-indene
molecular formula	:	C_9H_8
structural formula	:	
CAS reg no	:	95-13-6

Data from ACG91, Ric94.

3 Physical and chemical properties

molecular weight	:	116.15
boiling point	:	181.6°C
melting point	:	-1.8°C
flash point	:	78.33°C (closed cup)
vapour pressure	:	at 25°C: 0.15 kPa
solubility in water	:	insoluble
Log $P_{octanol/water}$	:	2.92
conversion factors (20°C, 101.3 kPa)	:	1 ppm = 4.8 mg/m^3 1 mg/m^3 = 0.21 ppm

Data from ACG91, Dys76, NLM98, Ric94.

Indene is a colourless liquid. An odour threshold of 0.015-0.06 ppm (0.07-0.32 mg/m^3) has been reported in humans. Indene oxidises readily in air and forms polymers on exposure to air and sunlight (ACG91, Dys76, Ric94).

4 Uses

Indene is used in the preparation of coumarone-indene resins, in paint and coating manufacture, in tile manufacture, and as a chemical synthesis intermediate (ACG91, Ric94).

5 Biotransformation and kinetics

In rats, the occurrence of 1,2-epoxyindene was described as an intermediate in the conversion of indene into *trans*-indane-1,2-diol and into *S*-(hydroxyindanyl)glutathione by liver preparations. In *in vivo* experiments in rats, significant amounts of 1-hydroxyindan-2-ylmercapturic acid were excreted in urine of animals dosed with indene and a number of its derivatives, including the 1,2-epoxyindene (Ker78, see Annex I for a metabolism scheme for indene).

Male Hartley guinea pigs were administered 14.3 and 100 mg/kg indene by intraperitoneal injection. The animals showed the presence of two isomers of hydroxy(methylthio)indane in urine. The major isomer, 2-hydroxy-1-methylthioindane (I) was present as 5.9-9.0% of the administered dose after 24 hours, while lower amounts (0.2-0.9) of another minor isomer (II)

were observed. A significant amount of isomer I was found as a urinary metabolite of indene oxide (12.7-15.3% of 12.5 mg/kg, ip). To further elucidate the route of formation of isomer I, the glutathione and mercapturic acid conjugates of indene oxide were synthesised and administered to the guinea pig. It was found that isomer I was present as a significant urinary metabolite of both conjugates of indene oxide, comprising 6.6-12.6% and 5.7% of the dose of the glutathione (11.6-18.5 mg/kg bw, ip) and mercapturic acid conjugates (8.1 mg/kg bw, ip), respectively. The results indicate that the formation of a hydroxy(methylthio)indane is a significant route of metabolism for indene in the guinea pig, and that this metabolite arises via further metabolism of conjugates in the glutathione pathway. In male Sprague-Dawley rats, isomer I was found to be a minor metabolite (Bar86).

The oxidation of indene to *cis*- and/or *trans*-1,2-dihydroxyindane was demonstrated *in vitro* in rats and rabbits. This reaction was mediated by liver microsomes in the presence of NADPH-generating systems (NLM98).

Based on the physico-chemical properties of indene (molecular weight: 116.15, log $P_{octanol/water}$: 2.92), significant skin absorption is considered likely.

6 Effects and mechanism of action

Human data

Quantitative indene vapour inhalation exposure of human subjects has not been reported. However, by analogy between chemical structure and toxicological effects of related monoaromatic hydrocarbons (not specified), inhalation of indene vapours can be expected to cause irritation of the mucous membranes (ACG91).

Sensitising actions of coumarone and indene, used in copolymerisation when making coumarone-indene resins, have been noticed. The use of these resins contaminated with traces of monomers can cause allergic dermatitis (data not further specified) (NLM98).

Animal data

ACGIH stated that liquid indene can remove natural tissue fats and oils on prolonged or repeated contact with the skin which may lead to dermatitis (ACG91). However, no local cutaneous toxicity developed from painting the shaved skin of rats one to 8 times with 0.1 mL of indene liquid. Guinea pigs were

similarly unaffected by 3 applications of 0.5 mL of indene, indicating that repeated dermal contact failed to elicit skin irritation (ACG91).

The acute inhalation 4-hour LC_{50} for indene in rats was reported to be >5000 mg/m^3 (>1050 ppm) (Ter87) and 14,000 mg/m^3 (2940 ppm) (Dys76, NIO98, NLM98). The aspiration of the liquid indene into the lung resulted in chemical pneumonitis, pulmonary oedema, and haemorrhage in laboratory animals (ACG91). The threshold of acute toxicity for rats was 200 mg/m^3 (approximately 42 ppm) (Dys76).

No data are available on dermal LD_{50} values.

The oral LD_{50} values of indene were 2300 and 1800 mg/kg bw for rats and mice, respectively (Dys76). Indene appears to be fairly well tolerated after oral administration. No evidence of systemic toxicity was seen in adult rabbits following a single dose of 1000 mg . However, when the same amount of indene was injected subcutaneously in rats, fatty livers and fatalities resulted. High oral doses of indene (2.5 mL of a 1:1 v/v mixture in olive oil) were fatal to rats, revealing characteristic changes in the liver, lungs, and gastrointestinal tract (ACG91). The intraperitoneal LD_{50} for indene was reported to be 2300±360 mg/kg and 1800±200 mg/kg for rats and mice, respectively (NLM98)

Rats exposed to the vapour of indene at concentrations of 800-900 ppm (3870-4356 mg/m^3), 7 hours/day, for 6 days, showed liver damage and occasionally splenic and renal injury. Severe haemorrhagic liver necrosis occurred in some rats. Histological changes in the kidneys consisted of focal necrosis resembling small infarcts. No changes in blood constituents or in the adrenals, pancreas, pituitary, ovaries, or testes were found. No deaths resulted from these exposures (study from 1939 cited in ACG91).

Continuous exposure of rats to indene vapours for 105 days at 3 mg/m^3 (0.63 ppm) was associated with elevated blood cholinesterase activity and inhibition of catalase in the exposed animals. Histological analysis of internal organs indicated haemodynamic disturbances. No evidence of toxicity (including body weight changes, haematology, free SH-protein levels, peroxidase activity) was observed at 0.6 mg/m^3 (0.13 ppm) (Dys76). The committee considers this study inadequate for use in deriving a health-based occupational exposure limit. Exposure was continuous and it was not clear whether a control group was included. No details, quantitative data, incidences were presented. Further, the toxicological relevance of a change in whole blood catalase activity is unclear while with respect to cholinesterase activity, it was not clear whether it was

measured in plasma or red blood cells, the former being toxicologically not relevant.

No evidence of generalised systemic toxicity was observed when painting the shaved skin of rats one to 8 times with 0.1 mL or of guinea pigs 3 times with 0.5 mL of indene liquid (ACG91).

Indene, tested at 12 dose levels ranging from 0.35 to 3485 µg/plate with and without metabolic activation, was negative in mutagenicity assays using *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 (Cur82, Flo80).

Indene inhibited growth of murine ascites sarcoma B P8 cells *in vitro* (100% inhibition at 1 mM, 9% inhibition at 0.1 mM) (Pil75).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for indene in the Netherlands is 45 mg/m^3 (10 ppm), 8-hour TWA.

Existing occupational exposure limits for indene in some European countries and in the USA are summarised in Annex II.

8 Assessment of health hazard

The committee did not find human data on the effects of indene following exposure by inhalation.

Oxidation of indene either or not followed by glutathione conjugation, has been demonstrated to be a major route of detoxification in rats and guinea pigs. In guinea pigs, up to 9% of an intraperitoneally administered dose of indene was excreted within 24 hours as the metabolite 2-hydroxy-1-methylthioindane. In rats, urinary excretion of mercapturic acids of indene has been described.

Indene was not irritating to the skin of rats and guinea pigs. The committee did not find data on the potential eye irritating or sensitising properties of indene.

Indene does not need classification on the basis of its acute inhalation toxicity (4-hour LC_{50}: >5000 mg/m^3) or acute oral toxicity (LD_{50} rat: 2300 mg/kg). There are no data available on acute dermal toxicity of indene.

Indene was negative in mutagenicity tests in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation.

The committee did not find adequate data on toxicity following intermittent repeated exposure by inhalation nor on carcinogenicity or reproduction toxicity.

The committee considers the toxicological data base on indene 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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ACG00 American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2000. Cincinnati OH, USA: ACGIH®, Inc, 2000: 67

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: 36.

Arb00a Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2000; (At-vejledning C.0.1).

Arb00b Arbetarskyddstyrelsen. Hygieniska gränsvärden och åtgärder mot luftföroreningar. Solna, Sweden: National Board of Occupational Safety and Health, 2000; (Ordinance AFS 2000/3).

Bar86 Bartels MJ, Horning EC, Horning MG. Formation of methylthio metabolites of indene in the guinea-pig and the rat. Drug Metab Dispos 1986; 14: 97-101.

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.

Cur82 Curvall M, Florin I, Jansson T. Mutagenicity of some indoles and related compounds in the Ames test. Toxicology 1982; 23: 1-10.

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).

Dys76 Dyshinevich NE. Hygienic studies of the maximum permissible emission level of indene from polymer construction materials. Gig Sanit 1976; 4: 104-5 (translated from article in Russian).

Flo80 Florin I, Rutberg L, Curvall M, *et al.* Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicology 1980; 18: 219-232.

HSE01 Health and Safety Executive (HSE). EH40/2001. Occupational Exposure Limits 2001. Sudbury (Suffolk), England: HSE Books, 2001: 19.

Ker78 Kerdel FA, Bick RJ, Hopkins RP, *et al.* The role of 1,2-epoxyindene in the metabolism of indene in vivo. Biochem Soc TRans 1978; ^: 785-7.

NIO98 National Institute of Occupational Safety and Health (NIOSH). Registry of Toxic Effects of Chemical Substances (RTECS) [CD-ROM, issue April 1998. SilverPlatter International, 1998 (last update indene file: December 1997).

NLM98 US National Library of Medicine (NLM). Hazardous Substances Data Bank (HSDB). [CD-ROM], issue April 1998. SilverPlatter International, 1998 (last update indene file: March 1998).

Pil75 Pilotti A, Ancker K, Arrhenius E, *et al.* Effects of tobacco and tobacco smoke constituents on cell multiplication in vitro. Toxicology 1975; 5: 49-62.

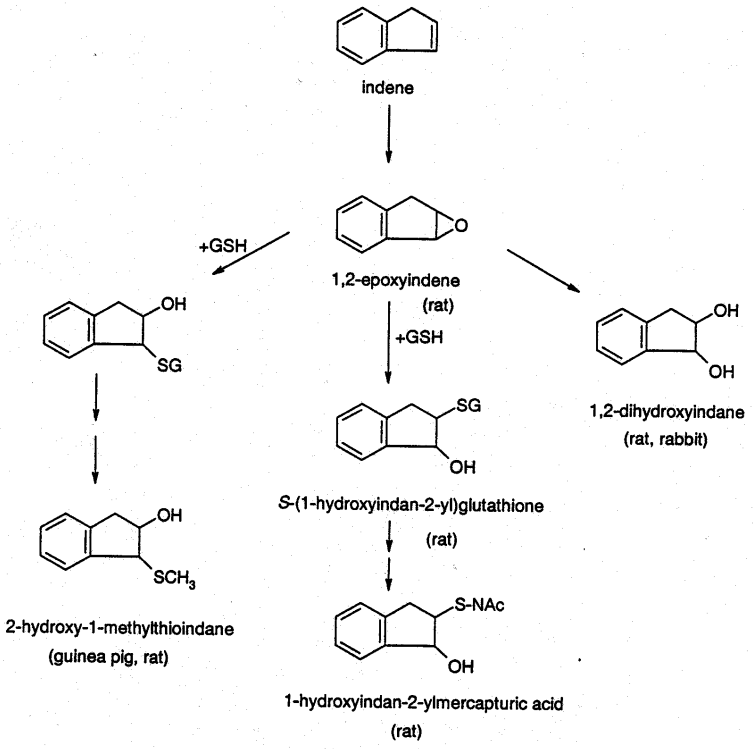
Ric94 Richardson ML, Gangolli S, eds. I19 1H-Indene. In: The dictionary of substances and their effects. (Vol. 5). Cambridge, UK: Royal Society of Chemistry 1994: 25-6.

SZW01 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2001. The Hague, the Netherlands: Sdu, Servicecentrum Uitgevers, 2001: 30.

Ter87 Terril JB. Acute inhalation toxicity study with indene in the rat. Rockville MD, USA: Hazleton Laboratories: 1987 (report submitted to US EPA by BP Chemicals Inc; available from NTIS, Springfield VA, USA: order no OTS0556080).

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

Annex I



Metabolism scheme for indene (Bar86, Ker78, NLM98).

Annex II

Occupational exposure limits for indene 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 of Social Affairs and Employment	10	45		administrative		SZW01
Germany						
-AGS	-	45	8 h			TRG00
-DFG MAK-Kommission	-	-				DFG01
Great-Britain						
-HSE	10	48	8 h	OES		HSE01
	15	72	15 min			
Sweden	-	-				Arb00b
Denmark	10	45	8 h			Arb00a
USA						
-ACGIH	10	48	8 h	TLV		ACG01
-OSHA	-	-				ACG00
-NIOSH	10	45	10 h	REL		ACG00
European Union						
-SCOEL	-	-				CEC00

[a] S = skin notation; this 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