Bornan-2-one (camphor, synthetic)

(CAS reg no: 76-22-2)

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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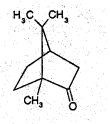
1 Introduction

The present document contains the assessment of the health hazard of bornan-2-one 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 A Spooren, Ph.D., and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of bornan-2-one has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the online data bases Medline, Toxline, and Chemical Abstracts covering the period 1966 to 26 April 1999 (19990426/UP), 1965 to 29 January 1999 (19990129/ED), and 1967 to 24 April 1999 (19990424/ED; vol 130, iss 18), respectively, using the following key words: camphor and the CAS registry numbers 76-22-2, 464-49-3, or 464-48-2. HSDB and RTECS, data-bases available from CD-ROM, were consulted as well (NIO99, NLM99). The final literature search has been carried out in April 1999.

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

2 Identity

name	:	bornan-2-one
synonyms	:	camphor[a], 2-bornanone, 2-camphanone, 2-keto-1,7,7-trimethylnorcamphane, 1,7,7,-trimethylnorcamphor, 1,7,7-trimethylbicyclo(2.2.1)heptan-2-one, 2-oxo-1,7,7-trimethyl-bicyclo[2.2.1]heptane
molecular formula	:	$C_{10}H_{16}O$
structural formula	:	
CAS reg no	:	76-22-2 (DL-camphor) 464-49-3 (D-camphor) 464-48-2 (L-camphor)

[a] Name used in this document

3 Physical and chemical properties

molecular weight	:	152,23
boiling point	:	204°C
melting point	:	180°C
flash point	:	66°C (closed cup)
vapour pressure	:	at 20°C: 24 Pa
solubility in water	:	insoluble
log $P_{octanol/water}$	:	3.04 (estimated)
conversion factors (20°C, 101.3 kPa)	:	1 ppm = 6.34 mg/m^3 1 mg/m^3 = 0.16 ppm

Data from ACG99, NLM99, http://esc.syres.com

Synthetic DL-camphor is a colourless to translucent or white crystalline substance with a characteristic aromatic odour. A natural form, derived from the gum of the camphor tree, is optically active. Otherwise, the natural and the synthetic material appear to be identical. Odour thresholds ranging from 0.018 to 16 ppm (0.11-100 mg/m^3) have been reported.

4 Uses

Camphor is used as a plasticiser for cellulose esters and ethers, in explosives, varnishes, lacquers, insecticides, moth and mildew preventives, tooth powder, pharmaceuticals, flavourings, embalming substances, cosmetics, and pyrotechnics. It is also used as a chemical intermediate (ACG99).

5 Biotransformation and kinetics

There were no data on the kinetics of camphor following exposure by inhalation.

Without providing details, it was stated that following ingestion of pure camphor or of alcoholic solutions, absorption is quite rapid, and constant from oil preparations. Camphor is slowly absorbed from subcutaneous or intramuscular depots (Ric93).

Gas chromatographic/mass spectrometry analysis of urine from two men having ingested 6-10 g camphor showed the presence of 6 metabolites. It was concluded that the main metabolic pathways are hydroxylation in the 3-, 5-, 8-,

and 9-position, and subsequent oxidation to a corresponding ketone and carbonic acid. No conjugated alcohols were detected, and only a glucuronidated carbonic acid was found (Köp82). From a case of intentional intoxication, in which camphor was detected in umbilical cord blood, the amniotic fluid, and fetal tissues (brain, liver, kidneys), it was seen that camphor can cross the placenta (Rig65).

The toxicokinetics of DL-camphor after dermal application were studied in $B6C3F_1$ mice and F344 rats. Single (3 dose levels) or repeated (7 days) doses were administered to male and female rats and mice; application sites were not occluded but either protected or unprotected from grooming (method of protection could not be derived from the available data). Single doses were approximately 40, 167, and 348 mg/kg for rats and approximately 176, 428, and 935 mg/kg for mice. Analyses concerned only DL-camphor, metabolites were not looked for. The experiments showed that approximately 70% of an uncovered dermally applied dose was lost in male rats due to volatilisation. A similar percentage lost by volatility was assumed for female rats and for mice, although the surface area and the dose volume administered were different for mice and rats. Less than 1% was recovered from the application site after 24 hours, indicating that the remaining 30% had penetrated into the skin.* Plasma kinetics after dermal and intravenous administration were compared for determination of the bioavailability. In mice, DL-camphor given as a single intravenous injection (47 mg/kg) was rapidly eliminated from the plasma to undetectable levels after 3 hours. After single dermal application, the $t_{½}$ ranged from 66 to 112 min and from 104 to 131 min for male and female mice, respectively. A dose-proportional increase in plasma concentration, although not linear, was observed after single dermal administration. A large apparent volume of distribution after dermal application was suggestive of an extensive tissue distribution. Elimination of DL-camphor appeared to be slower in mice (studied in males only) when the application site was protected from grooming, although plasma AUC was not changed. Mean plasma peak concentrations were higher after single *versus* repeated administration (studied in males only). In rats, a biphasic elimination was observed after a single intravenous dose (approximately 6.7 mg/kg). DL-Camphor was still detectable 10 hours after administration. After single dermal application, the $t_{½}$ ranged from 161 to 303 min and from 94 to 246 min for

* Camphor was recovered in volatiles traps. The possible contributions of volatility from exhaled camphor after absorption was studied in a separate intraperitoneal experiment. The appendix in which the methods used to measure camphor loss from the dermal application site was not present in the copy of the study report sent to the committee.

male and female rats, respectively. Dose proportionality (not linear) was observed after single dermal administration. Unlike in mice and in male rats, protection from grooming was found to affect bioavailability in female rats. In protected animals, 2-4% of the effective dermal dose (corrected for the 70% loss due to volatility) was bioavailable *versus* 7-8% in unprotected animals. Plasma kinetics were comparable for single *versus* repeated dermal exposure in both male and female rats (Gri96, Spa97).

Urinary excretion data from experiments in rabbits and dogs suggest that metabolism of camphor occurs either by hydroxylation of a methylene group (in conjunction with cytochrome P-450) or by reduction of the oxo group (Ric93, Rob69). In rabbits (n=5), *ca*. 59, 44, and 33% of single oral doses of 290-533 mg D-, 290-426 mg L-, and 122-259 mg DL-camphor/kg bw were excreted in the urine as glucuronides of 5-*endo*-hydroxycamphor and 3-*endo*-hydroxycamphor, borneol, and trace amounts of isoborneol. The proportions of borneol, 3-*endo*- and 5-*endo*-hydroxycamphor were 1.00:0.88:2.80 and 1.00:2.4:5.00 for D- and L-camphor, respectively (Rob69). According to Leibman and Ortiz, the analytical method applied by Robinson and Hussain was incapable of separating *endo*- and *exo*-isomers. In *in vivo* (one rabbit, one dog) experiments, the former authors found D-camphor to be metabolised to 3-hydrocamphor (probably *endo*) and both 5-*endo*- and 5-*exo*-hydroxycamphor. In *in vitro* (rabbit and rat liver preparations) experiments, interconversion of the 5-hydroxy isomers via 2,5-bornanedione is possible. In addition, borneol and some small amounts of isoborneol were formed in rabbits (Lei73).

Significant increases in activities of cytochrome P450, cytochrome b_5, aryl hydrocarbon hydroxylase, and glutathione S-transferase were found in the livers of female mice (Swiss; n=8) given daily doses of 300 mg/kg/bw camphor by gavage, for 20 days, while this was not seen after repeated dosing of 50 or 150 mg/kg bw (Ban95).

6 Effects and mechanism of action

Human data

Little is known about the risk of occupational exposure to camphor. The committee did find only one report, on a survey in a camphor-packaging plant. In this survey, concentrations of camphor dust and vapour up to *ca*. 200 mg/m^3 were found in a first sampling period. The industrial hygienists involved

experienced very slight (transient) eye irritation, a strong odour of camphor, and a (transient) olfactory fatigue during the first survey during which they themselves were exposed to levels of *ca*. 30 to 40 mg/m^3. The workers complained of similar symptoms. Due to exposure-reducing measures, concentrations were lowered to 3 to 3.5 mg/m^3 in a second sampling period, during which the hygienists noticed a slight odour of camphor only. After exposure-reducing measures had been introduced, 6 workers of which only 2 were actually exposed at that time were examined physically and interviewed. Apart from moderate inflammation of nose and throat in 4 of them, there were no significant findings. Besides shortness of breath on stair climbing and numbness in fingers in a rather heavy worker with an elevated blood pressure level, only symptoms concerning nose and throat were reported with relatively low frequency *(i.e.*, 1 or 2) (Gro69).

According to information cited by Flury and Zernike, headache was reported in celluloid workers — which were also exposed to other compounds such as acetone and amyl acetate — as well as one fatal case resulting from inhalation of the vapour of heated camphor with marked rigidity of the jaw muscles as the major symptom. According to cited other authors, camphor vapours may induce intoxications characterized by dyspnea and coma and that long-term exposure may cause significant disfunctioning, especially of the heart (Flu31).

Most data on the toxicity of camphor are from its incidental or accidental use as a drug.

Negative results were obtained when camphor in 10% petrolatum was patch tested in two cases who had shown acute eczema following topical application of a camphor-containing spray (Agu94).

The human lethal oral dose of camphor is estimated to be between 50 to 500 mg/kg bw. In children, 1 gram of camphor can be lethal (Gib89, Nav92a). Symptoms of camphor poisoning can usually be seen within 15-30 minutes after ingestion and include nausea, vomiting, and epigastric distress. Neurologic changes from camphor ingestion include anxiety, confusion, depression, headache, dizziness, twisting of facial muscles, hallucinations, and, in case of severe poisoning, convulsions, and coma (Com94, Sie86).

Autopsy results indicate that camphor can damage the liver (fatty deposits), kidney (swelling of the proximal tubules), and the brain (neuronal death) (Sie86, Sko77, Smi54). The fetus is also at risk for camphor poisoning since camphor crosses the placenta and the ability of the fetus to conjugate camphor's metabolites to glucuronic acid is low (Nav92a, Sie86). Camphor has occassionally

been used intentionally to induce abortion with varying results (see *e.g.*, Gos84, Rab97). However, no increase in malformation rates were found in a study on birth defects due to use of drugs during pregnancy. Out of the study group of 50,282 mother-child pairs, 168 women reported to have used camphor during lunar months 1-4. Of these, 10 had given birth to infants with malformations which was less than expected. In the group of 763 women who had used camphor at anytime in pregnancy, 13 malformed children were observed while 13.65 were expected (Hei77).

Animal data

Irritation

The committee did not find experimental animal data on the potential irritating or sensitising effects of camphor.

Single exposure

Exposure to 1300 mg/m^3 (200 ppm) of camphor, for 5-10 minutes, was reported to induce in mice amongst others restlessness, dyspnoea, dizziness, coma, convulsions, and, eventually, death from respiratory arrest (Flu31). Exposures of 400 to 1760 mg/m^3 (65-280 ppm), for 3 hours, were lethal to mice causing central nervous system injury (Izm82). Single exposure of unknown duration to 6 mg/m^3 (1 ppm) was stated to affect severely the heart function of mice and rabbits (no more data presented) (Heu13).

Smith and Margolis cited minimal lethal oral doses of 2000 and 1800 mg/kg bw for rabbits and guinea pigs, respectively. In their own experiments in rabbits (n=1/dose), single oral (gavage) doses of 1600 mg/kg bw and higher were lethal (dose range: 1000 to 4000 mg/kg bw). Tonic and clonic convulsions were seen in all animals within 5 to 40 minutes after administration. At autopsy, congestion and small focal haemorrhages were seen in the stomach (but may have been due to trauma from the stomach tube). No lesions were found in the brain, kidneys, lungs, liver, heart, pancreas, and the spleen (Smi54).

Following intraperitoneal injection, a minimal lethal dose of 900 mg/kg bw was reported in rats. Doses of 400 and 550 mg/kg bw induced convulsions in 50 and 100% of the rats, respectively (Sam39). Based on a series of experiments in which mice were given 1, 2, or 3 intraperitoneal injections of 300-400 mg/kg bw,

the authors stated that the LD_{50} was *ca*. 300 mg/kg bw. At autopsy, no significant lesions were seen in the animals given a single injection (Smi54).

For subcutaneous administration, a minimal lethal dose of 2200 mg/kg bw was reported in mice (ACG99).

Repeated exposure

No data from toxic effects in experimental animals following repeated inhalation exposure were found.

Convulsions and lesions in the brain similar to those found in human lethal cases were seen in mice given 2 or 3 intraperitoneal injections of 300-400 mg/kg bw (interval between dosing: 24 hours), and sacrificed 36 hours to 4 days after the first injection (Smi54).

Referring to a paper in Italian (dated 1936), it was stated that chronic experimental exposure to camphor induced fatty alteration in the liver and the kidneys (no more data presented) (Smi54).

Carcinogenicity

Application of 3 drops of 0.3-3.0% acetone solutions of camphor to the back skin of mice, once a week, for 1 year, concurrently with 5% croton oil (once/week, for 1 year; time space between croton oil and test substance application 3-4 days; vehicle: acetone) induced skin papillomas in 2 out of the 110 treated mice compared with 2/160 treated with croton oil alone. The first tumour appeared at month 6, the second between month 6 and 9; the first tumour in the croton oil group was seen at month 5. Treatment appeared to be very toxic: survival numbers were 21, 9, 4, and 2 (the 2 tumour-bearing animals) at 3, 6, 9, and 12 months, respectively (for crotonoil: 86, 58, 33, 13) (Gra53). [*The committee noticed that the way the study was presented suggests that dosing was adjusted because of irritation of the skin and that no control group treated with acetone alone was included]*.

In a short-term study primarily aimed at the induction of lung tumours in a pulmonary-tumour-prone strain, intraperitoneal injections — 3 times a week, for 8 weeks — of total doses of D-camphor (vehiculum: tricaprylin) of 3600 or 18,000 mg/kg bw (*i.e.*, doses of 150 and 750 mg/kg bw per injection, resp) into male and female A/He mice (n=15/sex/group) did not induce statistically significant increases of the number of mice with lung tumours or in the number of lung tumours per mouse. At week 24, the end of experiment, survival rates were 11/15

in high-dose males and 14/15 in high-dose females, low-dose males, and low-dose females. No abnormalities were reported in the liver, kidneys, spleen, thymus, intestine, and salivary and endocrine glands at necropsy (Sto73).

Mutagenicity and genotoxicity

Camphor was negative when tested both with and without adding a metabolic activating system from induced rat livers in *S. typhimurium* strains TA1535, TA 1538, TA98, and TA100 (concentration range: 4-2500 µg/plate; solvent: DMSO) (And78). In a separate test using strains TA97a, TA98, TA100, and TA102, results were negative as well (concentration range: 50-2500 µg/plate; solvent: ethanol) (Gom98). According to NTP*, D-camphor was negative in a *Salmonella*-test and in a chromosome aberrations test (no details available).

Camphor (tested as a 10% solution in ethanol) did not induce mitotic arrest or anaphase abnormalities in a grasshopper embryo assay (Lia83).

A single intraperitoneal injection of 76 mg/kg bw to mice (Swiss; n=4) caused a statistically significant increase in the frequency of SCE in bone marrow (3.70 SCE/metaphase *vs* 2.76 and 2.89 in untreated and vehicle-treated controls) in an experiment designed to examine the influence of camphor-pretreatment on the SCE induction by γ-irradiation (Goe89).

Reproduction toxicity

When 0, 100, 400, or 800 mg D-camphor/kg bw/day was administered by gavage to pregnant rats (Sprague-Dawley; n=26-29/group) on gestational days 6 through 15, maternal toxicity (hypoactivity during the first treatment days, increased water consumption, decreased food intake, decreased body weight gain during the treatment period, increased relative and absolute liver weights) was observed in the animals of the mid- and high-dose group, while no such effects were seen at 100 mg/kg bw. No effect on fetal growth, viability, or morphological development was found in any of the treated groups (Nav92a). In a separate study, administration by gavage of doses of D-camphor of 0, 216, 464, or 1000 mg/kg bw to pregnant rats (Sprague-Dawley; n=20/group), on gestational days 6 through 17, did neither result in evidence of embryotoxic or teratogenic effects. Some maternal toxicity was seen including salivation and reduced food intake in the mid- and high-dose group and more pronounced signs such as clonic convulsion, piloerection, reduced motility, and reduced body weight gain

* http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstatc/464493.html

in the high-dose group. At necropsy, ulceration of (the cardiac region of) the stomach was seen in 2 and 5 dams of the mid- and high-dose group, respectively (Leu97).

In pregnant rabbits (n=26/group) given D-camphor at oral (gavage) doses of 0, 50, 100, or 400 mg/kg bw/day on gestational days 6 through 19, no maternal toxicity (mortality, body weight, body weight gain, clinical signs, liver weights) was found in any of the experimental groups, but maternal weight gain tended to decrease with increasing dose during the treatment period. No effect on fetal growth, viability, or morphological development was seen in any of the treated groups (Nav92b). In a separate study, administration by gavage of doses of D-camphor of 0, 147, 316, or 681 mg/kg bw to pregnant rabbits (Himalayan; n=12/group), on gestational days 6 through 18, did neither result in evidence of embryotoxic or teratogenic effects. Maternal toxicity including reduced food intake, and body weight gain was seen in the high-dose group. Histological examination did not reveal any changes in any of the treatment groups (Leu97).

A single intraperitoneal injection of 100 mg/kg bw to 8-week-old male mice (strain A; n=5) caused statistically significant decreases in the number of resting primary spermatocytes when counted 2, 4, and 6 days after treatment. By day 8, these numbers did not differ from those from control animals in this experiment which was not aimed at the effects of camphor on reproductive organs but designed to examine the influence of camphor-pretreatment on effects of γ-irradiation in less vascularized and hypoxic tissues (Goe85).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for bornan-2-one (camphor) in the Netherlands is set at 12 mg/m^3 (2 ppm), 8-hour TWA.

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

8 Assessment of health hazard

The committee did not find data on the kinetics of camphor following inhalation exposure. Experiments in rats and mice showed that bioavalibility was low and independent of sex and species following uncovered skin application. Approximately 70% appeared to be lost by volatilization. Absorption from the gastrointestinal tract is rapid. Camphor was found to be metabolised by hydroxylation at several positions and subsequent oxidation to corresponding

ketones and carbonic acid or by reduction of the keto group. Human data indicated that camphor may cross the placenta.

The committee did not find relevant data concerning effects following long-term ocupational exposure. Symptoms of poisoning following incidental and accidental oral exposure included effects on the gastointestinal tract and the nervous system. At autopsy of lethal cases, effects on kidneys, liver, and brain were observed. Oral doses of 50 to 500 mg/kg bw were found to be lethal to adults.

The committee did not find experimental data on the potential irritation and sensitisation of camphor. Inhalation of concentrations of 400 to 1760 mg/m^3 (65-280 ppm), for 3 hours, induced effects on the central nervous system and mortality in mice. Minimum lethal oral doses of 1600 and 2000 mg/kg bw were reported for rabbits and guinea pigs, respectively. In the rabbits that died from exposure to camphor, only gross effects on the stomach were seen at autopsy. Single doses of 1000 mg/kg bw induced convulsions. The committee did not find data on LC_{50} or LD_{50} values.

Apart from oral teratogenicity studies and a dermal and intraperitoneal carcinogenicity study, the committee did not find data on the effects of camphor following repeated exposure. Considering the flaws in the carcinogenicity studies (high initial mortality in the dermal study; intraperitoneal injection as a less relevant route of administration, short duration, and lung tumours as an endpoint in a lung-tumour sensitive strain of mice in the intraperitoneal study), the committee feels that these studies are not informative with respect to the potential carcinogenicity of camphor. Camphor did not induce mutations when tested *in vitro* in bacteria (*S.typhimurium*) but caused a small but statistically significant increase in the frequency of SCE in bone marrow of intraperitoneally injected mice.

Camphor did not induce reproduction toxicity in rats and rabbits when administered by gavage during organogenesis at oral doses up to 1000 and *ca*. 700 mg/kg bw, respectively. Maternal toxicity was seen at doses of 400 and *ca*. 700 mg/kg bw in rats and rabbits, respectively.

The committee considers the toxicological data base on camphor 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.

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Annex

Occupational exposure limits for camphor 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	2	12	8 h	administrative		SZW01
Germany						
- AGS	2	13	8 h			TRG00
- DFG MAK-Kom.	2	13[c]	8 h	MAK		DFG01
Great Britain						
- HSE	2	13	8 h	OES		HSE01
	3	19	15 min			
Sweden	-	-				Arb00b
Denmark	2	12	8 h			Arb00a
USA						
- ACGIH	2	-	8 h	TLV	A4[d]	ACG01
- OSHA	3	-	15 min	STEL		
- NIOSH	-	2	8 h	PEL		ACG00
	-	2	10 h	REL		ACG00
European Union						
- SCOEL	-	-				CEC00

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

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

[c] Substance still being evaluated or the available toxicological data are indequate for classification and, therefore, not placed in one of the peak exposure limitation categories yet

[d] Classified in carcinogenicity category A4, *i.e.*, not classifiable as a human carcinogen: agents which cause concern that they could be carcinogenic for humans but which cannot be assessed conclusively because of a lack of data. In vitro or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agent into one of the other categories