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Adverse health effects of cigarette smoke: aldehydes

Crotonaldehyde, butyraldehyde, hexanal, and malonaldehyde

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Rapport in het kort

Gezondheidsschadelijke effecten van sigarettenrook : aldehyden

Er zijn meer toxicologische gegevens nodig om een goede risicoschatting van de gezondheidseffecten van aldehyden te maken. Ook moet meer onderzoek verricht worden naar de combinaties van toegevoegde stoffen in tabak onderling en met tabak zelf. Aldehyden ontstaan in sigarettenrook door verbranding van tabak en de aan tabak toegevoegde ingrediënten.
Dit rapport beschrijft de gegevens van een literatuurinventarisatie over de gezondheidseffecten van blootstelling aan de volgende aldehyden: crotonaldehyde, butyraldehyde, hexanal en malonaldehyde. Uit de beschikbare gegevens komt naar voren, dat crotonaldehyde de trilhaarfunctie van het long-epitheel *in vitro* remt. Voorts geeft crotonaldehyde irritatie van de ogen, huid en luchtwegen. Butyraldehyde, hexanal en malonaldehyde lijken minder toxisch, hoewel er onvoldoende data beschikbaar zijn voor een afdoende humane risicoschatting. Gegevens over de verslavende effecten van en de effecten na gecombineerde blootstelling aan deze aldehyden zijn niet beschreven.

Trefwoorden: tabaksrook, inhalatie, toxiciteit, aldehyden, suikers, verslaving, risicoschatting

Abstract

Adverse health effects of cigarette smoke: aldehydes

Crotonaldehyde in cigarette smoke can be concluded to induce airway damage in humans. This is one conclusion derived from the existing data found in the literature and reported here in the discussion on adverse health effects and possible addictive effects due to the exposure of crotonaldehyde, butyraldehyde, hexanal, and malonaldehyde in cigarette smoke. A previous RIVM report focused on acetaldehyde, formaldehyde, acrolein and propionaldehyde. Due to limited available data, it is not clear whether butyraldehyde, hexanal, and malonaldehyde in cigarette smoke induce similar damage. The exposure due to inhalation of the above-mentioned aldehydes in combination with each other or with other aldehydes remains a point of concern. In addition, it is not known whether sugars and glycerol additives in tobacco affect the concentration of aldehydes in cigarette smoke. For a proper risk assessment, further research on combined exposure and the contribution of added ingredients to the aldehyde concentration in cigarette smoke is necessary.

Key words: tobacco smoke, inhalation, toxicity, aldehydes, sugars, dependency, risk assessment

Contents

Samenvatting

In dit rapport worden de gezondheidseffecten van blootstelling aan aldehyden ten gevolge van het roken van sigaretten beschreven. Het is een vervolg op RIVM rapport 650270003 waarin de volgende aldehyden zijn onderzocht: acetaldehyde, formaldehyde, acroleïne en propionaldehyde. Dit literatuuronderzoek richt zich op crotonaldehyde, butyraldehyde, hexanal en malonaldehyde.

Aldehyden in sigarettenrook zijn verbrandingsproducten van tabak maar ook van aan tabak toegevoegde ingrediënten. Crotonaldehyde heeft een zwak ciliostatisch effect *in vitro*. De acute toxiciteit van crotonaldehyde bestaat voornamelijk uit irritatie van de ogen, huid en luchtwegen. Butyraldehyde, hexanal en malonaldehyde lijken minder toxisch maar, er zijn onvoldoende data beschikbaar voor een risicoschatting. Data over verslavende effecten en over gecombineerde blootstelling aan deze aldehyden zijn niet gevonden.

De belangrijkste conclusie is dat er slechts een beperkte dataset beschikbaar is wat betreft de inhalatoire blootstelling aan crotonaldehyde, butyraldehyde, hexanal en malonaldehyde. De beschikbare gegevens suggereren dat crotonaldehyde in sigarettenrook schadelijk is voor de luchtwegen. Het is niet duidelijk of butyraldehyde, hexanal of malonaldehyde in sigarettenrook aanleiding geven tot schade aan de luchtwegen. De gecombineerde blootstelling samen met andere aldehyden in sigarettenrook blijft een punt van onduidelijkheid. Ook de bijdrage van toegevoegde suikers en andere ingrediënten aan de concentratie van aldehyden in sigarettenrook is onduidelijk. Voor een goede risicoschatting zijn daarom meer data nodig. Onderzoek naar de gecombineerde blootstelling aan aldehyden en de bijdrage van toegevoegde ingrediënten aan de concentratie van aldehyden in sigarettenrook is daarvoor nodig.

Summary

This literature study discusses health effects of aldehyde exposure due to cigarette smoking, continuing on from a previous study (RIVM 650270003) in which acetaldehyde, formaldehyde, acrolein, and propionaldehyde were discussed. This study focuses on crotonaldehyde, butyraldehyde, hexanal, and malonaldehyde.

Aldehydes in cigarette smoke are combustion products from tobacco and arise from added ingredients as well. Crotonaldehyde shows a very weak ciliostatic effect *in vitro*. The acute toxicity of crotonaldehyde causes mainly irritation of the eyes, skin, and respiratory tract. Butyraldehyde, hexanal, and malonaldehyde seem less toxic; however, inhalation toxicology data are not sufficiently available for a risk assessment. Data on the addictive effects or on combined exposure of these aldehydes are missing.

There are insufficient data available on inhalation exposure to crotonaldehyde, butyraldehyde, hexanal, and malonaldehyde for a proper risk assessment. The existing data suggest that crotonaldehyde in cigarette smoke causes damage to the respiratory tract. It is unclear if butyraldehyde, hexanal, and malonaldehyde exposures due to cigarette smoking can cause damage to the respiratory tract. The exposure due to inhalation of the above aldehydes in combination with each other or with other aldehydes remains a point of concern. In addition, the contribution of ingredients added to tobacco to the concentration of aldehydes in cigarette smoke is unclear. For a proper risk assessment additional research to the effects of combined exposure and the contribution of ingredients added to tobacco to the concentration of aldehydes in cigarette smoke is required.

1 Introduction

Cigarette smoking is generally thought of as the main cause of early preventable death in humans. Smoking has been implicated as a major risk factor in chronic obstructive pulmonary diseases such as chronic bronchitis and emphysema, in carcinogenesis, and in cardiovascular disease (1). According to the 1989 Surgeon General's report, 'In 1985, smoking accounted for 87% of lung cancer deaths, 82% of chronic obstructive pulmonary disease (COPD) deaths, 21% of coronary heart disease (CHD) deaths, and 18% of stroke deaths in the US.' (2). Hence, prevention and quitting smoking are major public health goals. Recently, more interest has been developed in the composition of cigarettes and the possibility of harm reduction.

Although many components of tobacco are known to be toxic, little is known about the specific dose-response relationships of the individual toxins as they occur in cigarette smoke or about the interactions between the constituents of tobacco smoke. Main stream cigarette smoke consists of several thousands of compounds, many as yet unidentified. In general, cigarette smoke is thought of as a mucosal irritant, which has ciliatoxic and inflammatory properties. Aldehydes constitute a group of rather reactive compounds, which could account for these effects (3). Many different aldehydes have been reported in main stream cigarette smoke, the most abundant being acetaldehyde, formaldehyde, acrolein, and propionaldehyde (4). The effects of exposure to these aldehydes have been described in part 1 (5). Besides the already described aldehydes also crotonaldehyde, butyraldehyde, hexanal, and malonaldehyde are known aldehyde components of main stream cigarette smoke. These aldehydes are less often mentioned as the ones in part 1 and are therefore mentioned in part 2.

In this report the effects of exposure to crotonaldehyde, butyraldehyde, hexanal, and malonaldehyde on human health will be investigated using information in currently available literature. In the discussion also the effect of combined exposure will be discussed.

2 Methods

Publications on aldehydes were identified through Medline, Toxline and Current Contents, and from electronic citations in the Merck Index (2001), DOSE (6), RTECS (7) , HSDB (8), BIG (9), Martindale (2001), SAX Dangerous Properties of Industrial Materials (2001), and Comprehensive Toxicology (2001). Additional information was derived from the references cited in these publications and from publications on Internet.
The data of crotonaldehyde, butyraldehyde, hexanal, and malonaldehyde summarised in the fact sheets (cf. Appendices 1 to 4) have been retrieved till May 2002, September 2002, November 2002, and November 2002, respectively.

3 Results and discussion

3.1 Exposure levels

A certain percentage of the aldehydes in the vapour phase of smoke is derived directly from tobacco, however, most aldehydes are formed during smoking from precursors such as polysaccharides, pectins, proteins, and possibly, triglycerides in tobacco (10). In this way crotonaldehyde, butyraldehyde, hexanal, and malonaldehyde are formed. Aldehydes constitute a group of reactive compounds, which can account for damage at the local site of entry, e.g. the respiratory tract. The function of aldehydes in tobacco products is not known. Exposure data to the four investigated aldehydes in mainstream cigarette smoke are listed in Table 1.

Table 1 Exposure to crotonaldehyde, butyraldehyde, hexanal, and malonaldehyde originating from smoking 25 cigarettes compared with industrial occupational limits and residential exposure.

Exposure (mg)	25 cigarettes	Industrial occupational limits (TWA, or LTEL (8h))	Residential (8h)
Crotonaldehyde	1.8-5.7 (11,12)	60 (2)	-
Butyraldehyde	2.2-23.2 (13)	450 (5)	-
Hexanal	2.5-9.5 (13)	-	0.05-14.61 (14)
Malonaldehyde	0.24-0.66 (15)	-	-

-: currently no data available

The exposure varies from 0.24 to 23.2 mg per 25 cigarettes. Cigarette smoking has been considered to be the main cause of crotonaldehyde exposure to the general population. A large variation in the amount of butyraldehyde (2.2-23.2 mg per 25 cigarettes) in main stream smoke is reported in the available literature. The amount of hexanal varies between 2.5 and 9.5 mg per 25 cigarettes. Remarkable is that in one reference, the investigators reported not to be able to detect hexanal in mainstream cigarette smoke at all (16). The amount of malonaldehyde (0.24-0.66 mg per 25 cigarettes) in main stream cigarette smoke is low compared to other aldehydes (>1.8 mg/ 25 cigarettes). The exposure to crotonaldehyde and butyraldehyde via smoking does not exceed the occupational limit values (Industrial TWA in Table 1). However, it should be noted that these limit values are based on 8-hours continuous low exposure and not on smoking related repeated high peak exposure.

It is important to realise that only limited data are available on the amount of specific aldehydes in smoke, and that this can lead to an underestimation or overestimation of the amount in cigarette smoke. Also the method of analysis used differs substantially between the studies. In the case of hexanal and butyraldehyde only a single reference is available on the amount per cigarette. In that study the amount of aldehyde per cigarette was determined by placing a cigarette after lighting in a 1000 ml separatory funnel. The cock of the separatory funnel was opened gradually to draw the smoke into the separatory funnel. It took 20 seconds to completely smoke one cigarette. After the smoke was sucked into the funnel, an aqueous

cystamine solution was added in which the smoke was dissolved. The carbonyl compounds in the smoke were derivatized to thiazolidines and subsequently quantitatively analysed by gas chromatography with nitrogen-phosphorus detection (13). The amount of smoke trapped in this way, was not mentioned. Moreover, this method is not representative for actual smoking conditions. If aldehydes are determined with the smoking method according to the Federal Trade Commission, a fixed amount of the cigarette is trapped as mainstream smoke. According to that method every minute a puff of 35 ml is taken during 2 seconds. After approximately 10 puffs the cigarette is smoked until a butt length of 23 mm is left. The smoke volume obtained with this method is approximately 350 ml (10). The amount detected in this volume is presented as the amount per cigarette. Because the volume of the mainstream smoke depends on the smoking method, the quantified amount of the compounds per cigarette depends on the smoking method used. Therefore it is difficult to compare the levels of a mainstream compound with each other when determined from different methods.
Since aldehydes are very reactive compounds, it can be expected that aldehydes are not very well absorbed by the respiratory tract and that they will result in local damage to the respiratory tract (5). Therefore it is useful to have some indication of the local concentration in the respiratory tract of the different aldehydes when smoking a cigarette. As stated above it is already uncertain what the amounts per cigarette are. Moreover, it can be expected that during smoking the amount of smoke inhaled is diluted with air when taking a puff and is further diluted in the respiratory tract. These factors make it difficult to give an estimate of the local concentrations in the respiratory tract. The local concentrations should however provide additional information for a risk assessment on aldehyde exposure through cigarette smoking.
Most aldehydes are formed during smoking from precursors such as polysaccharides, pectins, proteins, and possibly, triglycerides in tobacco (10). Knowledge of the contribution of the added sugars and other ingredients of tobacco to the concentration of aldehydes in cigarette smoke is missing. For a proper risk assessment, research on the contribution of added sugars and other ingredients of tobacco to the concentration of aldehydes in cigarette smoke is therefore necessary.

3.2 Effects

3.2.1 Crotonaldehyde

Crotonaldehyde shows a very weak ciliostatic effect *in vitro* (14,17). The concentration that reduces the respiratory rate to 50% was reported to be 3.5 ppm (10 mg/m^3) in mice and 23.2 ppm (66.6 mg/m^3) in rats (11). Insufficient inhalation data are available to evaluate the pharmacodynamic effects of crotonaldehyde due to cigarette smoking. Further research is needed to test the reported ciliatoxicity. Data on the pharmacokinetic properties of crotonaldehyde are not available. For a critical assessment, research is needed, especially to obtain the local effects in the respiratory system during and after smoking related exposure to crotonaldehyde.
The acute toxicity of crotonaldehyde consists mainly of irritation of the eyes, skin, and respiratory tract (14,18). There is inconclusive evidence for the carcinogenicity of crotonaldehyde. Accordingly, IARC classifies crotonaldehyde in group 3 (11). There is evidence of adduct formation *in vivo* (12). Crotonaldehyde inhibits the metabolism of

acetaldehyde and formaldehyde *in vitro* (14). The existing data suggest that smoking-related crotonaldehyde exposures could lead to local damage in the respiratory tract depending on the amount of crotonaldehyde per cigarette. For details see Appendix 1.

3.2.2 Butyraldehyde

Butyraldehyde is considered to be safe as a food additive. Insufficient inhalation data are available to evaluate the pharmacodynamic effects of butyraldehyde due to cigarette smoking. Data on the pharmacokinetic properties of butyraldehyde were not found in the available literature. For a critical assessment research is needed, especially on the amount of exposure, local and systemic absorption and bioavailability during and after smoking.
Lesions of the nasal epithelium occured at 225 mg/m^3 at daily continuous exposures for 13 weeks in rats (19). Further research is needed to elucidate if butyraldehyde exposure through cigarette smoking is high enough to cause damage to the respiratory tract. Butyraldehyde is not included in a carcinogenic classification (18). For details see Appendix 2.

3.2.3 Hexanal

Hexanal is currently used as a food additive. Insufficient inhalation data are available to evaluate the pharmacodynamic effects of hexanal due to cigarette smoking. Data on the pharmacokinetic properties of hexanal were not found in the available literature. For a critical assessment research is needed, especially on the amount of exposure, local and systemic absorption and bioavailability during and after smoking.
The few available data suggest that the acute toxicity of hexanal is low and consists mainly of irritation of the eyes and skin (20). No data are available on damage to the respiratory tract after inhalation. Therefore, more research is needed to elucidate the effects of hexanal exposure through cigarette smoking. Hexanal is not included in a carcinogenic classification (18). For details see Appendix 3.

3.2.4 Malonaldehyde

Insufficient inhalation data are available to evaluate the pharmacodynamic effects of malonaldehyde due to cigarette smoking. After exposure to smoke in rats an increase in malonaldehyde levels of pulmonary tissue and plasma were found (21).
Malonaldehyde is a by-product of prostaglandin biosynthesis and an end-product of polyunsaturated lipid peroxidation (21). A large part of malonaldehyde will be oxidised to CO_2 and exhaled (14). For a critical assessment research is needed, especially on the amount of exposure, local and systemic absorption and bioavailability during and after smoking. Other aldehydes are known to induce mainly local effects at the site of exposure and little systemic effects, probably due to little absorption in the respiratory tract.
The acute oral toxicity of malonaldehyde is low (20,21). There is inadequate evidence for the carcinogenicity of malonaldehyde to experimental animals and to humans (21). No inhalation toxicological data are available. More data are needed on the toxicity of malonaldehyde through smoking related exposures. For details see Appendix 4.

3.3 Combined effects

Combined exposure to chemicals may result in toxicological interactions leading to a significant increase or decrease in the toxicity of the combination compared to the sum of the toxicity of the individual components of the mixture. No studies on the combined exposure of crotonaldehyde, butyraldehyde, hexanal, and malonaldehyde were found.

4 Conclusion

There are insufficient inhalation data available on inhalation exposure to crotonaldehyde, butyraldehyde, hexanal, and malonaldehyde for a proper risk assesment. The majority of the studies found in the literature dealt with oral exposure. Data on the pharmacokinetics and pharmacodynamics after inhalation are missing, while limited toxicological data are available.

The existing data suggest that crotonaldehyde in cigarette smoke causes damage to the respiratory tract. Unclear is if butyraldehyde, hexanal, and malonaldehyde exposures due to cigarette smoking may cause damage to the respiratory tract. Other factors that made it difficult to evaluate the inhalation effects of the aldehydes were the small number of references found in the available literature and the different methods used for the determination of the aldehydes in mainstream smoke. No data are available on the combined exposure to aldehydes. No data on addictive effects due to exposure to crotonaldehyde, butyraldehyde, hexanal, and malonaldehyde were found.

The combined exposure of different aldehydes remains a point of concern. In addition, the contribution of added ingredients of tobacco to the concentration of aldehydes in cigarette smoke is unclear. For a proper risk assessment research to the combined exposure and the contribution of added ingredients of tobacco to the concentration of aldehydes in cigarette smoke is required.

References

(1) Eiserich JP, van der Vliet A, Handelman GJ, Halliwell B, Cross CE. Dietary antioxidants and cigarette smoke-induced biomolecular damage: a complex interaction. Amer J Clin Nutr 1995; 62(suppl):1490S-1500S.

(2) US Department of Health and Human Services (DHHS). Reducing the health consequences of smoking: 25 years of progress. A report of the Surgeon General. 89-8411. 1989. Rockville, MD: Department of Health and Human Services.

(3) Dalham T, Rosengren A. Effect of Different Aldehydes on Tracheal Mucosa. Arch Otolaryng 1971; 93:496-500.

(4) IARC. Tobacco smoking. 38. 1986. Lyon, IARC. Evaluation of the carcinogenic risk of chemicals to humans.

(5) Andel I v, Schenk E, Rambali B, Wolterink G, Werken G vd, Stevenson H et al. The health-and addictive effects due to exposure to aldehydes of cigarette smoke part 1. 650270003. 2002. Bilthoven.

(6) The Dictionary of Substances and their Effects (DOSE); The Royal Society of Chemistry; 2001.

(7) The Registry of Toxic Effects of Chemical Substances (RTECS); The National Institute for Occupational Safety and Health (NIOSH); 2001.

(8) Hazardous Substances Data Bank (HSDB); The National Library of Medicine; 2001.

(9) Brandweer Informatiecentrum voor Gevaarlijke stoffen (BIG), 10th Edition.

(10) IARC. Tobacco smoking. 38. 1986. Lyon, IARC. Evaluation of the carcinogenic risk of chemicals to humans.

(11) Crotonaldehyde. Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals. Lyon: 1995: 373-392.

(12) Eder E, Schuler D, Budiawan. Cancer risk assessment for crotonaldehyde and 2-hexenal: an approach. IARC Sci Publ 1999; 150:219-232.

(13) Miyake T, Shibamoto T. Quantitative analysis by gas chromatography of volatile carbonyl compounds in cigarette smoke. J Chromatogr A 1995; 693:376-381.

(14) The hazardous Substance Data Bank (HSDB) through 2000/10. 2001. The National Library of Medicine.

(15) Witas T, Sledziewski P. Exhalation of malonaldehyde from the smoke of high grade cigarettes and effectiveness of filtering it. Nahrung 1990; 34:615-621.

(16) Kataoka H, Kondo T, Sumida A. Gas chromatographic determination of aldehydes in combustion smoke samples. Anal Chim Acta 1998; 358:269-275.

(17) Dalham T, Rosengren A. Effect of Different Aldehydes on Tracheal Mucosa. Arch Otolaryng 1971; 93:496-500.

(18) Brandweerinformatiecentrum voor gevaarlijke stoffen (BIG). versie 9.0. 2001. Belgium.

(19) Butyraldehyde: 9-day repeated vapor inhalation toxicity, vapor inhalation by dogs and rats for 12 and 13 weeks, respectivelyand a 12-week vapor inhalation study in rats with letter 020689. EPA /OTS ; Doc #86 890000097 1989.

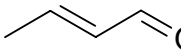
(20) Dictionary of substances and their effects (DOSE). The Royal Society of Chemistry, editor. 10/2000. 2001.

(21) Malonaldehyde. Allyl compounds, Aldehydes, Epoxides and Peroxides. Lyon: World Health Organization, IARC 1985: 163-177.

Appendix 1 Crotonaldehyde

GENERAL
IUPAC systematic name: crotonaldehyde (1)
Synonyms: 2-butenal; crotonal; crotonic-aldehyde; crotylaldehyde; β-methyl acrolein; propylene-aldehyde (2), 2-butenaldehyde; 1-formylpropene (1).
Molecular formula: C_4H_6O (2)

Molecular structure



Molecular weight: 70.09 g/mol (2) (3)
Alifatic: Yes
Aromatic: No
N containing: No
Halogen containing: No
CAS registry no.: 4170-30-3 (1) (3)
Storage:
R/S classification: R11, 23, 36/37/38, 50/53; S01/01, 29, 33, 45, 60,61 (3)
dangercode (transport): 663 (3)
Properties:

- melting point: -76.5°C (2); -74°C (1)
- boiling point: 102°C (2); 104-105°C (1)
- density: 0.853 g/cm^3 at 20°C (2); 0.8495 g/cm^3 at 20°C (1)
- refractive index: 1.4565 (21°C) (4)
- solubility: 18.1 g/100 g water at 20°C, miscible in all proportions with alcohol, ether, benzene, toluene, kerosine, gasoline and naphta (2).
- substance description:
  - color: water-white-colored (2)
  - liquid/gas/powder: liquid (2)
  - odor/taste: pungent, suffocating; odor detection in air: 2.10 x 10^{-2} mg/l of chemically pure gas (2).
- volatility: vapour pressure, 32 mm Hg [4.3 kPa] at 20°C, relative vapour density
- (air = 1), 2.4 (1)
- pK_a: No data available.
- PA: 197.2 kcal/mol (5)
- flammability:
  - FP = 13°C (2)
  - FL Limits = 2.1%-15.5% (2) (3)
  - IT = 232.2°C (2)
- decomposition temperature: 230°C (6)
- stability: Readily dimerizes when pure; slowly oxidizes to crotonic acid; polymerizes to become inflammable and explosive (1).
- vapour pressure/ vapour tension (20°C): 32 mm Hg [4.3 kPa] at 20°C (1), 19 mm Hg (7)
- vapour pressure (50°C): 165 hPa (3)
- relative density: 2.4 (1)
- octanol water partition coefficient, log P, log K_{OW}: 0.63 (1)
- conversion factor: 1 mg/ m^3 = 0.349 ppm; 1 ppm = 2.87 mg/m^3 (2).

Critical assessment
Crotonaldehyde is a rather volatile compound (relatively high vapor pressure). Two forms exist: trans- and cis-. Trans-crotonaldehyde is reactive, especially to (photochemically produced) oxidants (hydroxyl radicals), and degrades in that way rapidly (approx. half-life: 11 hours).
The aldehydegroup is a potential site for oxidation and adductformation. Contact between crotonaldehyde and alkaline materials such as caustics, ammonia, organic amines, or mineral acids may cause violent polymerization to occur; contact with strong oxidizers may cause fires and explosions (7).
Conclusion
Cis- and trans-crotonaldehyde are volatile short chain, mono-unsaturated compounds containing a reactive aldehyde group. Crotonaldehyde is readily converted by oxygen to hazardous peroxides and acids.

FUNCTION IN TOBACCO
No data available.

AMOUNT IN TOBACCO PRODUCTS
No data available.

AMOUNT IN SMOKE
- **main stream** Crotonaldehyde was detected in cigarette smoke at 10-228 µg/cigarette (1). Eiserich et al. (1995) calculated a concentration of crotonaldehyde in the respiratory tract lining fluid of 20 µmol/L per cigarette (8).
- **side stream** Sidestream smoke from burning cigarettes contained 280 µg crotonaldehyde per cigarette (2).

SOURCE
It seems likely that propionaldehyde is formed during smoking from precursors such as polysaccharides, pectins, proteins and possible triglycerides in tobacco (9).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE
Crotonaldehyde is released to the atmosphere from the combustion of wood (6-116 mg/kg (1)), polymers, and tobacco, in gasoline (0.09-1.33 ppm [0.26-3.82 mg/m^3] (1)), diesel (0.01-0.04 ppm [0.03-0.12 mg/m^3] (1)), and turbine engine exhausts, and in volcanic gases. It also may be released to the environment in emissions or wastewater resulting from its manufacture and use as a chemical intermediate. If released to the atmosphere, crotonaldehyde degrades rapidly (typical half-life of 11-12 hr) via reaction with photochemically produced hydroxyl radicals. Reaction with ozone also occurs, but the rate (average half-life of 15.5 days) is not significant in comparison to the hydroxyl radical reaction (2).
Crotonaldehyde has also been detected in biogenic emissions from pine (0.19 µg/m^3) and deciduous (0.49 µg/m^3) forests in Europe and in remote, high-altitude areas with scarce vegetation (e.g. Nepal; 0.24-3.32 µg/m^3) (1). An experimental vapor pressure of 30 mm Hg at 25ºC indicates that crotonaldehyde will exist almost entirely in the vapor phase in the ambient atmosphere.
Crotonaldehyde was found in many fruits (e.g. apples, guavas, grapes, strawberries and tomatoes) at concentrations of <0.01 ppm (0.01 mg/kg); in cabbage, cauliflower, Brussels sprouts, carrots and celery leaves at concentrations of 0.02-0.1 ppm (0.02 –0.1mg/kg) ; in bread, cheese, milk, meat, fish and beer at concentrations of 0-0.04 ppm (0- 0.04 mg/kg); and in wine at concentrations of 0-0.7 ppm (0-0.7 mg/kg). It was detected in samples of various liquors at <0.02-0.21 ppm (0.02 – 0.21 mg/kg). It has also been identified in wheat flavour essence (1).
Crotonaldehyde was released from seven of 11 samples of food packaging during heating in a microwave oven, at concentrations of 0.016-0.70 µg/cm^2. Crotonaldehyde was

qualitatively detected in 1 of 12 human milk samples collected from volunteers in 4 USA cities (2). The highest daily intake of crotonaldehyde is assumed to be derived from cigarette smoke (31-169 µg /kg body weight) (10).

Source	Concentration
Air, work place (production)	300-600 µg/m^3
Tobacco smoke	72-228 µg/cig
Fruit and vegetables	1.4-100 µg/kg
Meat	10-270 µg/kg
Wine	300-700 µg/L

Adapted from (10)

COMBUSTION PRODUCTS
No data available.

CONSENSUS REPORTS
There is inadequate evidence in humans for the carcinogenicity of crotonaldehyde. There is inadequate evidence in experimental animals for the carcinogenicity of crotonaldehyde. Overall evaluation: Crotonaldehyde is not classifiable as to its carcinogenicity to humans (Group 3) (1).

STANDARDS AND RECOMMENDATIONS
ADI: No data available.
TWA_{NL} = MAC: 6 mg/m^3 (1)
TWA_{D} =MAK: none; justifiably suspected of having carcinogenic potential (1).
TWA_{USA}: 2 ppm (6 mg/m^3) (2).
$STEL_{NL}$: No data available.
$STEL_{USA}$: 18 mg/m^3/15 min (11)
LTEL: No data available.
TLV-C: 0.3 ppm (0.84 mg/m^3), skin (2) (3). Confirmed animal carcinogen with unknown relevance to humans (2).
TLV-CARCINOGENICITY: No data available.
MAK-REPRODUCTION: No data available.

Others:
No data available.

Reference value:
No data available.

CLASS
EG Carc. Cat.: No data available.
IARC-category: group 3 (1).
CEC: No data available.

Critical assessment
The daily exposure to crotonaldehyde through cigarette smoking and environmental exposure is compared in the following table.

	25 cigarettes	Industrial TWA	Wine	Meat
Crotonaldehyde Exposure (µg)	1800-5700	60000	150-350 (0.5 L/day)	2-54 (200 g/day)

The main exposure to crotonaldehyde is through cigarette smoke. It seems likely that crotonaldehyde like other aldehydes, arises from incomplete combustion or pyrolysis of tobacco. Mainstream cigarette smoke contains 10-228 µg crotonaldehyde per cigarette.
Conclusion
The highest daily intake of crotonaldehyde is assumed to be derived from cigarette smoke.

Depending on the amount of crotonaldehyde in mainstream cigarette smoke, high local concentrations of crotonaldehyde can arise in the respiratory tract.

PHARMACODYNAMICS

Mechanism of action

No data available.

Pulmonary system

- **breathing frequency**: No data available.
- **tidal volume**: No data available.
- **lung compliance**: No data available.
- **airway resistance**: No data available.

Crotonaldehyde shows very weak ciliostatic effect *in vitro* (12).

Crotonaldehyde is a potent inhibitor of the ciliary activity at 5 min in chicken tracheal organ culture (2), no concentration mentioned.

The concentration that reduces the respiratory rate to 50% was reported to be 3.5 ppm (10.0 mg/m^3) in mice and 23.2 ppm (66.6 mg/m^3) in rats (1).

Cardiovascular system

- **blood pressure**: No data available.
- **heart rate**: No data available.

Renal system

- **diuresis**: No data available.
- **saluresis**: No data available.

Nervous system

- **central nervous system**: No data available.
- **autonomic system**: No data available.
- **peripheral nervous system:** Crotonaldehyde (0.01-1.00% wt/vol, at 20, 25, 30 and 35ºC) changes the excitability and conduction properties of frog sciatic nerve *in vitro*. It irreversibly reduced the amplitude of compounded action potential of the nerve and decreased conduction velocity up to complete block (2).

Other

Crotonaldehyde inhibits the activities of some enzymes in vitro, including cytochrome P450 and aldehyde dehydrogenase (1).

Critical assessment

Sufficient inhalation data are missing to evaluate the pharmacodynamic effects of crotonaldehyde due to cigarette smoking. Further research is needed to test the reported ciliatoxicity.

Conclusion

Research is necessary to elucidate the pharmacodynamic effects of crotonaldehyde due to cigarette smoking.

PHARMACOKINETICS

Absorption

No data available.

Bioavailability

No data available.

Distribution
No data available.

Metabolism
Rats dosed with crotonaldehyde (dose not mentioned) excrete 3-hydroxy-1-methylpropyl-mercapturic acid and occasional smaller quantities of 2-carboxy-1-methylethylmercapturic acid (2).

Excretion
No data available.

Kinetic parameters
No data available.

Critical assessment
Data on the pharmacokinetic properties of crotonaldehyde are missing. For a critical assessment research is needed, especially to obtain the amount of absorption and bioavailability after smoking related exposures to crotonaldehyde. Other aldehydes are known to induce mainly local effects at the site of exposure and little systemic effects, probably due to little absorption in the respiratory tract.

Conclusion
The kinetics of smoking related exposures to crotonaldehyde need further study.

TOXICOLOGY

Acute toxicity

Human

Crotonaldehyde is so highly irritant to the eyes that people are unable to remain in the presence of dangerous concentrations of 400 mg/m^3. At 45 ppm (129 mg/m^3) the odor is extremely obnoxious and there is considerable eye discomfort. The vapor is eye, skin, and respiratory tract irritant.

Exposures of 15 minutes to crotonaldehyde at 4.1 ppm (11.8 mg/m^3) were highly irritating to the nose and upper respiratory tract and produced lacrimation in human volunteers in 30 seconds. Another study found that 15 minute exposure to 15 ppm (42 mg/m^3) was detected as a strong but intolerable odor, and no irritation was reported for brief exposures. Brief exposures, after a few seconds at 45 ppm (126 mg/m^3), proved very disagreeable with conjunctival irritation prominent (2).

Animal

Inhalation:

LC50 rat inhalation: 85 ppm, 4 h (238 mg/m^3) (3)

LC50 rat inhalation 30 min: 1500 ppm (4200 mg/m^3); pulmonary edema was observed in the rats after the fatal exposure (2).

A lethal concentration for rats for a 4-hour exposure has been found to be: 100 ppm (280 mg/m^3). Changes in pulmonary performance resulted from single exposures at 10 ppm (28 mg/m^3) for 200 minutes. Rats (number of animals not mentioned) did not survive at 1650 ppm (4620 mg/m^3) for 10 minutes. Effects include respiratory distress, an excitatory stage, and terminal convulsions (2).

Oral:

LD50 rat oral: 206 mg/kg (3)

Crotonaldehyde was evaluated for acute oral toxicity in groups of male albino rats (strain not reported) administered single doses of 1% crotonaldehyde in a tergitol solution by oral gavage at levels of 1000 and 100 mg/kg body weight. Mortality was observed in all animals in the 1000 mg/kg dose group in ten minutes. The LD50 was determined to be approximately 300 mg/kg. Clinical observations included dark brown tanning and slight necrosis of the skin. Gross necropsy observations were not reported (2).

Crotonaldehyde was evaluated for acute oral toxicity in groups of 2 male and 2 female Sprague-Dawley albino rats administered single doses of crotonaldehyde by oral gavage at levels of 50, 160, 500, 1600, and 5000 mg/kg body weight. Mortality was observed in 1 female rat in the 160 mg/kg dose group, and in all animals dosed with 500, 1600, or 5000 mg/kg. An LD50 and gross necropsy observations were not reported. The clinical observations for the 500, 1600 and 5000 mg/kg dose group were severe convulsions immediately following dosing (2).
Acute oral toxicity was evaluated in groups of 5 male and 5 female Sprague-Dawley albino rats administered single doses of crotonaldehyde by oral gavage at levels of 64.5, 107.5, 180, 300, and 500 mg/kg bw. Mortality was observed in 14 animals out of 20 in the 180 mg/kg dose group and in all animals in the 300 and 500 mg/kg dose groups; the LD50 value for combined sexes is calculated to be 174 mg/kg with confidence limits 131-231 mg/kg. The LD50 was calculated to be 165 mg/kg in male rats (with 95% confidence limits of 107-254 mg/kg) and 175 mg/kg in female rats (with 95% confidence limits of 105-292 mg/kg). Clinical antemortem observations included lethargy, salivation, ataxia, lacrimation, soft feces and squinted eyes. No significant clinical signs were observed in animals living past day one (except one female exhibited extended salivation, rhinorrhea and wheezing). Gross necropsy observations of animals found dead included: dark areas (8/27), discoloration (13/27), mottling (10/27), and congestion (5/27) in the lungs; dark areas (3/27) in the spleen; distention with compound-colored fluid (14/27), distention with fluid (10/27) and distention with gas (15/27) in the stomach; and distention with gas (2/27) and fluid (14/27) in the intestines. Gross necropsy of animals sacrificed on the 14th day revealed discoloration of, dark red areas and white foci on the lungs, a dark red and slightly enlarged uterus in a female in the 64.5 mg/kg dose group, and a cyst and fluid in the uterus of a female in the 107.5 mg/kg dose group (2).
Dermal:
LD50 Rabbit dermal: 128 mg/kg (3).
Crotonaldehyde was evaluated for acute dermal toxicity in groups of 6 male and female guinea pigs, receiving single doses of undiluted crotonaldehyde at dose levels of 10 (2 groups dosed), 100 and 1000 mg/kg bw for 4 days, and at 100 or 1000 mg/kg for 2 and 24 hours. In the groups exposed for 2 and 24 hours, mortality was seen in all animals in the 1000 mg/kg dose group while no mortality was seen in the 100 mg/kg dose group; the LD50 value was estimated to be 300 mg/kg. In the group receiving a poultice for 4 days, mortality was observed in 1 out of 12 guinea pigs in the 10 mg/kg dose group and in all animals in the 1000 and 100 mg/kg dose groups; the LD50 was estimated as approximately 300 mg/kg. Clinical observations included tanning and slight necrosis of the skin. Gross necropsy revealed subcutaneous gelatinous exudate and evidence of damage to internal organs in the dose group which received 1000 mg/kg for 24 hours (2).
Intraperitoneal:
Intraperitoneal injection to rats of crotonaldehyde at 450 µmol/kg bw [31.5 mg/kg bw] decreased cytochrome P450 levels to 67% and ethylmorphine N-demethylase activity to 23% of control levels within 24 h. [Figure 2 of the paper shows that cytochrome P450 reductase activity at 24 h was 70% of the control value but not significantly different] (1).

Local tolerance
Human
Crotonaldehyde was evaluated for primary dermal irritation. The test substance was applied at a dosage of 0.01 ml (undiluted) to the skin of 5 human subjects. Continued applications produced confluent vesicular eruptions by sensitization. Burns were largely due to previous sensitization. Contact with the test substance caused pain within 15 seconds. No further information was submitted (2).
A textile worker was reported to have become sensitized to crotonaldehyde (no concentration reported) (1).

Animal
Crotonaldehyde was evaluated for primary dermal irritation. The test substance was applied to 2 test sites on the occluded backs and flanks of 6 young albino New Zealand rabbits at a dosage of 0.5 ml (undiluted) or 0.5 g (solid) for 4 hours. Clinical signs included severe erythema and edema, irreversible chemical burns, and subdermal hemorrhages. One animal died prior to the 24-hour observation. Mean primary irritation score was 8.0/8.0 and the test substance was classified as corrosive (2).

Repeated dose toxicity
Subacute
No data available.
Semichronic
Crotonaldehyde was evaluated for subchronic toxicity study, male and female Sprague-Dawley rats (5/sex/group) were fed diets containing crotonaldehyde at nominal dose levels of 0, 22, 44, 88 or 175 mg/kg/day for 14 days. Actual mean dosages (male/female) for the above groups were: 0/0, 19/17, 36/36, 73/68, and 139/136 mg/kg/day, respectively. There were no statistically significant differences between treated and control animals in the following: mortality, clinical signs of toxicity, body weight, food consumption, efficiency of food utilization (change in body weight/weekly food consumption), and absolute or relative organ weights. There were no exposure-related gross lesions observed in any of the treated groups (2).
Crotonaldehyde was administered by gavage to male and female Fischer 344 rats and B6C3F1 mice at doses of 2.5, 5, 10, 20, or 40 mg/kg bw/day on five days per week for 13 weeks. Dose related mortality was observed in rats at doses equal to or greater than 5 mg/kg bw/day, but no deaths were seen in mice. Dose-related lesions of the forestomach (hypertension, inflammation, hyperkeratosis and necrosis) were seen in rats at doses equal to or greater than 10 mg/ kg bw/day and in mice at 40 mg/kg bw/day. Acute inflammation of the nasal cavity was seen in rats at doses equal to or greater than 5 (males) and 20 mg/kg bw/day (females) (2).
Chronic
Groups of 23 - 27 male Fischer rats, six weeks of age, were given 0, 0.6 or 6.0 mmol/L crotonaldehyde (purity, >99%) in distilled drinking-water [e.g. 1.87 mg/kg bw/day and 15.51 mg/kg bw/ day] for 113 weeks. Survival was similar in all groups; 17, 13 and 16 rats in the three groups survived to 110 weeks. Throughout the study, those rats receiving the high dose of crotonaldehyde had lower body weights than either the controls or those at the low dose. Gross lesions and representative samples from all the major organs [unspecified] were taken for microscopic examination; particular attention was paid to lesions in the liver, including altered liver-cell foci. Hepatocellular carcinomas were seen in 0/23 control rats, 2/27 at the low dose and 0/23 at the high dose; and neoplastic nodules were found in 0/23 controls, 9/27 at the low dose [p=0.01]and 1/23 at the high dose. Altered liver-cell foci [considered by the authors to be precursors of hepatocellular neoplasms] were observed in 1/23 control rats, 23/27 at the low dose ($p<0.001$) and 13/23 at the high dose ($p<0.001$) (i.e. no dose response). Liver damage, reported as moderate to severe and including fatty metamorphosis, focal liver necrosis, fibrosis and cholestasis, was seen only in 10/23 rats given the high dose [$p<0.001$]; none of these 10 animals had preneoplastic or neoplastic lesions (1) (13).

Carcinogenicity
Human
Eder et al. (1999) reported an estimated cancer risk for the exposure to crotonaldehyde due to cigarette smoke. Based on a cancer incidence (of hepatocellular carcinomas) of 0.07 at a dose of 4.2 mg crotonaldehyde/kg bw/day from another study they interpreted this as a risk of 5.8-18 new cases per 10^4 smokers (assuming a consumption of 30 cigarettes per day). They state that this approach may lead to an overestimate of the cancer risk associated with

exposure to crotonaldehyde; the estimate based on their own study resulted in a 20-fold lower estimate of the carcinogenic risk of crotonaldehyde. They used dose-adduct levels relationship for their estimation in stead of hepatocellular carcinomas (10). Feron et al (1991) regarded crotonaldehyde as a potential oral carcinogen and thus a dietary cancer risk factor for humans (14).
Animal
See under chronic toxicity; Crotonaldehyde (0.6 mM in drinking water for 113 weeks) induced neoplastic lesions of the liver in 9 of 27 rats; 2 rats had hepatocellular carcinomas, and 9 rats had neoplastic nodules. It also caused liver cell foci in 23 of 27 rats. The incidences of tumors and foci were significantly higher than those of the control group (2). But lower than in the high dose group.

Reproduction toxicology
Human
No data available.
Animal
Oral or intraperitoneal administration of crotonaldehyde (no dose mentioned) damaged the spermatogenic cells of the mouse seminiferous tubules. Besides gross degeneration, polydiploidy was observed at all stages of spermatogenesis. Abnormal pairing of sex chromosomes occurs at diakinesis or metaphase I (2).

Mutagenicity
Human
No data available.
Animal
Crotonaldehyde displays a strong mutagenic activity for Salmonella typhimurium when tested in a modified liquid suspension procedure instead of the standard plate-incorporation Ames assay (2).
Crotonaldehyde was tested for the induction of sex-linked recessive lethal mutations in Drosophila melanogaster using a standard protocol approved by the National Toxicology Program. Canton-S wild-type males were tested with the concentrations that result in approximately 30% mortality after 72 hr of feeding or 24 hr after injection. Following treatment, males were mated individually to 3 harems of Basic virgin females to produce 3 broods for analysis. Crotonaldehyde was negative for lethal mutations after feeding 4000 ppm (4 g/kg) to males but positive for lethal mutations and translocations after injection of 3500 ppm (3.5 g/kg) (2).

Other
A reduced chemotactic responsiveness of polymorphonuclear leukocytes isolated from peripheral blood of smokers has previously been demonstrated and suggested to be an acute effect of smoking. Upon fractionation of cigarette smoke condensate, crotonaldehyde is one of the most potent inhibitors of polymorphonuclear leukocytes (2). To achieve a 50% inhibition of chemotaxis a concentration of 40 µM (2.8 mg/L) crotonaldehyde was necessary. To accomplish a 50% inhibition of 50% adherence a 218 µM (15.3 mg/L) concentration of crotonaldehyde was necessary (15).
In both human polymorphonuclear leucocytes and rat pulmonary alveolar macrophages there was a dose-related decrease in plasma membrane surface SH groups and soluble SH after crotonaldehyde treatment. For instance 100 µM crotonaldehyde resulted in a 28% decrease in plasma membrane surface sulphydryl groups. It has been suggested that changes in the SH status by reactive aldehydes can modulate the activity of the plasma membrane NADPH oxidase responsible for O_2^- production, crotonaldehyde was less effective than acrolein (16).
In the literature the hypothesis exists that DNA adducts with deoxyguanosine play a crucial role in the genotoxicity of crotonaldehyde (10). Crotonaldehyde binds to DNA and induces

DNA-protein cross-links in vitro. It modifies DNA by forming cyclic 1,N^2-propanedeoxyguanosine. These adducts occur in vivo also in the absence of exposure to either crotonaldehyde or acrolein. The estimated total numbers of adducts in DNA liver were 1.0-1.7/10^6 guanine bases for mice and 0.2-1.0 for rats and 0.3-2.0 for humans (1).
In untreated male Fischer 344 rats crotonaldehyde adducts were not detected, but crotonaldehyde adducts were found in the tissues of rats given single doses of 200 or 300 mg/kg bww and in the livers of rats after repeated doses of 1 or 10 mg/kg bw. Surprisingly adduct levels were higher 20 h after gavage than after 12 h. The adducts persist to a certain extent. The highest adduct levels were found in organs where cancer was induced in a long-term study and in an epidemiological workplace study (10).

Critical assessment
The acute toxicity of crotonaldehyde consists mainly of irritation of the eyes, skin and respiratory tract. Extremely high concentrations (e.g. 500 mg/kg in rats) result in terminal convulsions. There is inconclusive evidence for the carcinogenicity of crotonaldehyde. IARC classifies crotonaldehyde subsequently in group 3. There is evidence of adduct formation *in vivo*.

Conclusion
Smoking related crotonaldehyde exposures could lead to local damage in the respiratory tract depending on the amount of crotonaldehyde per cigarette.

INTERACTIONS

Chemical
Reacts violently with bases, strong oxidizing agents and polymerization initiators (1). Crotonaldehyde in smoke may react with protein –SH and $–NH_2$ groups by a Michael addition reaction that results in a protein-bound aldehyde functional group (8).
Crotonaldehyde is a α,β-unsaturated aldehyde. These aldehydes will generally be conjugated with glutathione or other thiol-containing molecules. The β-carbon of the unsaturated aldehyde is a prime target for soft electrophiles like glutathione or cysteine. In principle the reaction is reversible, and the alkylating aldehydes might be released at some other site. On reaction with cysteine, cyclic thiazolidines will be formed (14).

In vivo
Crotonaldehyde was oxidized by disrupted rat liver mitochondrial fractions or by intact mitochondria at rates that were only 10-15% those of acetaldehyde. Although a poor substrate for oxidation, crotonaldehyde is an effective inhibitor of the oxidation of acetaldehyde by mitochondrial aldehyde dehydrogenase, by intact mitochondria, and by isolated hepatocytes. Inhibition by crotonaldehyde was competitive with respect to acetaldehyde, and the Ki for crotonaldehyde was approximately 5-20 μM. Crotonaldehyde had no effect on the oxidation of glutamate or succinate. Very low levels of acetaldehyde were detected during the metabolism of ethanol. Crotonaldehyde increased the accumulation of acetaldehyde more than 10-fold, indicating that crotonaldehyde, besides inhibiting the oxidation of added acetaldehyde, also inhibited the oxidation of acetaldehyde generated by the metabolism of ethanol (2).
Crotonaldehyde was a potent inhibitor of mitochondrial oxidation of formaldehyde, but had no effect on the activity of formaldehyde dehydrogenase. In hepatocytes, crotonaldehyde produced approximately 30-40% inhibition of formaldehyde oxidation (2).
To study the toxic interaction between acetaldehyde and crotonaldehyde, the acute toxicity tests with mice intubated orally, the mutagenicity tests with *Salmonella typhimurium* LT2 his strains and, the DNA-synthesis inhibition tests with Hela cells were carried out. The combined acute toxic effects of the two aldehydes are additive. Acetaldehyde is not mutagenic in Ames test, but slightly inhibits cell DNA synthesis at concentration
400 μg/ml, while crotonaldehyde shows the mutagenic effect on the strain TA100 without S-9 and inhibits DNA synthesis significantly. Both the mutagenic activity and inhibition

effect on DNA synthesis of crotonaldehyde showed no change in the presence of acetaldehyde (2). Crotonaldehyde can form DNA adducts, see Toxicology; other.

Critical assessment

Chemical

Crotonaldehyde (cis- and –trans-) is a volatile short chain, mono-unsaturated compound, containing a reactive aldehyde group.

In vivo

Crotonaldehyde inhibits the metabolism of acetaldehyde and formaldehyde in vitro. Data on the effects of combined exposure to crotonaldehyde and other aldehydes on the respiratory tract are missing. Crotonaldehyde forms adducts with DNA.

Conclusion

Chemical

Crotonaldehyde is a volatile, reactive compound.

In vivo

More research is needed to evaluate the hazards of smoking related exposure levels to a mixture of aldehydes.

DEPENDENCY

No data available.

Effects of smoking cessation

No data available.

Critical assessment

Not relevant.

Conclusion

Not relevant.

COMMERCIAL USE

The main use of crotonaldehyde in the past was in the manufacture of n-butanol, but this proces has been largely displaced by the oxo process. Currently, the most extensive use of crotonaldehyde is in the manufacture of sorbic acid; crotonic acid is made commercially by oxidation of crotonaldehyde and 3-methoxybutanol by the reaction of methanol with crotonaldehyde, followed by reduction.

Crotonaldehyde has been used as a warning agent in fuel gases, for locating breaks and leaks in pipes. It has also been used in the preparation of rubber accelerators, in leather tanning, as an alcohol denaturant and as a stabilizer for tetraethyl-lead (1).

BENEFICIAL EFFECTS

No data available.

Critical assessment

Not relevant.

Conclusion

Not relevant.

SUMMARY AND FINAL CONCLUSION

Crotonaldehyde is one subtype of several other aldehydes present in cigarette smoke. A certain percentage of the aldehydes in the vapour phase of smoke is transferred directly from tobacco, however, most are formed during smoking from such precursors as polysaccharides, pectin's, proteins, and possibly, triglycerides in tobacco. The function of crotonaldehyde in tobacco products is not known. Crotonaldehyde was detected in mainstream cigarette smoke at 10-228 µg/cigarette.

The highest daily intake of crotonaldehyde is assumed to be derived from cigarette smoke.

Sufficient inhalation data are missing to evaluate the pharmacodynamic effects of crotonaldehyde due to cigarette smoking. Further research is needed to test the reported ciliatoxicity. Data on the pharmacokinetic properties of crotonaldehyde are missing. For a critical assessment research is needed, especially to obtain the amount of absorption and bioavailability after smoking related exposures to crotonaldehyde. Other aldehydes are known to induce mainly local effects at the site of exposure and little systemic effects. Expected effects are increased airway resistance and local damage to the respiratory tract.

The acute toxicity of crotonaldehyde consists mainly of irritation of the eyes, skin and respiratory tract. There is inconclusive evidence for the carcinogenicity of crotonaldehyde. IARC classifies crotonaldehyde subsequently in group 3. There is evidence of adduct formation *in vivo*. Smoking-related crotonaldehyde exposures could lead to local damage in the respiratory tract depending on the amount of crotonaldehyde per cigarette. There are no data on dependency available and there are no known beneficial effects of crotonaldehyde exposure through smoking.

No conclusions could be made based on the available information to assess the health risk of smoking related exposure to crotonaldehyde. The health risks of the exposure to crotonaldehyde due to cigarette smoking need to be studied. Expected effects according to other aldehydes are increased airway resistance and local damage of the respiratory tract. Another point of concern is the exposure of crotonaldehyde together with other aldehydes in cigarette smoke and further study on this combined exposure is needed.

DATE THIS SHEET WAS GENERATED

Based on literature available in May 2002.

REFERENCES

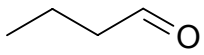
(1) Crotonaldehyde. Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals. Lyon: 1995: 373-392.
(2) The hazardous Substance Data Bank (HSDB). through 2000/10. 2001. The National Library of Medicine.
(3) Brandweerinformatiecentrum gevaarlijke stoffen (BIG). versie 9.0. 2001. Belgium.
(4) The Merck Index. versie 12:1 . 1996. Chapman & Hall EPD.
(5) Walder R, Franklin JL. Proton affinities of neutral molecules. Int J Mass Spectometry Ion Physics 1980; 36:85-112.
(6) Chemiekaarten®, 15e editie. 2000. Ten Hagen & Stam.
(7) OSHA, Occupational Safety and Health Administration. Occupational safety and health guideline for crotonaldehyde. OSHA U.S.Dep. of Labor. 2002.
(8) Eiserich JP, van der Vliet A, Handelman GJ, Halliwell B, Cross CE. Dietary antioxidants and cigarette smoke-induced biomolecular damage: a complex interaction. Amer J Clin Nutr 1995; 62(suppl):1490S-1500S.
(9) IARC. Tobacco smoking. 38. 1986. Lyon, IARC. Evaluation of the carcinogenic risk of chemicals to humans.
(10) Eder E, Schuler D, Budiawan. Cancer risk assessment for crotonaldehyde and 2-

hexenal: an approach. IARC Sci Publ 1999;(150):219-232.
(11) US Environmental Protection Agency. Ohmtads: Oil and Hazardous Materials, Technical Assistance Data System. US EPA. 2002.
(12) Dalham T, Rosengren A. Effect of Different Aldehydes on Tracheal Mucosa. Arch Otolaryng 1971; 93:496-500.
(13) Chung F-L, Tanaka T, Hecht SS. Induction of Liver Tumors in F344 Rats by Crotonaldehyde. Cancer Res 1986; 46:1285-1289.
(14) Feron VJ, Til HP, de Vrijer F, Woutersen RA, Cassee FR, van Bladeren PJ. Aldehydes: occurence, carcinogenic potential, mechanism of action and risk assessment. Mutation Res 1991; 259(363):385.
(15) Bridges RB, Hsieh L, Kaack DG. Effects of cigarette smoke and it constituents on the adherence of polymorphonuclear leukocytes. Infect Immunity 1980:1096-1101.
(16) Witz G, Lawrie NJ, Amoruso MA, Goldstein BD. Inhibition by reactive aldehydes of superoxide anion radical production from stimulated poly-morphnuclear leukocytes and pulmonary alveolar macrophages: Effects on cellular sulfhydryl groups and NADPH oxidase activity. Bioch Pharmacol 1987; 36(5):721-726.

Appendix 2 Butyraldehyde

GENERAL
IUPAC systematic name: butyraldehyde (1;2)
Synonyms: butanal, butyladehyde, butyric aldehyde (1), butal, butaldehyde, butalyde, n-butanal, butanaldehyde, n-butyl aldehyde, butyral, n-butyraldehyde, butyrylaldehyde (2).
Molecular formula: C_4H_8O (1) (2)

Molecular structure



Molecular weight: 72.11 g/mol (1) (2)
Alifatic: Yes
Aromatic: No
N containing: No
Halogen containing: No
CAS registry no.: 123-72-8 (1) (2)
Storage:
R/S classification: R11; S2, S9, S29, S33 (1).
dangercode (transport): 33 (3)
Properties:

- melting point: -99°C (1) (2)
- boiling point: 74.8°C (1) (2)
- density: 0.8016 g/cm^3 at 20°C (1) (2)
- refractive index: 1.3790 at 20°C (4).
- solubility: soluble in acetone, diethyl ether, ethanol, ethyl acetate, toluene (1). Solubility in water 71,000 mg/l at 25°C (2). Soluble in oils, soluble in benzene (2).
- substance description:
  - colorless (2)
  - liquid (2)
  - odor is characteristic, pungent, aldehyde odor (2); detectable at 4.6-39 ppb(5)(6).
- volatility: butyraldehyde is a rather volatile liquid.
- pK_a: Not applicable.
- PA: 189.7 kcal.mol^{-1}, 196.3 kcal.mol^{-1} (7)
- flammability:
  - FP = - 6.6°C (1)
  - FL Limits = 1.9% by volume- 12.5% by volume (2)
  - IT = 74.8°C (5)
- decomposition temperature: 230°C (8)
- stability: unstable under the influence of heath or light, unstable in air (3).
- vapour pressure/ vapour tension (20°C): 91.5 mm Hg at 20°C (1)
- vapour pressure (50°C): No data available
- relative density: 0.8 (water=1) (8)
- octanol water partition coefficient, log P, log K_{OW}: 1.18 (1) (8), 0.88 (2)
- conversion factor: 1 ppm = 2.9 mg/m^3; 1 mg/m^3 = 0.34 ppm

Critical assessment
The presence of the aldehyde-function in the structure is a fundamental reaction location. The typical reaction type is nucleophilic addition, e.g. adduct formation with DNA and proteins.

Butyraldehyde is easily oxidised in the presence of oxidants.
Conclusion
Butyraldehyde is a reactive volatile liquid, containing a typical reactive site for nucleophilic addition.

FUNCTION IN TOBACCO
No data available.

AMOUNT IN TOBACCO PRODUCTS
No data available.

AMOUNT IN SMOKE
- **main stream** In an analysis of volatile carbonyl compounds, butyraldehyde in main stream smoke varied between 88.6-928.3 µg/cigaret depending on the brand tested (9).
- **side stream** No data available.

SOURCE
It seems likely that butyraldehyde is formed during smoking from precursors such as polysaccharides, pectins, proteins and possible triglycerides in tobacco (10).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE
Butyraldehyde can be released to the atmosphere in emissions from tobacco smoke. Butyraldehyde is released to the environment in emissions from combustion processes such as gasoline and diesel engines and wood burning. It is formed in the atmosphere through photochemical oxidation of other hydrocarbons. The gas-phase concentration of butyraldehyde in ambient Los Angeles air during photochemical pollution episodes (July-Oct 1980) ranged from 0 to 7 ppb with a median concentration of about 1.5 ppb. A field monitoring study along a highway in Raleigh, North Carolina USA in May 1983 detected butyraldehyde levels of 2.88-7.29 ppb (2).
If released to the atmosphere, butyraldehyde will degrade readily by reaction with photochemically produced hydroxyl radicals and direct photolysis. During intense smog-pollution episodes, the natural formation rate of butyraldehyde can exceed the degradation rate. Physical removal from air by wet deposition can occur. If released to soil or water, the major degradation pathway is expected to be biodegradation.
Occupational exposure to butyraldehyde occurs through inhalation of vapour and dermal contact (2)
It occurs naturally in various plants. Butyraldehyde has been found in the essential oils from flowers, fruits, leaves, or bark of *Monarda fistulosa*, *Litsea cubeba,* Bulgarian clary sage, cajeput*, Eucalyptus cinerea, Eucalyptus globulus* as well as in apple and strawberry aromas, and in tea leaves. Butyraldehyde has been qualitatively detected as a volatile component of raw chicken breast muscle and fried chicken. Butyraldehyde was qualitatively detected in 6 of 12 samples of human milk. It has also been reported as synthetic flavoring agent in foods (2). It has been estimated that the daily intake of butyraldehyde through food only is 26 µg/day in Europe (0.44 µg/kg bw/day) (11).

COMBUSTION PRODUCTS
No data available.

CONSENSUS REPORTS
JECFA considered butyraldehyde as a food additive to have no safety concerns.
Butyraldehyde is not included in IARC carcinogenic classification (3).

STANDARDS AND RECOMMENDATIONS
ADI: Not determined (3)
TWA_{NL} = MAC: Not determined (8)
TWA_{D} =MAK: Not determined (3)
TWA_{USA}: 25 ppm (2).
$STEL_{NL}$: Not determined (3)

$STEL_{USA}$: No data available.
LTEL: No data available.
TLV-C: No data available.
TLV-CARCINOGENICITY: No data available.
MAK-REPRODUCTION: No data available.

Reference value: No data available

CLASS
EG Carc. Cat.:Not included (3)
IARC-category: Not included (3)
CEC: No data available.

Critical assessment
Butyraldehyde is formed during smoking from precursors such as polysaccharides, pectins, proteins and possibly triglycerides in tobacco. The amount of butyraldehyde in main stream cigarette smoke ranges from 88.6-928.3 µg/cigaret Butyraldehyde is currently used as a food additive. No information is available on the nature of the combustion products formed during cigarette smoking.
Conclusion
Because of the large variation in the amount of butyraldehyde in main stream smoke, no estimation can be made concerning the mean exposure of the general population to butyraldehyde due to cigarette smoking. Although butyraldehyde is considered safe as a food additive the occurrence of butyraldehyde in cigarette smoke should be a point of concern.

PHARMACODYNAMICS
Mechanism of action
No data available.

Pulmonary system
- **breathing frequency**: See below.
- **tidal volume**: No data available.
- **lung compliance**: No data available.
- **airway resistance**: No data available.

Respiration and heart beat were increased in male rabbits exposed to 10-20 ppm butyraldehyde (2).

Cardiovascular system
- **blood pressure**: No data available.
- **heart rate**: See above.

Renal system
- **diuresis**: No data available.
- **saluresis**: No data available.

Nervous system
- **central nervous system**: No data available.
- **autonomic system**: No data available.
- **peripheral nervous system**: The changes in excitability and conduction properties of frog sciatic nerve under the influence of butyraldehyde were examined in the concentration range 0.001-1.00% (WT/VOL) and at 20, 25, 30 and 35°C. It irreversibly reduced the amplitude of the action potential of the nerve and decreased the conduction velocity up to the complete block (2).

Other
No data.

Critical assessment
Sufficient inhalation data are missing to evaluate the pharmacodynamic effects of butyraldehyde due to cigarette smoking.
Conclusion
Research is necessary to elucidate the pharmacodynamic effects of butyraldehyde due to cigarette smoking exposures.

PHARMACOKINETICS
Absorption
No data available.

Bioavailability
No data available.

Distribution
No data available.

Metabolism
Butyraldehyde is oxidised to butyric acid by aldehyde dehydrogenase in mammals. Further oxidation to $CO_2(HCO_3-)$ occurs in the liver and gut (12).
Butyric acid is metabolised via the fatty acid and tricarboxylic acid pathways (13).

Excretion
No data available.

Kinetic parameters
No data available.

Critical assessment
Data on the pharmacokinetic properties of butyraldehyde are missing. For a critical assessment research is needed, especially to obtain the amount of absorption and bioavailability after smoking related exposures to butyraldehyde. Following inhalation, other aldehydes are known to induce mainly local effects at the site of exposure and little systemic effects probably due to little absorption in the respiratory tract.
Conclusion
The kinetics of smoking related exposures to butyraldehyde need further study.

TOXICOLOGY
Acute toxicity
Human
Exposure of humans to 230 ppm (414 mg/m^3) in air is non- irritating (6).
Animal
LC50 rat inhalation (0.5 hr): 60,000 ppm (108000 mg/m^3) (1)
LC50 rat inhalation: 20-50 mg/l/4 hr (1600 ppm/ 4 hr) (3)
LD50 rat oral: 5890 mg/kg (1)
LD50 rat oral: 2490 mg/kg (2)
After inhalation of high levels (duration of exposure and amount not mentioned) butyraldehyde in rats, mice, guinea pigs and rabbits, bronchial and alveolar inflammation and fatal pulmonary edema were reported (2).

Local tolerance
Human
In safety regulations for the use of industrial butyraldehyde it is listed as an eye, nose, skin and throat irritant (2).
Animal
Butyraldehyde (500 mg) applied on the skin of rabbits for 24 hours, caused severe irritation and 20 mg instilled into rabbit eye for 24 hours caused moderate irritation (1).

Repeated dose toxicity
Subacute
No data available.
Semichronic
Inhalation exposure of rats for 6 hours/day for 12 days to 1000 ppm (1800 mg/m^3) had no observable effects. Exposure to concentrations of butyraldehyde ranging from 293 to 2710 mg/m^3 for 6 hours/day, 5 days/week, for 4 weeks produced no effects at 930 mg/m^3, while at 2710 mg/m^3, oral discharge and increased adrenal and lung weights were observed (12).
Subchronic inhalation toxicity of butyraldehyde vapor was evaluated in groups of 3 male English A (SR) guinea pigs (GP), 5 male Swiss-Webster mice (SWM), 4 male New Zealand white rabbits (NZR), 4 male beagle dogs (d), 5/sex Sprague-Dawley rats (SDR), and 5/sex Fischer 344 rats (FR) exposed to measured concentrations of 0, 2000, 3100, and 6400 ppm (0, 3600, 5580, 11520 mg/m^3), 6 hour/day, 5 days/week for 9 days over a 2-week period. The majority of adverse effect levels noted for each species included: mortality in the 6400 ppm (11520 mg/m^3) groups (all test species); decreased body weights at 3100 ppm (5580 mg/m^3) and higher (GP, SWM), and in all SDR and FR treatment groups; decreased relative kidney weight (SDR) and liver weight (FR) in all exposure groups: and hemorrhage of the ethmoturbinates in 1 SDR at 6400 ppm (11520 mg/m^3). Exposure of Sprague-Dawley rats (20/sex/group) and beagle dogs (4 males) to butyraldehyde vapour at concentrations of 0, 125, 500, and 2000 ppm (0, 225, 900, 3600 mg/m^3) 6 hour/day, 5 days/week, for 13 weeks led to mortality (1 male SDR in the 2000 ppm (3600 mg/m^3) group); decreased alkaline phosphatase levels (SDR males at 500 ppm (900 mg/m^3)): elevated mean albumin levels (125 ppm; 225 mg/m^3), altered blood chemistry and decreased red blood cell and monocyte counts at 125 ppm (225 mg/m^3) and higher (SDR); lesions of nasal epithelium and mild interstitial pneumonia at 125 ppm (225 mg/m^3) and higher (SDR): and nasal mucosal lesions at 500 ppm (900 mg/m^3) and higher (D). Similar exposure of Fischer rats (15/sex/group) to concentrations of 0, 1.0, 10.0, and 50.0 ppm (0, 1.8, 18, 90 mg/m^3) induced increased relative kidney weights among high-dose males. No other adverse effects were observed in this species at these exposure levels (14).
Irritation, inflammation and necrosis of gastric mucosa and forestomach, possibly due to route of administration, were found in rats administered butyraldehyde at 1.2 g/kg/day for 13 weeks by gavage. Mild inflammatory lesions of the nasal cavity were seen in mice treated by gavage with 300 mg/kg/day and above, while the no-effect level was estimated to be 75 mg/kg/day (12).
Chronic
No data available.

Carcinogenicity
Human
Butyraldehyde is not included in IARC carcinogenic classification (3).
Animal
Butyraldehyde is not included in IARC carcinogenic classification (3).

Reproduction toxicology
Human
No data available.

Animal
Mice administered a single dose of 30 mg/kg by intraperitoneal injection, or 300 mg/kg/day (author-estimated dose) in drinking water for 50 days showed pathologic changes, including chromosomal and meiotic anomalies, in sperm at all stages of development (12).

Mutagenicity
Human
No data available.
Animal
Butyraldehyde was negative in the Salmonella assay. In Chinese hamster ovary cells it did not induce chromosomal aberrations, but was positive in a sister chromatid exchange assay. Negative results were obtained in the sex-linked recessive lethal assay with Drosophila and sister chromatid exchange test with human lymphocytes (12). In Salmonella typhimurium tester strains butyraldehyde was non-mutagenic (15).

Other
Butyraldehyde is able to form DNA-protein cross links (16).

Critical assessment
The acute toxicity of butyraldehyde is low and consists mainly of irritation of the eyes, skin and respiratory tract. Lesions of the nasal epithelium occur at 225 mg/m^3 at daily continuous exposures. Further study is needed to establish whether butyraldehyde exposure through cigarette smoking is high enough to cause damage to the respiratory tract. Butyraldehyde is not included in a carcinogenic classification.
Conclusion
Further study is needed to establish whether butyraldehyde exposure through cigarette smoking is high enough to cause damage to the respiratory tract.

INTERACTIONS
Chemical
This chemical is incompatible with oxidizers. It is also incompatible with strong bases and strong reducing agents. It can react vigorously with chlorosulfonic acid, nitric acid, oleum and sulfuric acid. It may react with acids, oxygen, peroxides, caustic soda, soda ash, amines and ammonia. It undergoes reduction, oxidation and condensation reactions. Polymerization may occur in the presence of heat, acids or alkalies. (4)

In vivo
No data available.

In vitro
Butyraldehyde reacts with hemoglobin *in vitro* to form imidazolidinones. When a smoke condensate was used butyraldehyde was not responsible for the formation of hemoglobin adducts (17).

Critical assessment
Chemical
The aldehydegroup present in the molecular structure of butyraldehyde is a potential site for oxidation, for reduction and for adduct formation.
In vivo
No data available.
In vitro
Butyraldehyde is not responsible for the formation of adducts with hemoglobin in smoke condensate.
Conclusion
Chemical: Few data were found for adduct formation although the chemical structural

suggests the potency to do so.
In vivo: No data available.
In vitro: Butyraldehyde is not responsible for the formation of adducts with hemoglobin in smoke condensate.

DEPENDENCY
No data available.

Effects of smoking cessation
No data available.

Critical assessment
Not relevant.
Conclusion
Not relevant.

COMMERCIAL USE
Butyraldehyde is used in rubber accelerators, synthetic resins, solvents, and plasticisers (1) (2), and has been reported as synthetic flavoring agent in foods (2).

BENEFICIAL EFFECTS
No data available.

Critical assessment
Not relevant.
Conclusion
Not relevant.

SUMMARY AND FINAL CONCLUSION
Butyraldehyde is one of several aldehydes present in cigarette smoke. A certain percentage of the aldehydes in the vapour phase of smoke is transferred directly from tobacco, however, most are formed during smoking from such precursors as polysaccharides, pectin's, proteins, and possibly, triglycerides in tobacco.
The amount of butyraldehyde in main stream cigarette smoke ranges from 88.6-928.3 µg/cigaret. Butyraldehyde is currently used as a food additive. No information is available on the nature of the combustion products formed during cigarette smoking. The majority of the occupational safety limits have not been determined.
Sufficient inhalation data are missing to evaluate the pharmacodynamic effects of butyraldehyde due to cigarette smoking. Data on the pharmacokinetic properties of butyraldehyde are also missing. For a critical assessment research is needed, especially on the amount of absorption and bioavailability after smoking related exposures to butyraldehyde. Other aldehydes are known to induce mainly local effects at the site of exposure and little systemic effects. Further study is needed to establish whether butyraldehyde exposure through cigarette smoking is high enough to cause damage to the respiratory tract. The combined exposure with other aldehydes in cigarette smoke remains a point of concern. Butyraldehyde is not included in a carcinogenic classification. There are no data on dependency available and there are no known beneficial effects of butyraldehyde exposure through smoking.
Further study is needed to establish whether butyraldehyde exposure through cigarette smoking is high enough to cause damage to the respiratory tract. The combined exposure with other aldehydes present in cigarette smoke remains a point of concern and needs further study.

DATE THIS SHEET WAS GENERATED
Based on literature available in September 2002.

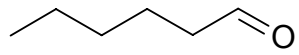
REFERENCES

(1) Dictionary of substances and their effects (DOSE). The Royal Society of Chemistry, editor. 10/2000. 2001.
(2) The hazardous Substance Data Bank (HSDB). through 2000/10. 2001. The National Library of Medicine (NLM).
(3) Brandweerinformatiecentrum gevaarlijke stoffen (BIG). versie 9.0. 2001. Belgium.
(4) National Toxicology Program. Chemical health and safety data. 2002.
(5) US Environmental Protection Agency. Oil and Hazardous Materials- Technical Assistance Datasystem (OHMTADS). 1994
(6) Health Effects Assessment for Butyraldehyde at the Decatur Plant (final report) with attachment and clover letter dated 122889. EPA /OTS ; Doc #86 900000051 1989.
(7) Walder R, Franklin JL. Proton Affinities of Neutral Molecules. Int J Mass Spectrom Ion Phys 1980; 36:85-112.
(8) Chemiekaarten®, Gegevens voor veilig werken met chemicaliën. 15e editie . 2000. Ten Hagen & Stam.
(9) Miyake T, Shibamoto T. Quantitative analysis by gas chromatography of volatile carbonyl compounds in cigarette smoke. J Chromatogr A 1995; 693:376-381.
(10) IARC. Tobacco smoking. 38. 1986. Lyon, IARC. Evaluation of the carcinogenic risk of chemicals to humans.
(11) The Forty-ninth meeting of the joint FAO/WHO expert committee on food additives (JECFA). Safety evaluation of certain food additives and contaminants 40, 147-188, 1998. Geneva, World Health Organization. WHO Food Additives Series.
(12) Health Effects Assessment for Butyraldehyde at the Nitro Plant (final report) with attachment and clover letter dated 122889. EPA /OTS ; Doc #86 900000054 1989.
(13) Joint FAO/WHO expert committee on Food Additives. Evaluation of certain food additives and contaminants. 884, 29-31, 1999. Geneva, World Health Organization. WHO Technical Report Series 884.
(14) Butyraldehyde: 9-day repeated vapor inhalation toxicity, vapor inhalation by dogs and rats for 12 and 13 weeks, respectivelyand a 12-week vapor inhalation study in rats with letter 020689. EPA /OTS; Doc #86 890000097 1989.
(15) Dillon D, Combes R., Zeiger E. The effectiveness of Salmonella strains TA100, TA102 and TA104 for detecting mutagenicity of some aldehydes and peroxides. Mutagenesis 1998; 13(1):19-26.
(16) Kuykendall JR, Bogdanffy MS. Efficiency of DNA-histone crosslinking induced by saturated and insaturated aldehydes in vitro. Mutation Res 1992; 183(2):131-136.
(17) Hoberman HD, San Georges RC. Reaction of Tobacco Smoke Aldehydes With Human Hemoglobin. J Biochem Toxicol 1988; 3:105-119.

Appendix 3 Hexanal

GENERAL
IUPAC systematic name: hexanal (1)
Synonyms: caproic-aldehyde, caproaldehyde, hexaldehyde (1), capronaldehyde, n-caproylaldehyde, hexoic-aldehyde, hexylaldehyde (2).
Molecular formula: $C_6H_{12}O$ (1) (2)

Molecular structure



Molecular weight: 100.16 g/mol (1)
Alifatic: Yes
Aromatic: No
N containing: No
Halogen containing: No
CAS registry no.: 66-25-1 (1)
Storage:
R/S classification: R10, 37; S 16, 23 (3).
dangercode (transport): 30 (3)
Properties:

- melting point: -56.3°C (1)
- boiling point: 128.7°C (1), 131°C (4)
- density: 0.8335 g/ml at 20°C (1) (5)
- refractive index: 1.4039 at 20°C (5)
- solubility: soluble in ethanol, propylene glycol and fixed oils (1). Slightly soluble in water, soluble in acetone, and in ether (2).
- substance description:
  - colorless (2)
  - liquid (2)
  - odor: characteristic fruity odour on dilution, strong green grass odour, sharp aldehyde odour (2).
  - taste: chrasteristic fruity taste on dilution, apple taste (2).
- volatility:
- pK_a: No data available.
- PA: No data available.
- flammability:
  - FP = 32°C (1)
  - FL Limits = No data available.
  - IT = 220°C (3)
- decomposition temperature: No data available.
- stability: Autooxidizes and polymerizes especially in the presence of traces of acid (2).
- vapour pressure/ vapour tension (20°C): 10.5 mm Hg (2).
- vapour pressure (50°C): No data available.
- relative density: 0.8335 (water =1) (3)
- octanol water partition coefficient, log P, log K_{OW}: 1.78 (1).
- conversion factor: 1mg/m^3 = 0.245 ppm; 1 ppm= 4.1 mg/m^3 (2)

Critical assessment
The presence of the aldehyde-function in the structure is a fundamental reaction location. The typical reaction type is nucleophilic addition, e.g. adduct formation with DNA and

proteins. Hexanal is easily oxidised in the presence of oxidants.

Conclusion

Hexanal is a fairly reactive volatile liquid, containing a typical reactive site for nucleophilic addition.

FUNCTION IN TOBACCO

No data available.

AMOUNT IN TOBACCO PRODUCTS

No data available.

AMOUNT IN SMOKE

- **main stream** Hexanal varies between 102.2±56.9 – 380.9±45.0 µg/cigarette (6). Another reference reported not detectable in mainstream cigarette smoke (7).
- **side stream** No data available.

SOURCE

A certain percentage of the aldehydes in the vapour phase of smoke is transferred directly from tobacco, where these compounds are formed by nonenzymatic browning reactions. However, most are formed during smoking from such precursors as polysaccharides, pectins, proteins, and possibly, triglycerides in tobacco (8).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

The general population will be exposed to hexanal via inhalation of ambient air, ingestion of food and drinking water, and dermal contact with vapours, food and other products containing hexanal. The production and use of hexanal as a food additive (flavour ingredient), in organic synthesis of plasticisers, rubber chemicals, dyes, synthetic resins, and insecticides, and in perfumery (at low concentrations) may result in its release to the environment through various waste streams. Hexanal has been identified in all types of water samples, engine exhaust, atmospheric samples, in several varieties of food including mother's milk, and in human adipose tissue. It also has been detected in the emissions of household waste, landfills, agricultural plants, and building materials (in indoor air) (2).

If released to the atmosphere, hexanal will exist in the vapour phase. Vapour-phase hexanal is degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals with an estimated half-life of about 13 hours. Hexanal is also degraded in the atmosphere by reaction with nitrate radicals with an estimated half-life of 3.4 years (2).

Hexanal has been identified in exhaust gases from gasoline and in diesel engines (0.2 ppm; 0.82 mg/m^3). Hexanal has been detected in fireplace emissions when burning cedar (split wood, 0.075 g/kg), red oak (split wood, 0.060 g/kg), and green ash (quartered logs, 0.027 g/kg) (2). The mean concentration of hexanal in the atmosphere over the Netherlands is 0.20 ppb (0.82 µg/m^3). The average dose of hexanal exposure based on outdoor concentrations of hexanal of the Dutch population through inhalation is 16.5 µg/day (6.0 mg/yr) (9).

The average concentration of hexanal in indoor and outdoor air in Northern Italy was 10 and < 2.0 µg/m^3 (respectively 2.4 and < 0. 49 ppb). Hexanal was detected in the air of all 26 houses tested for the presence of organic compounds. In 50 normal houses (residents report no problems) the average concentration was 6.60 µg/m^3 (1.6 ppb). Out of 38 sick houses (residents complained of problems) 5.3 percent had concentrations of hexanal 10-50 times higher than the median concentration of the normal houses (5.41 µg/m^3 hexanal; 1.3 ppb). In a study of new and recently renovated buildings in Switzerland, the 10^{th} , 50^{th} , and 90^{th} percentiles of the concentrations of hexanal detected were <5 µg/m^3 (1.2 ppb), 34 µg/m^3 (8.3 ppb), and 1461 µg/m^3 (356 ppb), respectively (2). These studies on indoor hexanal concentrations vary between <5-1461 µg/m^3. It is not clear what the cause of this large variation is. Also the relative exposure to hexanal through indoor exposure is expected to be much larger than the expected outdoor exposure mentioned above.

Hexanal was detected in water in the Rhine Delta at three locations: in the outlet of the

IJssel at Kampen (0.035 µg/L), downstream of Rotterdam harbor at Maassluis (0.054 and 0.036 µg/L), and in the semi-stagnant branch at Haringvliet (50.0 µg/mL) (2). Hexanal has been identified in samples of rainwater (0.007-0.010 µg/mL) collected at urban locations in California (2). Hexanal has been qualitatively identified in drinking water (2).
Hexanal has been found as a volatile component of sweet corn (cream can corn 14 µg/kg; kernel corn 24 µg/kg; frozen kernel corn 5µg/kg; fresh kernel corn 4 µg/kg; mature; 13183 µg/kg and ripe; 8398 µg/kg guava fruit (2). In beans 103 µg/kg; split peas 110 µg/kg, and lentils; 59 µg/kg. Also in scrambled eggs (supermarket eggs packed in polystyrene, 39 µg/kg; fresh eggs not stored, 32 µg/kg; and fresh eggs stored in polystyrene for 2 weeks, 59 µg/kg. In cooking oil, 3720 and 3039 µg/kg; Cantonese style roasted duck 67.72 µg/kg), and Cantonese style roasted duck gravy (736.66 µg/kg). Reported uses of hexanal in non-alcohol beverages is 1.3 mg/kg; in ice creams 2.8 mg/kg; in candy 3.6 mg/kg; in baked goods 4.2 mg/kg; in gelatins and puddings 2.0-2.5 mg/kg; in chewing gum 3.0 mg/kg (2). Hexanal was detected in 42 samples of mother's milk (2).

COMBUSTION PRODUCTS
No data available.

CONSENSUS REPORTS
Hexaldehyde has not been included in the IARC carcinogenicity class (3). Hexanal is used as a food additive and has been reviewed by a joint FAO/WHO Expert Committee on Food Additives which concluded that hexanal would not present safety concerns for the use of food additive at the current levels of intake (10).

STANDARDS AND RECOMMENDATIONS
ADI: 780 µg/day/ kg body weight in Europe and 260 µg/day/kg body weight in USA (10).
TWA_{NL} = MAC: No data available.
TWA_{D} =MAK: Not included (3).
TWA_{USA}: No data available.
$STEL_{NL}$: No data available.
$STEL_{USA}$: No data available.
LTEL: No data available.
TLV-C: Not included (3).
TLV-CARCINOGENICITY: Not included (3).
MAK-REPRODUCTION: No data available.

Others: No data available.

Reference value:
No data available.

CLASS
EG Carc. Cat.: Not included (3).
IARC-category: Not included (3).
CEC: No data available.

Critical assessment
Hexanal is formed during smoking from precursors such as polysaccharides, pectins, proteins and possible triglycerides in tobacco. The amount of hexanal in main stream cigarette smoke ranges from 102.2±56.9 – 380.9±45.0 µg/cigaret. When smoking 25 cigarettes a day this will correspond with a minimum intake of 2.5 mg hexanal a day and with a maximum of 9.5 mg hexanal intake a day. Information on the amount in side stream smoke is not available. Hexanal is currently used as a food additive. No information is available on the nature of the combustion products formed during cigarette smoking.
Conclusion
When smoking cigarettes, the accepted daily intake of hexanal through foods will not be exceeded. Although hexanal is considered safe as a food additive the occurrence of hexanal

in cigarette smoke should be a point of concern.

PHARMACODYNAMICS
Mechanism of action
No data available.

Pulmonary system
- **breathing frequency**: No data available.
- **tidal volume**: No data available.
- **lung compliance**: No data available.
- **airway resistance**: No data available.

Cardiovascular system
- **blood pressure**: No data available.
- **heart rate**: No data available.

Renal system
- **diuresis**: No data available.
- **saluresis**: No data available.

Nervous system
- **central nervous system**: No data available.
- **autonomic system**: No data available.

Other
Hexanal completely inhibited lecithin cholesterol acyltransferase activity at 10 and 50 mM *in vitro*. Reactive aldehydes form adducts with free sulfhydryl groups functioning in the active site of lecithin cholesterol acyltransferase to inhibit enzyme activity (2).

Critical assessment
Insufficient inhalation data are available to evaluate the pharmacodynamic effects of hexanal due to cigarette smoking.
Conclusion
Research is necessary to elucidate the pharmacodynamic effects of hexanal due to cigarette smoking exposures.

PHARMACOKINETICS
Absorption
No data available.

Bioavailability
No data available.

Distribution
No data available.

Metabolism
Hexanal is metabolised by hepatic microsomal aldehyde dehydrogenase *in vitro* (1).
Aldehydes are readily oxidised to organic acids, which in turn can serve as substrate for fatty acid oxidation pathways and the Krebs cyclus. Oxidation of aldehydes is catalysed by alcoholdehydrogenase, which has been found in the brain, erythrocytes, liver, kidney, heart and placenta (2).Hexanal is rapidly oxidised to hexanoic acid which is metabolised via the

fatty acid and tricarboxylic acid pathways (10).
Excretion
No data available.

Kinetic parameters
No data available.

Critical assessment
Data on the pharmacokinetic properties of hexanal are missing. For a critical assessment research is needed, especially to obtain the amount of absorption and bioavailability after smoking related exposures to hexanal. Following inhalation, other aldehydes are known to induce mainly local effects at the site of exposure and little systemic effects probably due to little absorption in the respiratory tract.
Conclusion
The kinetics of smoking related exposures to hexanal need further study.

TOXICOLOGY
Acute toxicity
Human
No data available.
Animal
LCLo rat inhalation: 2000 ppm/4 hr (8200 mg/m^3) (1)
LD50 rat oral: 4890 mg/kg (1)

Local tolerance
Human
No data available.
Animal
Dermal application of 10 mg to rabbits (24 hr) caused mild irritation. 100 mg instilled into rabbit eye (24 hr) caused mild irritation (1).

Repeated dose toxicity
Subacute
Up to 1000 mg/ml administered via drinking water (duration not specified) had no overt toxic effect and no changes in growth rate or haematological parameters were observed. Mild treatment-related morphologic changes (tissues unspecified) were observed in high dose groups, but these could not be related to any functional changes. Reduced lactate dehydrogenase activity was noted in female rats (1).
Rats receiving diets containing hexanal (dose not mentioned) for 3 weeks showed a decrease in serum cholesterol and triglyceride (2).
Semichronic
No data available.
Chronic
No data available.

Carcinogenicity
Human
Not included in IARC carcinogenic classification (3).
Animal
Not included in IARC carcinogenic classification (3).

Reproduction toxicology
Human
No data available.

Animal
No data available.

Mutagenicity
Human
No data available.
Animal
Mutagenicity was tested in V79 Chinese hamster lung cells. Hexanal induced a dose-dependent increase in the frequency over controls of both 6-thioguanine-, and ouabain-resistant mutants at concentrations ranging from 3 to 30 mM (11).
Salmonella typhimurium TA1531 with metabolic activation was weakly positive. 0.01 g hexanal incubated with human endothelial cells in Earl's solution caused no cytotoxicity (1).

Other
Hexanal fully inhibited lecithin:cholesterol acyltransferase (LCAT) *in vitro* at 10 mM (12).

Critical assessment
The acute toxicity of hexanal is low and consists mainly of irritation of the eyes and skin. During smoking high concentration peak exposures of short duration will occur. Correspondingly with other aldehyde exposure, it seems likely that these smoking related hexanal exposures could result in damage to the respiratory tract. Hexanal is not included in a carcinogenic classification.
Conclusion
More research on smoking related exposures to hexanal is needed to confirm the expected respiratory tract irritation.

INTERACTIONS
Chemical
The aldehydegroup present in the molecular structure of hexanal is a potential site for oxidation, for reduction and for adduct formation. Being an aldehyde, hexanal will interact with amino containing compounds. In more general terms: it will participate in nucleophilic addition reactions.

In vivo
No data available.

Critical assessment
Chemical
The aldehydegroup present in the molecular structure of hexanal is a potential site for oxidation, for reduction and for adduct formation. Nucleophilic addition and oxidisability are the most marked chemical features of hexanal.
In vivo
Not relevant.
Conclusion
Chemical
Hexanal is a marked compound for nucleophilic addition reactions and for reactions with oxidisers.
In vivo
Not relevant.

DEPENDENCY
No data available.

Effects of smoking cessation
No data available.

Critical assessment
Not relevant.
Conclusion
Not relevant.

COMMERCIAL USE
Hexanal is used as a food additive as a flavouring agent. Hexanal is also used for organic synthesis of plasticers, dyes, synthetic resins and insecticides. At low concentrations it is used in perfumery for fruity odours (2).

BENEFICIAL EFFECTS
No data available.

Critical assessment
Not relevant.
Conclusion
Not relevant.

SUMMARY AND FINAL CONCLUSION
Hexanal is one of several aldehydes present in cigarette smoke. A certain percentage of the aldehydes in the vapour phase of smoke is transferred directly from tobacco, however, most are formed during smoking from such precursors as polysaccharides, pectin's, proteins, and possibly, triglycerides in tobacco. Hexanal is a marked compound for nucleophilic addition reactions and for reactions with oxidisers.
The amount of hexanal in main stream cigarette smoke ranges from 102.2±56.9 – 380.9±45.0 µg/cig. Hexanal is currently used as a food additive. No information is available on the nature of the combustion products formed during cigarette smoking. The majority of the occupational safety limits have not been determined.
Insufficient inhalation data are available to evaluate the pharmacodynamic effects of hexanal due to cigarette smoking. Data on the pharmacokinetic properties of hexanal are also missing. For a critical assessment research is needed, especially on the amount of absorption and bioavailability after smoking related exposures to hexanal. Other aldehydes are known to induce mainly local effects at the site of exposure and little systemic effects. The acute toxicity of hexanal is low and consists mainly of irritation of the eyes and skin. During smoking high concentration peak exposures of short duration will occur. Correspondingly with other aldehyde exposure, it seems likely that these smoking related hexanal exposures could result in damage to the respiratory tract. Hexanal is not included in a carcinogenic classification.
The combined exposure with other aldehydes in cigarette smoke remains a point of concern. There are no data on dependency available and there are no known beneficial effects of hexanal exposure through smoking.
Hexanal exposures may cause irritation or damage to the respiratory tract. More research on smoking related exposures to hexanal is needed to elucidate the expected respiratory tract irritation. The combined exposure with other aldehydes present in cigarette smoke remains a point of concern and needs further study.

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REFERENCES

(1) Dictionary of substances and their effects (DOSE). The Royal Society of Chemistry, editor. 10/2000. 2001.

(2) The hazardous Substance Data Bank (HSDB). through 2000/10. 2001. The National Library of Medicine (NLM).

(3) Brandweerinformatiecentrum voor gevaarlijke stoffen (BIG). versie 9.0 . 2001. Belgium.

(4) NIOSH. Aldehydes, screening. NIOSH Manual of Analytical Methods. 1993.

(5) Physical-chemical properties and environmental fate Handbook. D. Mackay, editor. CRC netBase. 1999.

(6) Miyake T, Shibamoto T. Quantitative analysis by gas chromotography of volatile carbonyl compounds in cigarette smoke. J Chromatogr A 1995; 693:376-381.

(7) Kataoka H, Kondo T, Sumida A. Gas chromatographic determination of aldehydes in combustion smoke samples. Analytica Chimica Acta 1998; 358:269-275.

(8) IARC. Tobacco smoking. 38. 1986. Lyon, IARC. Evaluation of the carcinogenic risk of chemicals to humans.

(9) Guicherit R, Schulting FL. The occurence of organic chemicals in the atmosphere of the Netherlands. Sci Total Environm 1985; 43:193-219.

(10) Joint FAO/WHO expert committee on Food Additives. Evaluation of certain food additives and contaminants. 884, 29-31. 1999. Geneva, World Health Organization. WHO Technical Report Series 884.

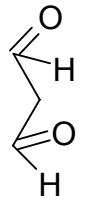
(11) Brambilla G, Cajelli E, Canonero R, Martelli A, Marinari UM. Mutagenicity in V79 Chinese hamster cells of n-alkanals produced by lipid peroxidation. Mutagenesis 1989; 4(4):277-279.

(12) Chen C, Loo G. Inhibition of lecithin: cholesterol acyltransferase activity in human blood plasma by cigarette smoke extract and reactive aldehydes. J Biochem Toxicol 1995; 10(3):121-128.

Appendix 4 Malonaldehyde

GENERAL
IUPAC systematic name: Malonaldehyde (1)
Synonyms: Malondialdehyde; malonic aldehyde; malonic dialdehyde; malonodialdehyde; malonyldialdehyde; MDA; NCI-C54842; 1,3-propanedial; 1,3-propanedialdehyde; 1,3-propanedione (1), propanedial (2)
Molecular formula: $C_3H_4O_2$ (1)

Molecular structure



Molecular weight: 72.1 g/mol (1)
Alifatic: Yes
Aromatic: No
N containing: No
Halogen containing: No
CAS registry no.: 542-78-9 (1)
Storage:
R/S classification: No data available.
dangercode (transport): No data available.
Properties:

- ➢ melting point: 72-74°C (1)
- ➢ boiling point: No data available.
- ➢ density: No data available.
- ➢ refractive index: No data available.
- ➢ solubility: No data available.
- ➢ substance description: Hygroscopic needles (1).
  - Color: No data available.
  - liquid/gas/powder: No data available.
  - odor/taste: No data available.
- ➢ volatility: No data available.
- ➢ pK_a: 4.46 (1)
- ➢ PA: No data available.
- ➢ flammability: No data available.
  - FP = No data available.
  - FL Limits = No data available.
  - IT = No data available.
- ➢ decomposition temperature: No data available.
- ➢ stability: Pure malonaldehyde is unstable. Although not containing a carboxylic group, it can act as an acid. When stored at –20°C pure malonaldehyde was stable (no notable degradation for 2 yrs) (3).
- ➢ vapour pressure/ vapour tension (20°C): No data available.
- ➢ vapour pressure (50°C): No data available.
- ➢ relative density: No data available.

➢ octanol water partition coefficient, log P, log K_{OW}: No data available.
➢ conversion factor: 1 ppm=2.95 mg/m^3 (at 760 mmHg and 25°C) (1). 1 mg/m^3=0.34 ppm.

Critical assessment
The chemical and physical properties of malonaldehyde are similar to acetaldehyde and other low-molecular-weight monoaldehydes and dialdehydes (3). As a pure compound it is unstable. It is easily oxidized – in vivo and in vitro - to malonic semialdehyde and by decarboxylation to acetaldehyde.
Malonaldehyde is able to act as an acid (proton donor) and to form a (less unstable) sodium salt.

Conclusion
Malonaldehyde is a rather reactive, unstable compound exhibiting the aldehyde properties of other low-molecular weight monoaldehydes and dialdehydes.

FUNCTION IN TOBACCO
No data available.

AMOUNT IN TOBACCO PRODUCTS
No data available.

AMOUNT IN SMOKE
- **main stream** In free form the amount ranges from 8.5 to 23.5 mg/kg filter cigarettes; assuming that one cigarettes weights 1 gram, this corresponds with 8.5 to 23.5 µg/cigarette (average of 16.9 µg/cigarette). Free and bounded form together ranged from 9.5 to 26.5 mg/kg filter cigarettes corresponding with 9.5 to 26.5 µg/cigarette (average of 19.0 µg/cigarette). In non-filter cigarettes these amounts are 43% and 53% higher for the free and the free and bound form together, respectively. (4).
- **side stream** No data available.

SOURCE
It seems likely that malonaldehyde is formed during smoking from precursors such as polysaccharides, pectins, proteins and possible triglycerides in tobacco (5).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE
Malonaldehyde has been detected in leaves of pea and cotton plants (1).
Malonaldehyde is found in many food stuffs and is present at generally high levels in rancid foods. It has been detected in fish meat, fish oil, rancid salmon oil, rancid nuts, rancid flour, orange juice essence, vegetable oils, fats, fresh frozen green beans, milk, milk fat, rye bread, and in raw, cured and cooked meats (1).
Concentrations of free malonaldehyde in commercial samples of refined groundnut oils ranged from 0.04-0.14 mg/kg, and the level in sunflower oil was 0.08 mg/kg. The total malonaldehyde (free and bound) concentrations were 0.53-4.36 mg/kg in groundnut oils and 0.98 mg/kg in sunflower oil (1).
Increased levels of malonaldehyde have been found in hamburger, chicken and beef as a result of cooking under a variety of conditions (e.g. microwave, frying, baking and boiling). Conversely, levels of malonaldehyde in frozen smoked trout and cheddar cheese decreased as a result of cooking. The formation of malonaldehyde in foods during cooking seemed to be dependent on many factors, including the degree of unsaturation of the fatty acids and the time length spent in contact with molecular oxygen. The amount found in cooked food samples may also depend on loss of free malonaldehyde due to its volatility or reactivity (1).

COMBUSTION PRODUCTS
No data available.

CONSENSUS REPORTS
In the absence of epidemiological data, IARC could not make an evaluation of the

carcinogenicity of malonaldehyde to humans. IARC stated that there is inadequate evidence for the carcinogenicity of malonaldehyde to experimental animals (1).

STANDARDS AND RECOMMENDATIONS

ADI: No data available.
TWA_{NL} = MAC: No data available.
TWA_{D} =MAK: No data available.
TWA_{USA}: No data available.
$STEL_{NL}$: No data available.
$STEL_{USA}$: No data available.
LTEL: No data available.
TLV-C: No data available.
TLV-CARCINOGENICITY: No data available.
MAK-REPRODUCTION: No data available.

Others: No data available.

Reference value:
In human subjects, mean levels of malonaldehyde (measured as the 2-thiobarbituric acid derivative) were 0.00342 µmol/ml (0.246 µg/ml) of serum in males and 0.0031 µmol/ml (0.223 µg/ml) in females (1).
Malonaldehyde levels were significantly higher in smokers (0.201 µmol/ml; 14.5 µg/ml) as compared to normal subjects (0.088 µmol/ml; 6.34 µg/ml) below the age of 30. The duration of smoking in all these subjects was below 5 years. However, in the age group of 30-50 years old malonaldehyde levels were elevated in subjects who were smoking for a period of less than 10 years (0.233 µmol/ml; 16.8 µg/ml). Malonaldehyde levels were normal in subjects with a history of smoking for more than 10 years. These differences in malonaldehyde levels in relation to duration of smoking persisted in the age group of 50 years and older (6).
It is unclear why there exists so much variation between the two studies in the malonaldehyde levels in non-smokers. In the second study is not mentioned if there is a relation between malonaldehyde levels and the amount smoked. Nor is mentioned when the malonaldehyde levels are measured (i.e. directly after smoking a cigarette?). Adaptation usually occurs in a period of weeks to months, in this study adaptation after 5 years has been described.

CLASS

EG Carc. Cat.: No data available.
IARC-category: group 3 (1).
CEC: No data available.

Critical assessment

Malonaldehyde is formed during smoking from precursors such as polysaccharides, pectins, proteins and possible triglycerides in tobacco. The amount of malonaldehyde in main stream cigarette smoke ranges from 9.5 to 26.5 µg/cigarette (free and bound form together). In non-filter cigarettes these amounts are 42.7% and 52.9% higher for the free and the free and bound form together, respectively. Malonaldehyde has been detected in many foodstuffs; for example in commercial samples of refined groundnut oils malonaldehyde ranged from 0.04-0.14 mg/kg. However, no acceptable daily intake level has been determined. No information is available on the nature of the combustion products formed during cigarette smoking.

Conclusion

The amount of malonaldehyde in main stream cigarette smoke is low compared to other aldehydes. It is unclear whether malonaldehyde exposure due to cigarette smoking exceeds the exposure from foodstuffs.

PHARMACODYNAMICS

Mechanism of action

No data available.

Pulmonary system

- **breathing frequency**: No data available.
- **tidal volume**: No data available.
- **lung compliance**: No data available.
- **airway resistance**: No data available.

Cardiovascular system

- **blood pressure**: No data available.
- **heart rate**: No data available.

Malonaldehyde had central vasoconstrictor effects in cats, which were independent of blood pressure changes (7) (dose and duration and type of exposure not mentioned).

Renal system

- **diuresis**: No data available.
- **saluresis**: No data available.

Nervous system

- **central nervous system**: No data available.
- **autonomic system**: No data available.

Critical assessment

Insufficient inhalation data are available to evaluate the pharmacodynamic effects of malonaldehyde due to cigarette smoking.

Conclusion

Research is necessary to elucidate the pharmacodynamic effects of malonaldehyde due to cigarette smoking exposures.

PHARMACOKINETICS

Absorption

No data available.

Bioavailability

No data available.

Distribution

No data available.

Metabolism

One study tested the role of aldehyde dehydrogenase (ALDH) in the metabolism of MDA *in vitro* with subcellular fractions and semipurified cytosolic preparations from rat livers. Two types of aldehyde dehydrogenases in the rat-liver cytosol fraction, with apparent Km for malonaldehyde of 16 µM and 128 µM, respectively, accounted for virtually all of the metabolising activity for 50 µM malonaldehyde in the postnuclear fraction (8). A similar low-Km aldehyde dehydrogenase has been reported in beef-liver cytosol. An aldehyde dehydrogenase in the mitochondria with a Km of 73 mM could account for the low metabolising activity of mitochondria (1).

Malonaldehyde has been detected in lipid-peroxidising microsomes and is found in animal tissue as an end-product of lipid peroxidation. It is also a side-product of prostaglandin and thromboxane biosynthesis. Malonaldehyde is present in blood platelets and in serum (1).

In vitro experiments showed metabolism to be primarily in mitochondria via reactions involving oxygen utilisation and CO_2 production. The apparent Km and Vmax were 0.5 mmol and 9.3 nmol/min/mg protein for oxygen uptake, respectively, and 2.0 mmol and 2.4 nmol/min/mg protein for CO_2 production (2).
A major urinary metabolite was identified as N-acetyl-epsilon-(2-propenal)lysine, primarily derived from N-alpha-(2-propenal)lysine, which is formed by the reaction of malonaldehyde with the epsilon-amino groups of N-terminal lysine residues in food proteins (9). Malonaldehyde is metabolised to malonic semialdehyde and by decarboxylation to acetaldehyde (3).

Excretion
Twelve hours after stomach intubation with 1,3-^{14}C Malonaldehyde (which C atom was radioactively labelled was not given), male Wistar rats showed 60-70%, 5-15% and 9-17% of administered radioactivity in expired carbon monoxide, faeces, and urine, respectively (2).

Kinetic parameters
No data available.

Other
A limited concentration-dependent uptake of malonaldehyde occurred (4% at concentrations of 0.1-1000 µM) by 24 hours in cultured mammalian cells. The limited uptake was suggested to be due in part to the interaction of malonaldehyde with constituents of the culture medium. However 83-89% of the malonaldehyde was oxidised to CO_2 by 24 hours, and approximately 5% was recovered in the major lipids (1).
Rats exposed to cigarette smoke inhalation for 30 and 60 minutes a day for 3 months showed increased malonaldehyde levels in lung tissue to 790.8 and 641.20 nmol/gram protein respectively (controls 513.73 nmol/gram protein) in a non-dose proportional manner. The blood and lung tissue levels of malonaldehyde were measured after 3 months. The malonaldehyde level in plasma (erythrocytes) increased from controls of 1.63 nmol/ml (0.117 µg/ml) to 4.13 and 4.10 nmol/ml respectively in a non-dose proportional manner (0.298 µg/ml; 0.296 µg/ml) (10).
In normal human subjects, mean levels of malonaldehyde (measured as the 2-thiobarbituric acid derivative) were 0.00342 µmol/ml (0.246 µg/ml) of serum in males and 0.0031 µmol/ml (0.223 µg/ml) in females (1).
Malonaldehyde levels were significantly higher in smokers (0.201 µmol/ml; 14.5 µg/ml) as compared to normal subjects (0.088 µmol/ml; 6.34 µg/ml) below the age of 30. The duration of smoking in all these subjects was below 5 years. However, in the age group of age 30-50 years old malonaldehyde levels were elevated in subjects who were smoking for a period of less than 10 years (0.233 µmol/ml; 16.8 µg/ml). Malonaldehyde levels were normal in subjects with a history of smoking for more than 10 years. These differences in malonaldehyde levels in relation to duration of smoking persisted in the age group of 50 years and older (6).
These high levels of malonaldehyde found in this study are not confirmed by the previous described human and rat study.
No data are available if the malonaldehyde in blood is due to absorption from cigarette smoke in the lungs or is the result of oxidative stress induced by smoking.

Critical assessment
Malonaldehyde is a by-product of prostaglandin biosynthesis and an end-product of polyunsaturated lipid peroxidation. A large part of oral malonaldehyde intake is oxidised to CO_2 and exhaled. After exposure to smoke in rats an increase in malonaldehyde levels of pulmonary tissue and plasma were found.
For a critical assessment, research is needed, especially to obtain the amount of absorption

and bioavailability after smoking related exposures to malonaldehyde. Other aldehydes are known to induce mainly local effects at the site of exposure and little systemic effects probably due to little absorption in the respiratory tract.

Conclusion

Malonaldehyde is an endogenous product of prostaglandin biosynthesis and of lipid peroxidation. A large part of malonaldehyde is oxidised to CO_2 and exhaled.

The kinetics of smoking related exposures to malonaldehyde need further study.

TOXICOLOGY

Since malonaldehyde is unstable and highly reactive, it is generally not available as a free compound and other forms were tested in the studies described below. Some of the biological effects of malonaldehyde may be due to impurities such as β-alkoxyacroleins (1).

Acute toxicity

Human

No data available.

Animal

LD50 mouse, oral: 606 mg/kg bw (1).

LD50 rat, oral: 632 mg/kg bw (given as the sodium enol salt) (9).

Local tolerance

Human

No data available.

Animal

No data available.

Repeated dose toxicity

Subacute

Subcutaneous injection were given to chickens of 1 ml 50% malonaldehyde in corn oil/kg 3 times a week for 4 weeks. Plasma cholesterol and triglyceride levels were not significantly affected by the treatment. Degenerated cells (type not mentioned) without stainable lipid were frequently observed in the arteries of treated chickens. It is suggested that malonaldehyde is a potent angiotoxin (9).

Semichronic

Mouse skin application; One group of 30 female Swiss mice, 55 days old, were given daily skin applications of 12 mg malonaldehyde (purity unspecified) in 0.25 ml aceton for nine weeks. As it appeared that this treatment was to toxic (toxic effects not mentioned), the remaining mice received daily skin applications of 0.36 mg malonaldehyde in 0.25 ml acetone for 39 weeks. Another group of mice of the same strain and sex received daily skin applications of 0.36 mg malonaldehyde in 0.25 ml acetone for 48 weeks. A control group of 30 female mice was used (whether the group was treated with vehicle or was untreated was not specified). Of the 30 mice treated with 12 mg malonaldehyde, 12 died in weeks 4-6; none had a tumor. In weeks 7-9 six more mice of this group died; five had tumours, four with a liver carcinoma, three of which had metastasised, and one with a carcinoma of the rectum. In the subsequent 39 weeks, no mortality occurred and no further tumour was found in this group. In the group treated with the 0.36 mg malonaldehyde throughout the experiment, one skin tumour, classified as keratocanthoma, occurred at week 43. At termination (week 48), two animals of the control group had died; no skin tumour occurred in the controls. IARC noted the short duration of the experiment and found it difficult to relate the early occurence of liver carcinoma to the skin application of malonaldehyde (1).

Two groups of 40 female random-bred Swiss Webster mice, eight weeks old, were given skin applications of 0 (controls) or 0.6 mg free malonaldehyde (purity unspecified) in 0.05 ml methanol per animal thrice weekly for life. The solution in methanol also contained

unhydrolysed malonaldehyde bis(dimethylacetal), resulting in test solutions containing 0.6 mg malonaldehyde + 21.5 mg malonaldehyde bis(dimethylacetal) per 0.05 ml. Four intermediate groups were started, but, due to an unfavourable shift in the equilibrium reaction between malonaldehyde and malonaldehyde bis(dimethylacetal) in the test solutions, these groups were terminated at weeks 36-39. The control group and the high dose group were treated for life. Mortality at week 52 was 4/40 in the high-dose group and 11/40 in the control group, and at week 80, 17/40 in the high-dose group and 25/46 in the control group: by week 120 all mice were dead. The predominant types of tumour in control and treated animals were pulmonary adenomas, haemangiosarcomas, granulosa-cell tumours of the ovaries and malignant lymphomas. Only one skin tumour was found, a papilloma in an intermediate group. After adjusting for survival, the incidence of malignant lymphomas 17/40 in the high dose group appeared to be statistically significantly higher ($p<0.001$) than that (6/40) in the control group. However, the authors stated that both lymphomas incidences were within the normal range for malignant lymphomas in the strain of mice used. IARC noted that no data on the incidence of malignant lymphomas in historical controls were available (1).

Six groups of 40 male and 40 female SENCAR mice, seven weeks old, were given skin applications of 20, 50, 100, 200 or 500 µg sodium malonaldehyde (stated to be pure and prepared by a method avoiding the presence of mutagenic or carcinogenic impurities;however, purity and impurities were unspecified) or 50.5 µg benzo[a]pyrene (positive control) in 0.2 ml solvent (20% dimethylsulphoxide, 80% aceton) per animal twice weekly for 52 weeks. Mortality at week 52 was 3/80 mice in the low- and high-dose groups and ranged from 4-6/80 mice in the mid-dose groups, whereas all except two females of the positive-control group had died. None of the animals treated with sodium malonaldehyde developed skin tumours whereas 296 skin tumours (papillomas and carcinomas) were counted in 77 positive controls (1).

Five groups of 50 female ICR Swiss mice, six to eight weeks old, were given sodium malonaldehyde (purity >98%, impurities not specified, but not including the β-alkoxyacroleins impurities) in the drinking-water (pH 4.0) at concentrations providing 0, 0.1, 1 or 10 mg/kg bw/day for 12 months, at which time the surviving animals were killed. Mortality rates at termination were 13, 12, 12, and 28% ($p<0.05$) in the 0, 0.1, 1 or 10 mg/kg bw-dose groups respectively. The incidences of hyperplastic liver nodules were 0/97, 1/49, 2/50 and 2/48 in the same groups, respectively. The incidences of hepatomas were 0/97, 0/49, 2/50 and 0/48 respectively; and the incidences of liver haemangiomas were 1/97, 1/49, 0/50, and 4/48. Tumours were found in the stomach in 3/48 high-dose animals (one lymphoma, one squamous-cell carcinoma); whereas no gastric tumour occurred in the control or in the mid-dose animals. IARC noted the short duration of the experiment and that the incidences of the individual tumours in the treatment groups were not statistically different from those in controls (1).

In a two-stage mouse-skin assay, groups of 30 female Swiss mice, 55 days old, received a single skin application of 6 or 12 mg malonaldehyde (purity unspecified) or 0.125 mg 7,12-dimethylbenz[a]anthracene (DMBA) (positive control) in 0.25 ml acetone. After three weeks, all mice were given skin applications of 0.25 ml 0.1% croton oil in acetone daily on five days a week for 30 weeks. Controls included groups of mice treated only with DMBA, malonaldehyde, croton oil or acetone, or receiving no treatment. At week 30, when the experiment was terminated, skin tumours classified as keratoacanthomas occurred in 16/30 animals treated with 6 mg and in 16/30 treated with 12 mg malonaldehyde and in 29/30 of the mice treated with DMBA. No tumour occurred in the control groups (1).

In a two-stage mouse-skin assay, six groups of 40 male and 40 female SENCAR mice, seven weeks old, received a single skin application of 20, 50, 100, 200 or 500 µg sodium malonaldehyde (stated to be pure and prepared by a method avoiding the presence of mutagenic or carcinogenic impurities;however, purity and impurites were unspecified) or 50.5 µ benzo[a]pyrene (positive control) in 0.2 ml solvent (20% dimethylsulphoxide, 80%

acetone). One week after this treatment, application of 2 µg 12-O-tetradecanoylphorbol 13-acetate (TPA) in 0.2 ml solvent (20% dimethylsulphoxide, 80% acetone) was begun, twice weekly for a period of at most 41 weeks. At week 42 the incidence of skin papillomas was 22/74, 22/78, 14/74, 15/78 and 18/79 in the groups receiving 20, 50, 100, 200 or 500 µg sodium malonaldehyde, respectively and 229/65 in the positive-control group. (The number of tumour-bearing animals was not given). It was stated that TPA has been shown previously to produce skin-tumour yields in uninitiated SENCAR mice that were similar to those found in animals treated with sodium malonaldehyde. (IARC noted the short duration of the experiment and the use of historical controls rather than concomitant TPA controls) (1).
In a two-stage mouse-skin assay, six groups of 40 male and 40 female SENCAR mice, seven weeks old, received a single skin application of 20, 50, 100, 200 or 500 µg sodium malonaldehyde (stated to be pure and prepared by a method avoiding the presence of mutagenic or carcinogenic impurities; however, purity and impurites were unspecified) or 2 µg TPA (positive controls) in 0.2 ml solvent (20% dimethylsulphoxide, 80% acetone) twice weekly for 28 weeks. This treatment was begun one week after initiation with a single application of 50.5 µg benzo[a]pyrene in 0.2 ml solvent (20% dimethylsulphoxide, 80% acetone) to the skin (no mouse treated with the benzo[a]pyrene solution alone was used). At week 28, the incidences of skin papillomas were 2/78, 3/78, 6/77, 1/78 and 2/80 in the groups receiving 20, 50, 100, 200 or 500 µg sodium malonaldehyde, respectively and 360/78 in the positive-control group. IARC noted that the number of tumour-bearing animals was not given (1).
Chronic.
No data available

Carcinogenicity
Human
In the absence of epidemiological data, IARC could not make an evaluation of the carcinogenicity of malonaldehyde to humans (1).
Animal
Three groups of 25 male and 25 female random-bred Swiss mice, eight weeks old, were given malonaldehyde bis(dimethylacetal) in the drinking water, on six days per week for life, at levels that resulted, following hydrolysis, in concentrations of malonaldehyde of 0.125, 0.25, and 0.5% (dose 312, 625, and 1250 mg/kg bw/day). Since methanol is also produced on hydrolysis of the bis(dimethylacetal), three control groups were given appropriate levels of methanol in the drinking-water. At week 80, mortality in the 0.5% malonaldehyde group was 25/25 males and 22/25 females, compared with 20/25 males and 14/25 females in the corresponding methanol-control group. The overall mortality in high-dose treated animals was statistically significantly different from that in controls ($p<0.01$). There was no statistically significant difference in mortality between the lower-dose malonaldehyde groups and corresponding controls. Pulmonary tumors (adenomas and one carcinoma), blood-vessel tumours (haemangiomas and haemangioendotheliomas) and malignant lymphomas were the predominant types of tumour in the control and the treated animals. None of the tumour types was significantly increased in incidence in malonaldehyde-treated animals compared with methanol-treated controls. IARC noted the high mortality and the lack of untreated controls (1).
IARC stated that there is inadequate evidence for the carcinogenicity of malonaldehyde to experimental animals (1).

Reproduction toxicology
Human
No data available.

Animal
No data available.

Mutagenicity
Human
No data available.
Animal
Highly purified malonaldehyde is weakly mutagenic to *Salmonella typhimurium* TA102, TA104, TA2638 and *his* D3052. Negative results were reported in *S. typhimurium* TA1535, TA1537 and TA1538; and the activity of malonaldehyde in strains his D3052 as well as several other *S. typhimurium* stains may be attributable partly or entirely to mutagenic impurities. Malonaldehyde was also reported to be mutagenic to *Escherichia coli* (1).
Malonaldehyde induced somatic mutations, but not sex-linked recessive lethal mutations, in *Drosophila melanogaster* (1).
In cultured rat-skin fibroblasts, the compound induced micronuclei, chromosomal aberration and aneuploidies. It induced resistance to thymidine and methotrexate in mouse L5178 lymphoma cells in the absence of an exogenous metabolic system (1).

Other
Malonaldehyde is one of the aldehydes responsible for the 'thiobarbituric acid (TBA)-reactive'material found in human serum. Increased levels of serum TBA-reactive material have been reported following a myocardial infarction (1).
N-alpha-(2-propenal)lysine, which is formed by the reaction of malonaldehyde with the epsilon-amino groups of N-terminal lysine residues in food proteins, is the predominant form in which dietary malonaldehyde is absorbed. This form is non-mutagenic and it does not give rise to free malonaldehyde in the urine. These findings mitigate the concern over possible toxicological effects of malonaldehyde in the diet (11). Malonaldehyde completely inhibited lecithin:cholesterol acyltransferase (LCAT) *in vitro* at 50 mM (12).

Critical assessment
The acute oral toxicity of malonaldehyde is low. Evidence for the carcinogenicity of malonaldehyde to experimental animals and to humans is inadequate. No toxicological data are available following inhalation. Some reports can be biased by impurities in the malonaldehyde solution used.
Conclusion
Data are needed on the toxicity of malonaldehyde through inhalation.

INTERACTIONS
Chemical
Reacts with proteins, the conjugate base is much less reactive (1).

In vivo
Malonaldehyde forms DNA adducts in humans; adducts of deoxyadenosine and deoxyguanosine occur at higher concentrations in normal breast tissues from cancer patients than in those from non-cancer patients (9).

In vitro
Malonaldehyde binds to DNA *in vitro* and forms covalent adducts with nucleotides. The extent of DNA cross-linking *in vitro* correlates with the formation of fluorescent adducts. These adducts are likely to be Schiff bases. A loss of DNA-template activity also occurred *in vivo*. Malonaldehyde forms a variety of fluorescent and nonfluorescent adducts, such as amino-immunoproppene derivatives, with the amino groups of some amino acids, proteins and phospholipids. Protein adducts often involve cross-links and malonaldehyde may also cross-link membrane proteins to each other, cross-link haemoglobin to the cell membrane

and can probably cross-link membrane lipids (1).

Critical assessment
Chemical
The aldehyde groups present in the molecular structure of malonaldehydes are potential sites for oxidation, for reduction and for adduct formation.
Being an aldehyde, malonaldehyde interacts with amino containing compounds.
In more general terms: it will participate in nucleophilic addition reactions.
In vivo
Malonaldehyde can form DNA adducts.
Conclusion
Chemical
Malonaldehyde is a marked compound for nucleophilic addition reactions and for reactions with oxidizers; a proton can readily be abstracted from the compound.
In vivo
Malonaldehyde can form DNA adducts.

DEPENDENCY
No data available.

Effects of smoking cessation
No data available.

Critical assessment
Not relevant.
Conclusion
Not relevant.

COMMERCIAL USE
No evidence was found that malonaldehyde is produced in commercial quantities in the USA, western Europe or Japan. The dimethyl and diethyl acetals of malonaldehyde, 1,1,3,3-tetramethoxypropane and 1,1,3,3-tetraethoxypropane, are used to generate (by hydrolysis) free malonaldehyde for laboratory purposes. No evidence was found that any of these compounds is used for commercial applications (1).

BENEFICIAL EFFECTS
No data available.

Critical assessment
Not relevant.
Conclusion
Not relevant.

SUMMARY AND FINAL CONCLUSION
Malonaldehyde is one of several aldehydes present in cigarette smoke. Malonaldehyde is formed during smoking from precursors such as polysaccharides, pectins, proteins and possibly triglycerides in tobacco. Malonaldehyde is a marked compound for nucleophilic addition reactions and for reactions with oxidizers.
The amount of malonaldehyde in main stream cigarette smoke ranges from 9.5 to 26.5 µg/cigaret (free and bound form together), which is low compared with other aldehydes in smoke. In non-filter cigarettes these amounts are 42.7% and 52.9% higher for the free and the free and bound form together, respectively. Malonaldehyde has been detected in many foodstuffs; in commercial samples of refined groundnut oils malonaldehyde ranged from 0.04-0.14 mg/kg for instance. However, no acceptable daily intake level has been determined. It is unclear whether malonaldehyde exposure due to

cigarette smoking exceeds the exposure to foodstuffs. No information is available on the nature of the combustion products formed during cigarette smoking.
After exposure to smoke an increase in malonaldehyde levels of pulmonary tissue and plasma were found. Insufficient inhalation data are available to evaluate the pharmacodynamic effects of malonaldehyde due to cigarette smoking.
Malonaldehyde is a by-product of prostaglandin biosynthesis and an end-product of polyunsaturated lipid peroxidation. A large part of malonaldehyde will be oxidised to CO_2 and exhaled. Research is needed to obtain the amount of absorption and bioavailability after smoking related exposures to malonaldehyde. Other aldehydes are known to induce mainly local effects at the site of exposure and little systemic effects, probably due to little absorption in the respiratory tract.
The acute oral toxicity of malonaldehyde is low. There is inadequate evidence for the carcinogenicity of malonaldehyde to experimental animals and to humans. No toxicological data are available based on inhalation toxicology. During smoking high concentration peak exposures of short duration will occur. More data are needed on the toxicity of malonaldehyde through smoking related exposures.
The combined exposure with other aldehydes in cigarette smoke remains a point of concern. There are no data on dependency available and there are no known beneficial effects of malonaldehyde exposure through smoking.
The amount of malonaldehyde in main stream cigarette smoke is low compared with other aldehydes. No conclusions could be made based on the available information on the health risk of smoking related exposure to malonaldehyde. The health risks of the exposure to malonaldehyde due to cigarette smoking need to be studied. Another point of concern is the exposure of malonaldehyde together with other aldehydes in cigarette smoke and further study on this combined exposure is needed.

DATE THIS SHEET WAS GENERATED
Based on literature available in November 2002.

REFERENCES

(1) Malonaldehyde. Allyl compounds, Aldehydes, Epoxides and Peroxides. Lyon: World Health Organization, IARC 1985: 163-177.
(2) The hazardous Substance Data Bank (HSDB). through 2000/10. 2001. The National Library of Medicine.
(3) DHHS (NIOSH). Carcinogenicity of Acetaldehyde and Malonaldehyde, and Mutagenicity of Related Low-Molecular-Weight Aldehydes. Curr Intelligence Bull 1991; 55(91-112).
(4) Witas T, Sledziewski P. Exhalation of malonaldehyde from the smoke of high grade cigarettes and effectiveness of filtering it. Nahrung 1990; 34(7):615-621.
(5) IARC. Tobacco smoking. 38. 1986. Lyon, IARC. Evaluation of the carcinogenic risk of chemicals to humans.
(6) Nadiger HA, Mathew CA, Sadasivudu B. Serum malanodialdehyde (TBA reactive substance) levels in cigarette smokers. Atherosclerosis 1987; 64(1):71-73.
(7) Mirzoyan SA, Mkrtchian SL, Manukian AA. Cerebral vasoconstrictor effects of malonic dialdehyde. Experientia 1993; 56:19.
(8) Hjelle JJ, Petersen DR. Metabolism of malondialdehyde by rat liver aldehyde dehydrogenase. Toxicol Appl Pharmacol 1983; 70(1):57-66.
(9) Dictionary of substances and their effects (DOSE). The Royal Society of Chemistry. 10/2000. 2001.
(10) Ozan E, Kukner A, Canpolat L, Oner H, Gezen MR, Yilmaz S et al. Histological and biochemical effects of cigarette smoke on lungs. Acta Physiol Hung 2001; 88:301-315.

(11) Draper HH, Hadley M. A review of recent studies on the metabolism of exogenous and endogenous malondialdehyde. Xenobiotica 1990; 20(9):901-907.
(12) Chen C, Loo G. Inhibition of lecithin: cholesterol acyltransferase activity in human blood plasma by cigarette smoke extract and reactive aldehydes. J Biochem Toxicol 1995; 10(3):121-128.

List of abbreviations

- **CAS registry no.**: Chemical Abstracts Service Registry Number is a numeric designation assigned by the American Chemical Societys Chemical Abstracts Service and uniquely identifies a specific chemical compound. This entry allows one to conclusively identify a material regardless of the name or naming system used.
- **R**: Risk phrases: Warnings on the label about the harmful propertie(s) of the substance.
- **S**: Safety phrases: Directions on the label about the necessary safety precautions to handle the substance. See appendix 1.
- **PA**: proton affinity in the gas phase, kcal/mol
- **FP**: Flash point in °C, which is the minimum temperature at which the vapor pressure of a liquid is sufficient to form an ignitable mixture with air near the surface of the liquid.
- **FL Limits**: Flammable limits (often called explosive limits) in %, which specify the range of concentration of the vapor in air (in percent by volume) for which a flame can propagate. Below the lower flammable limit, the gas mixture is too lean to burn; above the upper flammable limit, the mixture is too rich. Values refer to ambient temperature and pressure and are dependent on the precise test conditions.
- **IT**: Ignition temperature (sometimes called autoignition temperature) in °C, which is the minimum remperature required for self-sustained combustion in the absence of an external ignition source.
- **ADI**: Acceptable Daily Intake.
- **TWA**: Time Weighed Average.
- **MAC**: Maximum Acceptable Concentration.
- **STEL**: Short-term exposure limit for airborne contaminants, which should not be exceeded for more than 15 min. A “C” following a value indicates a ceiling limit which should not be exceeded even for very brief periods because of acute toxic effects of the substance.
- **LTEL**: Long-Term Exposure Limit (8 hours exposure). Exposure limit: maximum concentration of a chemical agent as time-weighed average of a reference period (8 h/day; 40 h/week) above which no employee may be exposed.
- **TLV-C**: Treshold Limit Value.
- **MAK-reproduction**: Classification of substances on foetal harm according to the German MAK-Werte-Liste.

➢ A = The substance is clearly able to cause foetal harm.
➢ B = Possible risk on foetal harm.
➢ C = In compliance with MAK-value, risk of foetal harm is not to be feared.
➢ D = Foetal toxicity stil unclear. Based on the available information, classification in group A-C is not possible (yet).

- **IARC-category**:

➢ Group 1: The agent is carcinogenic to humans.
➢ Group 2A: The agent is probably carcinogenic to humans.
➢ Group 2B: The agent is possibly carcinogenic to humans.

➢ Group 3: The agent is not classifiable as to its carcinogenicity to humans.
➢ Group 4: The agent is probably not carcinogenic to humans.

- **CEC**:

➢ C = corrosive
➢ E = explosive
➢ F = highly flammable
➢ F+ = extremely flammable
➢ O = oxidising
➢ T = toxic
➢ T+ = very toxic
➢ Xi = irritant
➢ Xn = harmful

RISK AND SAFETY CLASSIFICATION

- Risk classification
- R1 Explosive when dry
- R2 Risk of explosion by shock, friction, fire or other sources of ignition
- R3 Extreme risk of explosion by shock, friction, fire or other source of ignition
- R4 Forms very sensitive explosive metallic compounds
- R5 Heating may cause an explosion
- R6 Explosive with or without contact with air
- R7 May cause fire
- R8 Contact with combustible material may cause fire
- R9 Explosive when mixed with combustible material
- R10 Flammable
- R11 Highly flammable
- R12 Extremely flammable

- R14 Reacts violently with water
- R15 Contact with water liberates extremely flammable gases
- R16 Explosive when mixed with oxidising substances
- R17 Spontaneously flammable in air
- R18 In use, may form flammable/explosive vapour-air mixture
- R19 May form explosive peroxides
- R20 Harmful by inhalation
- R21 Harmful in contact with skin
- R22 Harmful if swallowed
- R23 Toxic by inhalation
- R24 Toxic in contact with skin
- R25 Toxic if swallowed
- R26 Very toxic by inhalation
- R27 Very toxic in contact with skin
- R28 Very toxic if swallowed

- R29 Contact with water liberates toxic gas
- R30 Can become highly flammable in use
- R31 Contact with acids liberates toxic gas
- R32 Contact with acids liberates very toxic gas
- R33 Danger of cumulative effects
- R34 Causes burns
- R35 Causes severe burns
- R36 Irritating to eyes
- R37 Irritating to respiratory system
- R38 Irritating to skin
- R39 Danger of very serious irreversible effects
- R40 Limited evidence of a carcinogenic effect
- R41 Risk of serious damage to eyes
- R42 May cause sensitisation by inhalation
- R43 May cause sensitisation by skin contact
- R44 Risk of explosion if heated under confinement
- R45 May cause cancer
- R46 May cause heritable genetic damage

- R48 Danger of serious damage to health by prolonged exposure
- R49 May cause cancer by inhalation
- R50 Very toxic to aquatic organisms
- R51 Toxic to aquatic organisms
- R52 Harmful to aquatic organisms
- R53 May cause long-term adverse effects in the aquatic environment
- R54 Toxic to flora
- R55 Toxic to fauna
- R56 Toxic to soil organisms
- R57 Toxic to bees
- R58 May cause long-term adverse effects in the environment
- R59 Dangerous for the ozone layer.
- R60 May impair fertility
- R61 May cause harm to the unborn child
- R62 Possible risk of impaired fertility
- R63 Possible risk of harm to the unborn child.
- R64 May cause harm to breastfed babies
- R65 Harmful: may cause lung damage if swallowed
- R66 Repeated exposure may cause skin dryness or cracking
- R67 Vapours may cause drowsiness and dizziness
- R68 Possible risk of irreversible effects

- Safety classification
- S1 Keep locked up
- S2 Keep out of the reach of children

- S3 Keep in a cool place
- S4 Keep away from living quarters
- S5 Keep contents under ... (appropriate liquid to be specified by the manufacturer)
- S6 Keep under ... (inert gas to be specified by the manufacturer)
- S7 Keep container tightly closed
- S8 Keep container dry
- S9 Keep container in a well-ventilated place

- S12 Do not keep the container sealed
- S13 Keep away from food, drink and animal feedingstuffs
- S14 Keep away from ... (incompatible materials to be indicated by the manufacturer)
- S15 Keep away from heat
- S16 Keep away from sources of ignition - No smoking
- S17 Keep away from combustible material
- S18 Handle and open container with care

- S20 When using do not eat or drink
- S21 When using do not smoke
- S22 Do not breathe dust
- S23 Do not breathe gas/fumes/vapour/spray (appropriate wording to be specified by the manufacturer)
- S24 Avoid contact with skin
- S25 Avoid contact with eyes
- S26 In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
- S27 Take off immediately all contaminated clothing.
- S28 After contact with skin, wash immediately with plenty of ... (to be specified by the manufacturer).
- S29 Do not empty into drains
- S30 Never add water to this product

- S33 Take precautionary measures against static discharges

- S35 This material and its container must be disposed of in a safe way.
- S36 Wear suitable protective clothing
- S37 Wear suitable gloves
- S38 In case of insufficient ventilation, wear suitable respiratory equipment
- S39 Wear eye/face protection
- S40 To clean the floor and all objects contaminated by this material use ... (to be specified by the manufacturer)
- S41 In case of fire and/or explosion do not breathe fumes
- S42 During fumigation/spraying wear suitable respiratory equipment (appropriate wording to be specified by the manufacturer)

- S43 In case of fire use ... (indicate in the space the precise type of fire-fighting equipment. If water increases the risk add: Never use water).

- S45 In case of accident or if you feel unwell seek medical advice immediately (show the label where possible).
- S46 If swallowed, seek medical advice immediately and show this container or label.
- S47 Keep at temperature not exceeding ... °C (to be specified by the manufacturer).
- S48 Keep wetted with .... (appropriate material to be specified by the manufacturer).
- S49 Keep only in the original container.
- S50 Do not mix with ... (to be specified by the manufacturer)
- S51 Use only in well-ventilated areas
- S52 Not recommended for interior use on large surface areas
- S53 Avoid exposure - Obtain special instructions before use

- S56 Dispose of this material and its container to hazardous or special waste collection point.
- S57 Use appropriate containment to avoid environmental contamination

- S59 Refer to manufacturer for information on recovery/recycling
- S60 This material and its container must be disposed of as hazardous waste
- S61 Avoid release to the environment. Refer to special instructions/Safety data sheet
- S62 If swallowed, do not induce vomiting: seek medical advice immediately and show this container or label.
- S63 In case of accident by inhalation: remove casualty to fresh air and keep at rest.
- S64 If swallowed, rinse mouth with water, (only if the person is conscious).