RIVM report 650270003/2002

The health- and addictive effects due to exposure to aldehydes of cigarette smoke
Part 1; Acetaldehyde, Formaldehyde, Acrolein and Propionaldehyde

I. van Andel, E. Schenk, B. Rambali, G. Wolterink, G. van de Werken, H. Stevenson, L. A.G.J.M. van Aerts, and W. Vleeming

This investigation is performed for the account of the Directorate for Public Health of the Ministry of Health, Welfare and Sports and of the Inspectorate for Health Protection and Veterinary Public Health, within the framework of project 650270 ‘Reduction of Health and Addiction risks of smokers’

RIVM, P.O. Box 1, 3720 BA Bilthoven, telephone: 31 - 30 - 274 91 11; telefax: 31 - 30 - 274 29 71

Abstract

In the desk study presented here, health effects and possible addictive effects of aldehyde exposure due to cigarette smoking are discussed. In the light of currently available literature the health effects of exposure to acetaldehyde, formaldehyde, acrolein and propionaldehyde were assessed. All aldehydes cause pathological damage to the respiratory tract and reach high peak concentrations in the respiratory tract during smoking. In rats, combined exposure of the above-mentioned aldehydes leads to a significant increase in damage to the respiratory tract and to a decrease in breathing frequency. The combined effect is, at most, the sum of the individual effects; no dose addition or potentiation occurs at minimal-observed-effect levels (MOEL). However, it's uncertain if the extent of the combined effects during cigarette smoking take place, when high peak concentrations occur. Although there is some evidence from studies on animals that acetaldehyde has addictive properties, we found no such evidence for inhaled aldehydes.

Contents

Samenvatting

In dit rapport worden de gezondheids- en mogelijke verslavende effecten van blootstelling aan aldehyden ten gevolge van het roken van sigaretten beschreven. Dit literatuuronderzoek richt zich met name op acetaldehyde, formaldehyde, acrolein, en propionaldehyde.
Aldehyden in sigarettenrook zijn verbrandingsproducten van tabak maar vooral ook van aan tabak toegevoegde suikers. Alle aldehyden veroorzaken pathologische schade aan de luchtwegen als gevolg van hoge piekconcentraties tijdens het roken. Acetaldehyde is genotoxisch en beschreven als een kankerverwekkende stof in proefdieren. Voor blootstelling aan formaldehyde zijn er aanwijzingen dat het kan leiden tot kanker in de bovenste luchtwegen en tot een verhoogde luchtwegweerstand. Acrolein verlaagt de ademfrequentie en remt de ciliaire bewegingen in de luchtwegen. Voor propionaldehyde zijn er aanwijzingen dat het ciliatoxische en slijm coagulerende eigenschappen heeft. Het is niet duidelijk of en in welke mate geïnhaleerde aldehyden de bloedbaan bereiken.
In ratten leidt een gecombineerde blootstelling aan de genoemde aldehyden tot een significante toename van de schade aan de luchtwegen en tot een afname van de ademfrequentie. Bij zeer lage concentraties wordt als gevolg van combineren geen potentiering van de schade gezien. Onduidelijk is of tijdens het roken van sigaretten, waarbij hoge piek concentraties ontstaan, potentiering van de schade optreedt.
Alhoewel er vanuit dierexperimenteel onderzoek aanwijzingen zijn dat met name acetaldehyde verslavende eigenschappen heeft, is in de geraadpleegde literatuur geen onderbouwing gevonden voor verslaving aan geïnhaleerde aldehyden.
De conclusie van dit onderzoek is dat de geraadpleegde literatuur de schadelijkheid van geïnhaleerde aldehyden ondubbelzinnig aantoont. Mogelijk wordt de aan roken gerelateerde schade nog onderschat omdat in de literatuur veelal wordt uitgegaan van 8 uurs blootstellingen aan relatief lage concentraties. Meer onderzoek naar de schadelijkheid van hoge piek blootstellingen aan aldehyden tijdens roken is nodig om te komen tot een goede risicoschatting. Daarnaast dient de bijdrage die aan tabak toegevoegde suikers en andere ingrediënten leveren aan de concentratie aldehyden in de rook nauwkeuriger in kaart gebracht te worden.

Summary

In the desk study presented here health effects and possible addictive effects of aldehyde exposure due to cigarette smoking are discussed. In the light of currently available literature, the health effects of exposure to acetaldehyde, formaldehyde, acrolein and propionaldehyde were assessed.

Aldehydes in cigarette smoke are combustion products from tobacco and arise especially from added sugars as well. All aldehydes cause pathological damage to the respiratory tract through their high peak concentrations during smoking. Acetaldehyde is genotoxic and listed as an animal carcinogen. Formaldehyde exposure may lead to cancer in the tissues of initial contact, i.e. the upper respiratory tract, and may induce increased airway resistance. Acrolein causes a decrease in respiratory rate and an inhibition of ciliatory tract movement. Propionaldehyde may have ciliatoxic and mucus coagulating properties. It remains unclear if and in what amount inhaled aldehydes reach the bloodstream.

In rats, combined exposure of the above-mentioned aldehydes leads to a significant increase in damage to the respiratory tract and a decrease in breathing frequency. At low doses of combined exposure, no potentiation of the damage occurs. It remains unclear if potentiation of the damage will occur at high peak concentrations during cigarette smoking. Although there is some evidence from studies in animals that especially acetaldehyde has addictive properties, we found no such evidence for inhaled aldehydes.

From the currently available literature it can be concluded that inhaled aldehydes are clearly harmful to human airways. Although the existing data are conclusive on the toxicity of inhaled aldehydes, the use of these data to assess the health effects of aldehyde exposure due to cigarette smoking may lead to an underestimation of the toxicity. This is because the reported toxicity, in general, is based on eight hours exposure to relatively low concentrations. More research on the smoking-related high-peak exposure would be necessary for a correct estimation of the harmful effects of exposure to aldehydes due to cigarette smoking. In addition, the contribution of the added sugars and other ingredients from tobacco to the concentration of aldehydes in cigarette smoke needs to be thoroughly investigated.

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).

In this report the effect of exposure to each of these aldehydes on human health and addiction will be investigated using information in currently available literature. In the discussion also the effect of combined exposure will be discussed. Evaluation of the remaining aldehydes will be published in part 2.

1.1 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. American Journal of Clinical Nutrition 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.
Ref Type: Report

(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.
Ref Type: Report

2. Method

Publications on aldehydes were identified through Medline, Toxline and Current Contents and from electronic citations in the Merck Index (2001), DOSE (1), RTECS (2) , HSDB (3), BIG (4), 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.

2.1 References

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

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

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

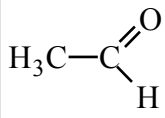
(4) Brandweer Informatiecentrum voor Gevaarlijke stoffen (BIG) (Firedepartment Informationcentre for Hazardous substances); versie 10 (10th edition).

3. Results

3.1 Acetaldehyde

GENERAL
IUPAC systematic name: Acetaldehyde (1)
Synonyms: ethanal, acetic aldehyde, aldehyde, ethylaldehyde, acetylaldehyde, diethylacetal, 1,1-diethoxy ethane, Fema No. 2003, NCI-C56326, octowy aldehyd (polish), RCRA waste number U001 (1-7)
Molecular formula: C_2H_4O (1-4;6;8;9)

Molecular structure



Molecular weight: 44.1 g/mol (1-4;6;8;9)
Alifatic: yes
Aromatic: no
N containing: no
Halogen containing: no
CAS registry no.: 75-07-0 (1-4;6;9)
Storage:
R/S classification: R12, R36/37, R40; S(02), S16, S33, S36/37 (2;7;9)
dangercode (transport): 33 = very flammable liquid (flashpoint <23°C) (2;9)
Properties:

- melting point: -121 °C – -123.5 °C (1-6;8;9)
- boiling point: 20 – 21 °C (1-9)
- density: 0.7834 g/mL (18 °C) (8); 0.566 g/cm^3 (20 °C) (3); 0.7780 (d^{20}_4) (6)
- refractive index: 1.3316 (20 °C) (5;8); 1.33113 (20/D) (1;6)
- solubility: qualitative H_2O; EtOH 5; ether (8); in water, ethanol, ether, acetone, acetic acid, toluene, xylene, benzin, nafta, terpentine (9); infinite in water (2;3); miscible with water (1;3-7); with alcohol (4;5); with ether (4); with most organic solvents (7); with most common solvents (1;6)
- substance description:
  - colorless (1;2;4;6;8;9)
  - liquid or gas, depending on the surrounding temperature (8); fuming, forming haze (9); liquid (2); fuming liquid (4); volatile liquid (1;6)
  - pungent, fruity odor (4;9); typical odor (2); characteristic, pungent odor (5;7); pungent suffocating odor (1;6)
- volatility: vapour pressure, 755 mm Hg at 20 °C (6)
- pK_a: $K_a = 0.7 \times 10^{-14}$ at 0 °C (1;10)

pK_b = 13.57 at 25 °C (10)

- ➢ PA: 188.9 kcal/mol (11)
- ➢ flammability:
  - FP = -39 °C; (8); -38 °C (1;5;6;9); -40 °C (2)
  - FL Limits = 4.0-60 %; (8;9); 4.0-57 % (2;4); 73 – 1040 g/cm^3 (9); 4.5 – 60.5 vol % acetaldehyde (1)
  - IT = 175 °C (8); 140 °C (2;9); IT_{auto} = 185 – 193 °C (1)
- ➢ decomposition temperature: >400 °C (6;9)
- ➢ stability:
- ➢ vapour pressure/ vapour tension (20 °C): E 990 hPa (2;9)
- ➢ vapour pressure (50 °C): E 2794 hPa (9)
- ➢ relative density: E 0.8 (2;9)
- ➢ octanol water partition coefficient, log P: 0.5 (9); 0.4 (2), log K_{OW}: 0.06 - 0.53 (3)
- ➢ conversion factor: 1 ppm = 1.8 mg/m^3 at 760 mm Hg and 25 °C (6)

Critical assessment

Acetaldehyde is a rather reactive compound due to the polarity of its carbonyl group. That feature is the origin of its most typical, corresponding reaction type, i.e. nucleophilic addition. Nucleophilic addition with amine containing compounds,such as proteins and DNA, occurs within bio-organic conditions, causing adducts.
Reduction of acetaldehyde to alcohol (ethanol) is an additional reaction occurring in biological systems. The reaction is of enzymatic origin; it is related to the presence of co-enzyme NADH.
Solved in water, acetaldehyde does not influence pH. However, in gas phase acetaldehyde behaves as a base, due to its proton affinity (PA). The PA of acetaldehyde is in between that of water and ammonia, so acetaldehyde possesses a gas phase basicity in between water and ammonia.

Conclusion

- Acetaldehyde reacts wih amine-containing compounds like proteins and DNA, forming adducts.
- In biological systems acetaldehyde can be reduced to alcohol (ethanol).
- In gas fase acetaldehyde exhibits base properties.

FUNCTION IN TOBACCO

No data available. See Source.

AMOUNT IN TOBACCO PRODUCTS

No data available.

AMOUNT IN SMOKE

0.87 – 1.22 or 1.14 – 1.37 mg/cigarette depending on the method of detection.
0.09 – 0.27 mg/cigarette in three types of low tar cigarettes. (1;6)

- **main stream**

Assuming that smoke contains about 1 mg acetaldehyde per cigarette, that 20 cigarettes are smoked per day, and a mean adult body weight of 64 kg (WHO), intake from mainstream smoke would be about 300 µg/kg body weight per day. (1)
0.25 – 1.25 mg in main stream smoke (12).
Acetaldehyde may occur in the vapor phase of cigarette smoke at levels up to 2000 ppm (1.1 g/m^3). (13)

- **side stream**

No data available.

SOURCE

Acetaldehyde occurs in tobacco leaves and is found as a combustion product in tobacco smoke. (6)

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Levels of acetaldehyde in ambient air generally average 5 µg/m^3 ($3x10^{-3}$ ppm). Concentrations in water are generally less than 0.1 g/L. Analysis of a wide range of foodstuffs in the Netherlands showed that concentrations, generally less than 1 mg/kg, occasionally ranged up to several 100 mg/kg, particularly in some fruit juices and vinegar. (1)
By far, the main source of exposure to acetaldehyde for the majority of the general population is through the metabolism of alcohol. Cigarette smoke is also a significant source of exposure. With respect to other media, the general population is exposed to acetaldehyde principally from food and beverages, and, to a lesser extent, from air. The contribution from drinking-water is negligible. (1)

COMBUSTION PRODUCTS

Decomposes above 400 °C to form mainly methane and carbon monoxide. (6)

CONSENSUS REPORTS

There is inadequate evidence for the carcinogenicity of acetaldehyde to humans. There is sufficient evidence for the carcinogenicity of acetaldehyde to experimental animals. (1;6)
On the basis of this evidence acetaldehyde is categorized in group 2B. (14)
Acetaldehyde has been tested by inhalation in rats and hamsters. It produced malignant tumours of the nasal mucosa in rats and malignant tumours of the larynx in hamsters at toxic exposure levels causing tissue injury. (7)
Acetaldehyde was mutagenic to bacteria and yeast and induced mutations in

Drosophila melanogaster. It induced DNA damage in and was mutagenic to mammalian cells *in vitro* and was clastogenic to rat embryo cells *in vivo*. (1;7)
No adequate epidemiological data were available to assess the carcinogenicity of acetaldehyde to humans. (7)

STANDARDS AND RECOMMENDATIONS
ADI: no data available.
TWA_{NL} = MAC: 100 ppm/ 180 mg/m^3 (2;6)
TWA_D =MAK: 50 ppm/ 91 mg/m^3 (4;6;9)
TWA_{USA}: 100 ppm (180 mg/m^3) (4)
$STEL_{NL,B}$: 50 ppm/ 92 mg/m^3 (9)
$STEL_{USA}$: 150 ppm (270 mg/m^3) (4)
LTEL: 20 ppm/ 37 mg/m^3 (9)
TLV-C: 25 ppm C/ 45 mg/m^3 C (8;9)
TLV-CARCINOGENICITY: A3 (9)
MAK-REPRODUCTION: D (9)

Others:

Reference value:
The concentration of acetaldehyde in the whole blood of four fasting, normal human subjects was reported to be 1.30 µmol/L (57 µg/L). (6) In other studies, normal values of 1.4 ± 0.3 µmol/L (15) and 15.63 ± 3.61 µmol/L (16) have been reported.
The more than 10 times difference in reported normal whole blood acetaldehyde levels needs further study. This marked difference is most likely related to earlier reported problems and pitfalls in acetaldehyde determinations. (17)

CLASS
EG Carc. Cat.: 3 (9)
IARC-category: 2B (7;9;14)
CEC: F+, Xi; R 12-36/37-40; S 16-33-36/37. (7)

Critical assessment
It is reported that the concentration acetaldehyde in smoke amounts 2000 ppm. Occupational standards vary from 20 to 100 ppm for the 8-hour values and from 25 to 150 ppm for 15 minutes values. In the context of smoking, 15 minutes values as well as 8-hour values are relevant.

Conclusion
Exposure via smoking exceeds both of these limit values.
The more than 10 times difference in reported normal whole blood acetaldehyde levels needs further study.

PHARMACODYNAMICS

Mechanism of action

Direct vapor phase exposure to acetaldehyde resulted in time-dependent ciliary slowing with complete ciliastasis reached by 4 hr in ciliated bovine bronchial airway epithelial cells (18). Acetaldehyde-induced cilia dysfunction may be related to direct cilia ATPase inactivation and adduct formation with cilia dynein and tubulin. This may be an important mechanism by which airway host defences are impaired in clinical settings where acetaldehyde exposure occurs, e.g., with cigarette smoking (19).

Acetaldehyde also has been shown to increase collagen production by stellate cells in culture (20). Moreover, acetaldehyde from cigarette smoke inhibited fibroblast-mediated collagen gel contraction in vitro. This inhibition may be mediated, at least in part, by a decrease in fibroblast fibronectin production which may contribute to inhibition of repair and to the development of pulmonary emphysema (21;22).

Aldehyde-induced inhibition of DNA repair and potentiation of N-nitrosocompound-induced mutagenesis in cultured human cells (23).

Pulmonary system

- **breathing frequency**:
  Acetaldehyde has been shown to decrease breathing frequency in rats (24).
- **tidal volume**: No data available.
- **lung compliance**: No data available.
- **airway resistance**:
  Acetaldehyde induces bronchoconstriction indirectly via histamine release (25-27). In addition, acetaldehyde has been shown to induce bronchial hyperresponsiveness in patients with asthma by mechanisms other than histamine release (28).
  Acetaldehyde may occur in the vapor phase of cigarette smoke at levels up to 2000 ppm (3.6 g/m^3). Chronic inhalation exposure of rats to acetaldehyde at levels of 0 (controls), 750, 1500 or 3000----1000 ppm (1.8 g/m^3) resulted in a high incidence of nasal carcinomas, both squamous cell carcinomas of the respiratory epithelium and adenocarcinomas of the olfactory epithelium (13). Acetaldehyde may significantly contribute to the induction of bronchogenic cancer by cigarette smoke in man (13). It has been reported that acetaldehyde inhibits angiotensin-converting enzyme activity of bovine lung (29).

Cardiovascular system

- **blood pressure**: Adducts with proteins may effect blood pressure, see interactions.
- **heart rate**: Adducts with proteins may effect heart rate, see interactions.

Renal system

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

Nervous system

- **central nervous system**: Acetaldehyde or its adducts with biogenic amines may effect the CNS, see dependency.
- **autonomic system**: No clear data available.

Other

Acetaldehyde-induced emesis seems to be mediated via a peripheral site (30)
Aldehyde dehydrogenase-2 (ALDH2) eliminates most of the acetaldehyde produced during alcohol metabolism. In some drinkers, a mutant ALDH2 allele contributes to diminished activity of the enzyme, dramatically increasing the risk for oesophageal cancer. This suggests a general role of acetaldehyde, a recognised animal carcinogen, in the development of human cancers (31).

Critical assessment

Acetaldehyde, at levels available in cigarette smoke, has been shown to induce bronchoconstriction and damage of respiratory epithelium.

Conclusion

The pharmacodynamic profile of acetaldehyde may contribute to the development of pulmonary emphysema and cancer in man.

PHARMACOKINETICS

Absorption

Available studies on toxicity indicate that acetaldehyde is absorbed through the lungs and gastrointestinal tract; however, no adequate quantitative studies have been identified. Absorption through the skin is probable. (1)
An increase in plasma levels was not determined in smokers. (15;16)

Bioavailability

No data available.

Distribution

Distribution of acetaldehyde to brain interstitial fluid, but not to brain cells, has been demonstrated following ip injection of ethanol. A high affinity, low Km ALDH may be important in maintaining low levels of acetaldehyde in the brain during the metabolism of ethanol. (1)
Acetaldehyde is taken up by red blood cells and, following ethanol consumption in humans and in baboons, in vivo, intracellular levels can be 10 times higher than plasma levels. (1)
Following inhalation by rats, acetaldehyde is distributed to the blood, liver, kidney, spleen, heart and other muscle tissues. (1)
Low levels were detected in embryos after maternal ip injection (mouse) and following maternal exposure to ethanol (mouse and rat). Potential production of acetaldehyde has also been observed in rat fetuses and in the human placenta, in vitro. Partial transfer of acetaldehyde from maternal to fetal blood may occur. (1)
Acetaldehyde has been detected in mother's milk in the USA. (6)

Metabolism

The major pathway is oxidation to acetate under the influence of NAD-dependent aldehyde dehydrogenase (ALDH). Acetate enters the citric acid cycle as acetyl-CoA and is then metabolized to carbon dioxide and ketone bodies. There are several isoenzymes of ALDH with different kinetic and binding parameters that influence acetaldehyde oxidation rates. (1;6)
Human: most important metabolic site is the liver, some metabolism in the renal tubules. (1;6)
Several isoenzymic forms of ALDH have been identified in the human liver and other tissues. There is polymorphism for the mitochondrial ALDH. Subjects who are homozygous or heterozygous for a point mutation in the mitochondrial ALDH corresponding gene have low activity of this enzyme (ALDH2), metabolize acetaldehyde slowly, are intolerant of ethanol and also have a dramatically increased risk for oesophageal cancer. (1;6;31)
ALDH activity has been localized in the respiratory tract epithelium (excluding olfactory epithelium) in rats, in the renal cortex and tubules in the dog, rat, guinea-

pig, and baboon, and in the testis in the mouse. (1;6)
Acetaldehyde is metabolized by mouse and rat embryonic tissue in vitro.
Acetaldehyde crosses the rat placenta, in spite of placental metabolism.
The metabolism of acetaldehyde can be inhibited by crotonaldehyde, dimethylmaleate, phorone, disulfiram, and calcium carbamide. (1;6)

Excretion
Following oral administration, virtually no unchanged acetaldehyde is excreted in the urine. (1)

Kinetic parameters
No data available.

Critical assessment
Due to its reactivity the systemic bioavailability of acetaldehyde after inhalation of low concentrations will be low. Additionally, acetaldehyde will be metabolised in the respiratory tract.
High peripheral plasma levels are required to detect acetaldehyde in brain. This is not likely to occur by exposure via smoking.

Conclusion
Kinetic data indicate that systemic effects of acetaldehyde exposure by smoking are not likely. Potential effects will be limited to the respiratory tract.

TOXICOLOGY
Acute toxicity
Human
A human irritant by inhalation. (4)
See local tolerance.
Animal
LD_{50}s in rats and LC_{50}s in rats and Syrian hamsters showed that the acute toxicity of acetaldehyde is low. (1)
LC_{50} rat = 24 g/m^3 (13333 ppm)/4 h. (1)
LD_{50} inhalation rat: E 23 mg/l/4h (23 g/m^3/4h) (9)
E 13300 ppm (24 g/m^3)/4h (9)
LC_{50} rat = 37 g/m^3 (20556 ppm)/0.5 h. (1;4)
LC_{50} Syrian hamster = 31 g/m^3 (17222 ppm)/4 h. (1)
= 17000 ppm (31 g/m^3)/4h (4)
Inhalation-Mouse LC50:1500 ppm (2.7 g/m^3)/4h (4)
Little harmful via the respiratory tract (LC50 inh rat 20/50 mg/l/4h (20/50 mg/m^3/4h

(11111/27778 ppm)) (9)
Adequate studies on the potential neurotoxicity of acetaldehyde were not identified. (1)
Poison by intratracheal and intravenous routes. A skin and severe eye irritant. A narcotic. (4)

Local tolerance
Human
Inhalation-Human TCLo (LOAEL):134 ppm (241 mg/m^3)/30 min.: Pulmonary system effects (4)
In limited studies on human volunteers, acetaldehyde was mildly irritating to the upper respiratory tract following exposure for very short periods to concentrations exceeding approximately 240 mg/m^3 (133 ppm). (1;9)
On the basis of data on irritancy in humans, a tolerable concentration of 2 mg/m^3 (1.1 ppm) has been derived. (1)
Animal
No data available.

Repeated dose toxicity
Subacute
The NOAEL for respiratory effects following inhalation was 275 mg/m^3 (150ppm) in rats exposed for 6 h/d, 5d/w during 4 weeks. The LOAEL was 437 mg/m^3 (243 ppm) in rats exposed for 8h/d, 5d/w during 5 weeks. At lowest-observed-effect levels, degenerative changes were observed in the olfactory epithelium in rats. Degenerative changes in the respiratory epithelium and larynx were observed at higher concentrations. (1)
Semichronic
The NOAEL for respiratory effects following inhalation was 700 mg/m^3 (389 ppm) in hamsters exposed for 6h/d, 5d/w during 13 weeks. At lowest-observed-effect levels, degenerative changes were observed in the trachea in hamsters (2400 mg/m^3 (1333 ppm)). Degenerative changes in the respiratory epithelium and larynx were observed at higher concentrations. (1)
Chronic
No cumulative effects. (9)
Inhalation-Rat TCLo (LOAEL):1410 ppm (3.7 g/m^3)/6h/65w-I:Equivocal tumorigenic agent. (4)
Adequate studies on the potential neurotoxicity of acetaldehyde were not identified. (1)

Carcinogenicity
Human
This substance may reasonably be anticipated to be carcinogenic. (5;8)
Carcinogenic properties for humans are unclear. (9)

One limited investigation in which the incidence of cancer was examined in workers exposed to acetaldehyde and other compounds was inadequate for the evaluation of carcinogenicity of acetaldehyde in humans. (1;6)
Animal
Inhalation-Rat TCLo (LOAEL):735 ppm (1.3 mg/m^3)/6h/2y-I:Carcinogenic effects (4)
Acetaldehyde is a confirmed carcinogen with experimental carcinogenic and tumorigenic data. (4)
Increased incidences of tumours have been observed in inhalation studies on rats and hamsters exposed to acetaldehyde. In rats, there were dose-related increases in nasal adenocarcinomas and squamous cell carcinomas (significant at all doses). However, in hamsters increases in nasal and laryngeal carcinomas were non-significant. All concentrations of acetaldehyde administered in the studies induced chronic tissue damage in the respiratory tract. (1;6)
The mechanism of induction of tumours by acetaldehyde has not been well studied. (1)

Reproduction toxicology
Human
Foetal risk is unclear (9)
Animal
An experimental teratogen. Other experimental reproductive effects. (4)
In several studies, parenteral exposure (intraperitoneal or intravenous) of pregnant rats and mice to acetaldehyde induces fetal malformations. In the majority of these studies, maternal toxicity was not evaluated. No data on reproductive toxicity were identified. (1;6)

Mutagenicity
Human
Not included in mutagenicity class (EG.MAK) (9)
Human mutation data reported. (4)
Animal
Microsomal Mutageniticity Assay-Salmonella typhimurium 10 μL/plate (4)
DNA Repair-Escherichia coli 10 μL/plate (4)
Sister Chromatid Exchange-Human:lymphocyte 20 ppm (36 g/m^3)/48h (4)
Acetaldehyde is genotoxic in vitro, inducing gene mutations, clastogenic effects, and sister-chromatid exchanges (SCEs) in mammalian cells in the absence of exogenous metabolic activation. However, negative results were reported in adequate tests on Salmonella. Following ip injection, acetaldehyde induced SCEs in the bone marrow of Chinese hamsters and mice. However, acetaldehyde administered ip did not increase the frequency of micronuclei in early mouse spermatids. There is indirect evidence from in vitro and in vivo studies to suggest that acetaldehyde can induce

protein-DNA and DNA-DNA cross-links. (1;6)

Other

Critical assessment
The acute toxicity of acetaldehyde is low. On sub-acute or semi-chronic inhalatory exposure to relatively low concentrations the effects are limited to the sites of initial contact (i.e. olfactory epithelium, trachea, larynx).
Due to the low systemic bioavailability after inhalation, it is not likely that acetaldehyde exposure via smoking causes reproductive toxicity.
Acetaldehyde is genotoxic in vitro (gene mutations, clastogenic effects, sister chromatid exchanges (SCEs) and in vivo (SCEs in bone marrow cells).
After chronic inhalatory exposure acetaldehyde induces damage of the respiratory tract. Acetaldehyde is carcinogenic after chronic inhalation in rats (nasal adenocarcinomas, squamous cell carcinomas). The mechanism through which acetaldehyde induces carcinomas is not known. In humans exposure to acetaldehyde for a short period is mildly irritating to the eyes and upper respiratory tract.

Conclusion
Chronic inhalatory exposure to acetaldehyde may lead to tissue damage and cancer in the respiratory tract.

INTERACTIONS
Chemical
Influenced by a rising temperature, acetaldehyde decomposes and forms acrid/flammable gasses/fumes as methane, acetic acid vapours, carbonmonoxide, carbondioxide. (4;9)
Acetaldehyde is supposed to form peroxides and is able to auto-oxidize to form acetaldehyde monoperacetate. (2)
It is a highly reactive compound which undergoes numerous condensation, addition and polymerization reactions. (6) It can react violently with acid anhydrides, alcohols, ketones, phenols, NH_3, HCN, H_2S, halogens, P, isocyanates, strong alkalies, and amines. (1;2;4;9) It polymerizes violently in the presence of traces of metals or acids (4) and readily to a less volatile, unreactive trimer, paraldehyde or to the solid polymer, metaldehyde (7).

In vivo
Acetaldehyde forms stable and unstable adducts with proteins. This can impair protein function, as evidenced by inhibition of enzyme activity, impaired histone-

DNA binding, and inhibition of polymerization of tubulin. (7) **Serum protein-acetaldehyde adducts** are elevated in persons and animals consuming ethanol. These adducts may have toxic properties on IL-2 secretion (32). **In the blood coagulation pathway** acetaldehyde, by forming an adduct with proteins of the blood coagulation pathway, may either increase or decrease the clotting time (33-36). Within **the renin-angiotensin system (RAS)** an interaction of acetaldehyde with plasma proteins of this system may enhance the activity of the RAS cascade and may contribute to hypertension (37). However, acetaldehyde may also produce inhibition of the angiotensin-converting enzyme activity resulting in vasodilatation (29)
Unstable adducts of acetaldehyde of undetermined significance occur in vitro with nucleic acids. (7)
Acetaldehyde can react with various macromolecules in the body, preferentially those containing lysine residues, which can lead to marked alterations in the biological function of these molecules. (7)
Tetrahydropapaveroline (THP), a condensation product of ethanol-derived acetaldehyde, has been shown to potentiate cardiac function through a beta-adrenergic mechanism in myocardial muscle preparations from rats. This cardiac inotropic response, however, is markedly diminished in hypertension, which is due possibly to alterations in beta-adrenergic signal transduction (38).
Salsolinol, a condensation product of dopamine with acetaldehyde may have some rewarding effect in rats with and without conditioned fear stress,. This rewarding effect may be potentiated by psychological stress and may involve the endogenous central opioid system, i.e., mu-opioid receptor (39). Opioid receptors also seems to be involved in salsolinol-induced arrhythmias while salsolinol may produce tachycardia through a beta-adrenergic mechanism (40). Furthermore, it has been suggested that salsolinol may have a modulatory role on the GABA/benzodiazepine (BZP) receptor complex (41).
histamine metabolic pathways in the body acetaldehyde can effectively compete with the metabolites of histamine, methylimidazole acetaldehyde, and imidazole acetaldehyde. The involvement of the brain histamine system in the mechanisms of the central actions of acetaldehyde is poorly studied and understood (42)
Drug-chemical interaction. Metronidazole or cotrimoxazole (antimicrobial agents) may enhance accumulation of acetaldehyde in blood induced by antialcohol drugs like disulfiram or nitrefazole (43-45)
Acetaldehyde-opiates interaction (46) as well as an involvement of acetaldehyde in voluntary alcohol intake has been suggested (47)
The toxicity studies with mixtures of aldehydes showed that histopathological changes and cell proliferation of the nasal epithelium induced by mixtures of formaldehyde, acetaldehyde and/or acrolein appeared to be more severe and more extensive, both in the respiratory and the olfactory part of the nose, than those observed after exposure to the individual aldehydes at comparable exposure levels. However the combined effect of the mixtures was at most the sum of the individual effects. Neither dose addition nor potentiating interactions occurred upon exposure to

combinations of these aldehydes at exposure levels slightly below or around the minimal-observed-effect level (MOEL) (20).
Sensory irritation of (mixtures of) formaldehyde (10 ppm; 12 mg/m^3), acetaldehyde (13.8 ppm) and acrolein (9.2 ppm) (30 min) as measured by the decrease in breathing frequency (DBF) studied in rats, appeared to be more marked than the sensory irritation expected for each of the individual aldehydes, but less marked than the sum of the irritant activities of the individual aldehydes. The irritant potencies of the mixtures could be accurately described by a mechanistic model for competitive agonism (20). The DBF due to exposure to irritants is caused by binding of a chemical to the trigeminal nerve receptor (20).
It was concluded that the combined exposure to these aldehydes (formaldehyde, acetaldehyde and acrolein) at the No-Observed-Effect-Levels is not associated with greater hazard than that associated with exposure to the individual chemicals.

Critical assessment

Chemical

Acetaldehyde has a potency to react with a lot of compounds.

In vivo

In vivo interaction data for acetaldehyde are known from studies on ethanol-derived acetaldehyde. These data show that acetaldehyde interacts with several physiologic and patho-physiologic systems. The role of acetaldehyde from cigarette smoke in the above mentioned interactions is poorly studied and understood. Mixtures of formaldehyde, acetaldehyde and acrolein cause stronger sensory irritation than that of the individual aldehydes but less than the sum of the individual potencies. This is a result of competition for a common receptor.

Conclusion

Chemical

The relevance of the possible reactions of acetaldehyde with other components in tobacco smoke is unclear yet.

In vivo

Based on current knowledge it is unclear if acetaldehyde from cigarette smoke causes systemic interactions. Additional systemic effects due to the simultaneous exposure to other aldehydes may occur during cigarette smoking.

DEPENDENCY

Acetaldehyde is suspected to be involved in smoke and alcohol addiction (47-55). It is unlikely that acetaldehyde from cigarette smoke has direct reinforcing properties in man because there is no evidence that acetaldehyde from smoke reaches the brain, since a comparison between smokers and non-smokers showed no difference in blood acetaldehyde levels (15;16). This does not exclude a role for acetaldehyde in smoke

addiction since several possible condensation products of acetaldehyde e.g. with biogenic amines are probably involved in the addictive properties of acetaldehyde (41;56-63). On the other hand it seems unlikely that these condensation products are involved in smoke addiction since e.g. the most important one, salsolinol, cannot cross the blood-brain barrier (64).

Effects of smoking cessation
No data available.

Critical assessment
In the literature a role for acetaldehyde in smoke addiction has been suggested but such a role is as yet not proved. Supporting data are mainly derived from studies on alcoholism. The finding of no difference in acetaldehyde levels between smokers and non smokers, and the inability of several condensation products to cross the blood-brain barrier, contradict this hypothesis.

Conclusion
A role of acetaldehyde in smoke in tobacco addiction seems unlikely but can not be excluded.

COMMERCIAL USE
Manufacturing of paraldehyde, acetic acid, butanol, perfumes, flavors, aniline dyes, plastics, synthetic rubber; silvering mirrors, hardening gelatin fibers. Flavoring agent in foods and beverages. (2;5)

BENEFICIAL EFFECTS
Not relevant.

Critical assessment
Not relevant.

Conclusion
Not relevant.

SUMMARY AND FINAL CONCLUSION
Exposure to acetaldehyde via smoking exceeds the 8 hours and 15 min. occupational standards 10 -100 times. In animals chronic inhalatory exposure to acetaldehyde leads to tissue damage in the respiratory tract and to the induction of bronchogenic cancer. Acetaldehyde is genotoxic and a confirmed animal carcinogen. Due to its reactivity and to metabolising in the respiratory tract the systemic bioavailability of

acetaldehyde from cigarette smoke will be low. However, the formation of several systemic active adducts can not be excluded but in smokers this phenomenon is poorly studied. A role of acetaldehyde in smoke in tobacco addiction, as suggested in some reports, seems unlikely but can not be excluded.

Due to its direct damaging effects on the respiratory tract it is recommended to reduce the content of acetaldehyde in cigarette smoke 10 -100 fold. The systemic pathophysiologic role of acetaldehyde from cigarette smoke is poorly understood and needs further study.

DATE THIS SHEET WAS GENERATED
Based on literature available in January 2001.

3.1.1 References

(1) Environmental Health Criteria 167, Acetaldehyde. Geneva: World Health Organization, 1995.

(2) Chemiekaarten®, Gegevens voor veilig werken met chemicaliën. 15e editie . 2000. Ten Hagen & Stam.
Ref Type: Electronic Citation

(3) Physical-chemical properties and environmental fate Handbook. D.Mackay, editor. CRC netBase . 1999.
Ref Type: Electronic Citation

(4) SAX Dangerous Properties of Industrial Materials. Richard J.Lewis Sr, editor. 10th edition, Version 2.0 . 1999. John Wiley & Sons, Inc.
Ref Type: Electronic Citation

(5) The Merck Index. versie 12:1 . 1996. Chapman & Hall EPD.
Ref Type: Electronic Citation

(6) Acetaldehyde. Allyl compounds, Aldehydes, Epoxides and Peroxides. Lyon: World Health Organization, International Agency for Research on Cancer, 1985: 101-132.

(7) Acetaldehyde. In: A.Berlin, M.Draper, J.Duffus, M.Th.van der Venne, editors. The toxicology of chemicals 1. Carcinogenicity, Summary review of the scientific evidence. Luxembourg: Commission of the European Communities, 1991: 95-100.

(8) Handbook of Chemistry and Physics. 79th edition . 1999. CRC, Electronic version by William Andrew Publishing, USA.
Ref Type: Electronic Citation

(9) Brandweerinformatiecentrum voor gevaarlijke stoffen (BIG). versie 9.0 . 2001. Belgium.
Ref Type: Electronic Citation

(10) The hazardous Substance Data Bank (HSDB). through 2000/10 . 2001. The National Library of Medicine (NLM).
Ref Type: Electronic Citation

(11) A.G.Harrison. Chemical Ionaziation Mass Spectometry. Boca Raton: CRC Press, 1983.

(12) Houlgate PR, Dhingra KS, Nash SJ, Evans WH. Determination of formaldehyde and acetaldehyde in mainstream cigarette smoke by high-

performance liquid chromatography. Analyst, 1989; VOL 114, ISS 3, 1989, P355 60.

(13) Feron VJ, Kuper CF, Spit BJ, Reuzel PG, Woutersen RA. Glass fibers and vapor phase components of cigarette smoke as cofactors in experimental respiratory tract carcinogenesis. Carcinog Compr Surv 1985; 8:93-118.

(14) Acetaldehyde. Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1 to 42. Lyon: World Health Organization, International Agency for Research on Cancer, 1987: 77-78.

(15) Jauhonen P, Baraona E, Miyakawa H, Lieber CS. Origin of breath acetaldehyde during ethanol oxidation. Effect of long-term cigarette smoking. J Lab Clin Med 1982; 100(6):908-916.

(16) McLaughlin SD, Scott BK, Peterson CM. The effect of cigarette smoking on breath and whole blood-associated acetaldehyde. Alcohol 1990; 7(4):285-287.

(17) Eriksson CJ. Problems and pitfalls in acetaldehyde determinations. Alcohol-Clin-Exp-Res 1980; 4(1):22-29.

(18) Sisson JH, Tuma DJ. Vapor phase exposure to acetaldehyde generated from ethanol inhibits bovine bronchial epithelial cell ciliary motility. Alcohol Clin Exp Res 1994; 18(5):1252-1255.

(19) Sisson JH, Tuma DJ, Rennard SI. Acetaldehyde-mediated cilia dysfunction in bovine bronchial epithelial cells [published errata appear in Am J Physiol 1992 Feb;262(2 Pt 1):section L following table of contents and 1992 Jun;262(6 Pt 3):section L following table of contents]. Am J Physiol 1991; 260(2 Pt 1):L29-L36.

(20) Wang L, Attard FA, Tankersley LR, Potter JJ, Mezey E. Effect of retinoic acid on the enhancing effect of acetaldehyde on mouse type I collagen expression. Arch Biochem Biophys 2000; 376(1):191-198.

(21) Carnevali S, Nakamura Y, Mio T, Liu X, Takigawa K, Romberger DJ et al. Cigarette smoke extract inhibits fibroblast-mediated collagen gel contraction. Am J Physiol 1998; 274(4 Pt 1):L591-L598.

(22) Nakamura Y, Romberger DJ, Tate L, Ertl RF, Kawamoto M, Adachi Y et al. Cigarette smoke inhibits lung fibroblast proliferation and chemotaxis. Am J Respir Crit Care Med 1995; 151(5):1497-1503.

(23) Grafstrom RC, Curren RD, Yang LL, Harris CC. Aldehyde-induced inhibition of DNA repair and potentiation of N-nitrosocompound-induced mutagenesis

in cultured human cells. Prog Clin Biol Res 1986; 209A:255-264.

(24) Cassee FR, Arts JH, Groten JP, Feron VJ. Sensory irritation to mixtures of formaldehyde, acrolein, and acetaldehyde in rats. Arch Toxicol 1996; 70(6):329-337.

(25) Berti F, Rossoni G, Della BD, Trento F, Bernareggi M, Robuschi M. Influence of acetaldehyde on airway resistance and plasma exudation in the guinea-pig. Arzneimittelforschung 1994; 44(12):1342-1346.

(26) Berti F, Rossoni G, Buschi A, Villa LM, Trento F, Della BD et al. Influence of theophylline on both bronchoconstriction and plasma extravasation induced by acetaldehyde in guinea-pigs. Arzneimittelforschung 1994; 44(3):323-326.

(27) Rossoni G, Berti F, Buschi A, Villa LM, Bella DD. New data concerning the antianaphylactic and antihistaminic activity of nimesulide. Drugs 1993; 46 Suppl 1:22-28.

(28) Myou S, Fujimura M, Nishi K, Matsuda M, Ohka T, Matsuda T. Potentiating effect of inhaled acetaldehyde on bronchial responsiveness to methacholine in asthmatic subjects. Thorax 1994; 49(7):644-648.

(29) Thevananther S, Brecher AS. Acetaldehyde inhibits angiotensin-converting enzyme activity of bovine lung. Alcohol 1993; 10(6):545-548.

(30) Chen Y, Saito H, Matsuki N. Ethanol-induced emesis in the house musk shrew, Suncus murinus. Life Sci 1997; 60(4-5):253-261.

(31) Yokoyama A, Muramatsu T, Ohmori T, Yokoyama T, Okuyama K, Takahashi H et al. Alcohol-related cancers and aldehyde dehydrogenase-2 in Japanese alcoholics. Carcinogenesis 1998; 19(8):1383-1387.

(32) Braun KP, Pearce RB, Peterson CM. Acetaldehyde-serum protein adducts inhibit interleukin-2 secretion in concanavalin A-stimulated murine splenocytes: a potential common pathway for ethanol-induced immunomodulation. Alcohol Clin Exp Res 1995; 19(2):345-349.

(33) Brecher A, Koterba AP, Basista MH. Coagulation protein function. III. Effect of acetaldehyde upon the activation of prothrombin. Alcohol 1996; 13(5):423-429.

(34) Brecher AS, Koterba AP, Basista MH. Coagulation protein function. IV. Effect of acetaldehyde upon factor X and factor Xa, the proteins at the gateway to the common coagulation pathway. Alcohol 1996; 13(6):539-545.

(35) Koterba AP, Smolen S, Joseph A, Basista MH, Brecher AS. Coagulation

protein function. II. Influence of thiols upon acetaldehyde effects. Alcohol 1995; 12(1):49-57.

(36) Basista MH, Joseph A, Smolen S, Koterba A, Brecher AS. Acetaldehyde alters coagulation protein function. Dig Dis Sci 1994; 39(11):2421-2425.

(37) Thevananther S, Brecher AS. Interaction of acetaldehyde with plasma proteins of the renin-angiotensin system. Alcohol 1994; 11(6):493-499.

(38) Ren J, Smude BW, Pavlik ML, Brown RA. Diminished cardiac contractile response to tetrahydropapaveroline in hypertension: role of beta-adrenoceptors and intracellular Ca(2+). Alcohol 2000; 21(2):149-159.

(39) Matsuzawa S, Suzuki T, Misawa M. Involvement of mu-opioid receptor in the salsolinol-associated place preference in rats exposed to conditioned fear stress. Alcohol Clin Exp Res 2000; 24(3):366-372.

(40) Sokolova NA, Chudakov LI, Ashmarin IP, Vinogradova TM, Volodin ND, Vlasov GP et al. [The positive chronotropic effects of salsolinol on the isolated rat heart]. Fiziol Zh SSSR Im I M Sechenova 1990; 76(8):1043-1047.

(41) Kuriyama K, Ohkuma S, Taguchi J, Hashimoto T. Alcohol, acetaldehyde and salsolinol-induced alterations in functions of cerebral GABA/benzodiazepine receptor complex. Physiol Behav 1987; 40(3):393-399.

(42) Zimatkin SM, Anichtchik OV. Alcohol-histamine interactions. Alcohol Alcohol 1999; 34(2):141-147.

(43) Heelon MW, White M. Disulfiram-cotrimoxazole reaction. Pharmacotherapy 1998; 18(4):869-870.

(44) Cina SJ, Russell RA, Conradi SE. Sudden death due to metronidazole/ethanol interaction. Am J Forensic Med Pathol 1996; 17(4):343-346.

(45) Suokas A, Kupari M, Pettersson J, Lindros K. The nitrefazole-ethanol interaction in man: cardiovascular responses and the accumulation of acetaldehyde and catecholamines. Alcohol Clin Exp Res 1985; 9(3):221-227.

(46) Ng-Cheong-Ton JM, Amit Z. Acetaldehyde and morphine interaction in the preexposure conditioned taste aversion paradigm in the rat. Neurosci Lett 1985; 61(1-2):131-134.

(47) Myers W, Ng K, Singer G. Ethanol preference in rats with a prior history of acetaldehyde self-administration. Experientia 1984; 40(9):1008-1010.

(48) Takayama S, Uyeno ET. Intravenous self-administration of ethanol and

acetaldehyde by rats. Japanese Journal of Psychopharmocology 5(4); 329 334 1985.

(49) Smith BR, Amit Z, Splawinsky J. Conditioned place preference induced by intraventricular infusions of acetaldehyde. Alcohol 1984; 1(3):193-195.

(50) Singer GaMWD. Cigarettes and Alcohol: is there a common link. The Pharmacology of Nicotine. ICSU Press by IRL Oxford . Washingthon, 1988: 408-409.

(51) Myers WD, Ng KT, Singer G. Intravenous self-administration of acetaldehyde in the rat as a function of schedule, food deprivation and photoperiod. Pharmacol Biochem Behav 1982; 17(4):807-811.

(52) Myers WD, Ng KT, Marzuki S, Myers RD, Singer G. Alteration of alcohol drinking in the rat by peripherally self-administered acetaldehyde. Alcohol 1984; 1(3):229-236.

(53) Brown ZW, Amit Z, Rockman GE. Intraventricular self-administration of acetaldehyde, but not ethanol, in naive laboratory rats. Psychopharmacology Berl 1979; 64(3):271-276.

(54) Amit Z, Smith BR. A multi-dimensional examination of the positive reinforcing properties of acetaldehyde. Alcohol 1985; 2(2): 367 - 370.

(55) Bates C. Tobacco additives. 1999.
Ref Type: Internet Communication

(56) Clow A, Topham A, Saunders JB, Murray R, Sandler M. The role of salsolinol in alcohol intake and withdrawal. Prog Clin Biol Res 1985; 183:101-113.

(57) Collins MA, Bigdeli MG. Tetrahydroisoquinolines in vivo. I. Rat brain formation of salsolinol, a condensation product of dopamine and acetaldehyde, under certain conditions during ethanol intoxication. Life Sci 1975; 16(4):585-601.

(58) Collins MA, Nijm WP, Borge GF, Teas G, Goldfarb C. Dopamine-related tetrahydroisoquinolines: significant urinary excretion by alcoholics after alcohol consumption. Science 1979; 206(4423):1184-1186.

(59) Myers WD, Ng KT, Singer G, Smythe GA, Duncan MW. Dopamine and salsolinol levels in rat hypothalami and striatum after schedule-induced self-injection (SISI) of ethanol and acetaldehyde. Brain Res 1985; 358(1-2):122-128.

(60) Putscher I, Haber H, Winkler A, Fickel J, Melzig MF. Effect of S(-)- and R(+)-salsolinol on the POMC gene expression and ACTH release of an anterior pituitary cell line. Alcohol 1995; 12(5):447-452.

(61) Reddy BV, Sarkar DK. Effect of alcohol, acetaldehyde, and salsolinol on beta-endorphin secretion from the hypothalamic neurons in primary cultures. Alcohol Clin Exp Res 1993; 17(6):1261-1267.

(62) Smolen TN, Howerton TC, Collins AC. Effects of ethanol and salsolinol on catecholamine function in LS and SS mice. Pharmacol Biochem Behav 1984; 20(1):125-131.

(63) Vernay D, Eschalier A, Durif F, Aumaitre O, Rigal B, Ben Sadoun A et al. [Salsolinol, an endogenous molecule. Possible implications in alcoholism, Parkinson's disease and pain]. Encephale 1989; 15(6):511-516.

(64) Minami M, Takahashi T, Maruyama W, Takahashi A, Dostert P, Nagatsu T et al. Inhibition of tyrosine hydroxylase by R and S enantiomers of salsolinol, 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline. J Neurochem 1992; 58(6):2097-2101.

3.2 Formaldehyde

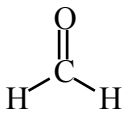
GENERAL

IUPAC systematic name: Formaldehyde (1;2), methanal (3;4).

Synonyms: methanal, oxomethane, oxymethylene, methylene-oxide, methylaldehyde (1;4), formic aldehyde, methyl oxide (3)

Molecular formula: CH_2O (1;2;4)

Molecular structure



Molecular weight: 30.0 (2-5)

Alifatic: no

Aromatic: no

N containing: no

Halogen containing:no

CAS registry no.: 50-00-0 (1-3)

Storage:

R/S classification: R 23/ 24/ 25, R34, R40; S1/2, S26, S36/ 37/ 39, S45, S51 (1)

dangercode (transport): no data available

Properties:

- melting point: -92 °C (1;3;5), -118 °C (2;4)
- boiling point: -19.5 °C (1;5), -19 °C (2;4), -21 °C (3)
- density: 1.081-1.085 (25 °C) (1), d_4^{-20} 0.08153 (2); d 1.067 (air = 1.000) (2;5), 0.815 at 20 °C/4 °C (3)
- refractive index: 1.3746 at 20 °C (5)
- solubility: water: 550 g/L, miscible with diethyl ether, ethanol (1-3),acetone, benzene, chloroform (2;5)
- substance description
  - color: colourless (2-5)
  - liquid/gas/powder: gas or liquid (5), gas (4)
  - odor/taste: pungent, suffocating odour (2;3;5)
- volatility: vapour pressure is 26.7 kPa at –33 °C (2).
- pK_a: no data available
- PA: 161 – 176 kcal/mol (6).
- flammability:
  - FP = 60 °C (5;7)
  - FL Limits = 7-73 % (7)
  - IT = 430 °C (2)

- ➢ decomposition temperature: uncatalysed decomposition is very slow below 300 °C (2;4)
- ➢ stability:
  polymerizes at lower temperatures; undergoes self-condensation (5)
  decomposes in aqueous solution (aging effect) (5)
- ➢ vapour pressure/ vapour tension (20 °C): 4.4 hPa (5).
- ➢ vapour pressure (50 °C): no data available
- ➢ relative density: E 0.815 (-20 °C) (8)
- ➢ octanol water partition coefficient: log P: 0.35 (1), log K_{OW}: 0.35 (3;5)
- ➢ conversion factor: 1 ppm=1.2 mg/m^3 at 25 °C, 1066 mbar, 1mg/m^3 =0.83 ppm (4).

Critical assessment

Formaldehyde is a volatile,very reactive, water-soluble, low molecular compound, occurring in air e.g.

- as a photo-oxidation product of atmospheric hydrocarbons e.g. emitted from automobiles, combustion in power plants, manufacturing facilities, incinerators and petroleum refineries.
- due to mission from urea-formalddehyde foam insulation and resins.

Nucleophilic addition is its most characteristic and typical way of reaction.

Conclusion

Formaldehyde is a very reactive volatile that can easily condense with numerous compounds. The typical reaction type is nucleophilic addition.

FUNCTION IN TOBACCO

No data available.

AMOUNT IN TOBACCO PRODUCTS

No data available.

AMOUNT IN SMOKE

- **main stream**

A ‘pack-a-day’ smoker may inhale as much as 0.4-2.0 mg formaldehyde (3).
Depending on the method of detection several amounts have been reported:
45.2-73.1 and 37.5-44.5 µg/cigarette (2).
70-100µg/cigarette (non filtered) (9)
3.4-283 µg/cigarette (10).
Tobacco smoke contains an average of 48 mg/m^3 formaldehyde(4).
Concentrations of 60-130 mg/m^3, measured in mainstream smoke, would lead to an

average daily intake of 1 mg formaldehyde per day (daily consumption: 20 cigarettes) (4).

- **side stream**

Side stream: main stream relative distribution: 0.1 : 50 (non filtered) (9).
In a 50-m^3 chamber with one air exchange per hour, 6 cigarettes smoked in 15 min yield over 0.12 mg/m^3. In a 30-m^3 chamber with 0.2-0.3 air exchanges per hour, the yield of 5-10 cigarettes was 0.21-0.35 mg/m^3, with one air exchange per hour the yield is 0.05-0.07 mg/m^3. This concentration is in the same range as that likely to be found in the rooms of most conventional buildings where there is no smoking (4).

Smoking 2 mg formaldehyde a day corresponds with a systemic dose of 0.028 mg/kg bodyweight. For a low yield cigarette (< 0.8 mg nicotine/cig) the local concentration of formaldehyde in the lung will be 73 mg/m^3.

SOURCE

A certain percentage of the aldehydes in the vapour phase of smoking 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, pectin's, proteins, and possibly, triglycerides in tobacco (9). In an IARC article on Group 2A carcinogens in mainstream smoke the suggested formation mechanism is destructive distillation and pyrolysis from the precursors: cellulose, starch, pectins, lignin and sugars (10).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Formaldehyde occurs in air as a product of the natural photooxidation of atmospheric hydrocarbons emitted form sources such as automobile exhaust (2), and as one of the volatile compounds formed in the early stages of decomposition of plant residues in the soil (3). Although formaldehyde is a natural component of ambient air, anthropogenic sources usually contribute the most formaldehyde in populated regions, since the ambient levels are generally < 1 $\mu g/m^3$ in remote areas and 1- 20 $\mu g/m^3$ (0.00083- 0.0166 ppm) in urban areas. Urban air concentrations in heavy traffic or during severe inversions can be up to 100 $\mu g/m^3$ (0.083 ppm) (3). Automobile exhaust itself has also been reported to contain formaldehyde at concentrations of 29-34 ppm (35.7-41.8 mg/m^3) (2).
Formaldehyde may occur in indoor air as an emission from urea-formaldehyde foam insulation or from particleboard containing adhesives based on urea-formaldehyde resins (2). Smoke is also an important source of indoor formaldehyde (4). Other indoor sources of formaldehyde are gas cookers; open fireplaces; other building materials made with adhesives containing formaldehyde such as plastic surfaces and certain parquet varnishes; carpeting, drapes and curtains; paints, coatings and wood preservatives; disinfectants and sterilising agents (4). Levels in rooms in which there is tobacco smoking can exceed 100 $\mu g/m^3$ (see also side stream smoke above) (4).

The mean levels in conventional homes with no urea-formaldehyde foam insulation were 25-60 μg/m^3 (0.021-0.05 ppm) (3).
Formaldehyde may be present in foods either naturally or as a result of contamination (2). Fruits and vegetables typically contain 3-60 mg/kg, milk and milk products about 1 mg/kg, meat and fish 6-20 mg/kg. Drinking water normally contains <0.1 mg/L (3). Hexamethylenetetramine, which is used as a food additive, has been reported to decompose gradually to formaldehyde under acid conditions or in the presence of proteins (2). The quantity of formaldehyde ingested with food depends on the composition of the meal and, for an average adult, may range from 1.5-14 mg/day (4).
The contributions of various atmospheric environments to the average human daily intake has been calculated to be 0.02 mg/day for outdoor air, 0.5-2 mg/day for indoor conventional buildings, < 1-10 mg/day for buildings with source of formaldehyde, 0.2-0.8 mg/day for work places without occupational use of formaldehyde, 4 mg/day for work places using formaldehyde, and 0-1 mg/day for environmental tobacco smoke (4).
Assuming a daily respiratory rate of 20 m^3 for an average adult and assuming 100% retention and absorption, one can calculate inhalation exposure per day. Average time estimates lead to the conclusion that people spend 60-70 % of their time in home, 25 % at work and 10 % outdoors. Given exposure levels of 50-100 μg/m^3 in indoor air, and 5-10 μg/m^3 in outdoor air, the daily intake form air is about 1,000 μg/day (11).

COMBUSTION PRODUCTS

Formaldehyde decomposes into methanol and carbon monoxide at temperatures above 150 °C, although uncatalysed decomposition is slow below 300 °C (4).

CONSENSUS REPORTS

There is some differentiation between the several consensus reports. IARC (1995) states that there is limited evidence for carcinogenicity to humans, and there is sufficient evidence for carcinogenicity to animals. On the basis of this evidence formaldehyde is placed in IARC classification group 2A (1). WHO (1989) concludes that the available human evidence indicates that formaldehyde does not have a high carcinogenic potential. While some studies have indicated an excess of cancer in exposed individuals or populations, only nasal or nasopharyngeal tumours are likely to be causally related to formaldehyde exposure. Formaldehyde does not have any adverse effects on reproduction and is not teratogenic. Formaldehyde in vitro interferes with DNA repair in human cells, but there are no data relating to mutagenic outcomes (4). While ECETOC (1995) states: Epidemiological studies of formaldehyde industry workers, professionals who use formaldehyde, and numerous case-control investigations have failed to establish a relationship between formaldehyde exposure and increase cancer risk in humans (12). This conclusion is in variance with the IARC decision to keep formaldehyde classified as 2A. RIVM states

in an exploratory report (1992): Based on animal data formaldehyde is considered to be a carcinogen, causing tumours on the site of entry (nasal cavity) (11).
There is growing evidence that it is concentration rather than dose that determines the cytotoxic effects of formaldehyde on the nasal mucosa of rats (4).

STANDARDS AND RECOMMENDATIONS
ADI: No data available
TWA_{NL} = MAC: 1.5 mg/m^3 (1.2 ppm) (3)
TWA_D =MAK: 2 mg/m^3 (1.66 ppm) maximum 30 min (1979) (2), 0.6 mg/m^3 (0.45 ppm) (1993) (3)
TWA_{USA}: 3.7 mg/m^3 (3 ppm) (2)
$STEL_{NL}$: 2 ppm (2.5 mg/m^3) (8)
$STEL_{USA}$: ceiling limit 0.3 ppm (0.37 mg/m^3) (1)
LTEL: 2 ppm (2.5 mg/m^3) (8)
TLV-C: 0.3 ppm (0.37 mg/m^3) (8)
TLV-CARCINOGENICITY: A2 (8)
MAK-REPRODUCTION: C (8)

Others:
The European Union has adopted a Directive that imposes concentration limits for formaldehyde in cosmetics. This substance is permitted at a maximal concentration of 0.2 % in all cosmetic formulations except nail hardeners, oral hygiene products and oral dispensers. Nail hardeners and oral hygiene products may contain maximal concentrations of 5 and 0.1 % respectively, whereas formaldehyde is prohibited for use in aerosol dispensers.
Guidelines for ambient levels of formaldehyde in living spaces have been set in several countries and range from 0.05-0.4 ppm (0.06-0.5 mg/m^3), with a preference for 0.1 ppm (0.12 mg/m^3) (3).
The Dutch Health Council (1984) recommended the following three limit values:
120 μg/m^3 as ceiling value (based on 30 min. means);
40 μg/m^3 as 98-percentile value (based on 24 h means);
30 μg/m^3 as 95-percentile value (based on 24 h means) (11).

Reference value:
The concentration of endogenous formaldehyde in human blood is about 2-3 mg/L (3;4). Exposure of humans to 2.3 mg/m^3 (1.9 ppm) formaldehyde for 40 minutes does not alter the concentration of formaldehyde in the blood (3).

CLASS
EG Carc. Cat.: 2 (8)
IARC-category: 2A (3)
CEC: No data available.

Critical assessment

Comparison of daily formaldehyde consumption through cigarette smoking and environmental exposure:

	25 cigarettes	industrial TWA (8h)	residential (8h)
Formaldehyde Exposure (mg)	1.25	15	1

Risk assessment of formaldehyde in current framework is based on well-established occupational limit values ranging from 1.5-3.7 mg/m^3, assuming an inhalation volume of 10 m^3/working day in workers.
For a low yield cigarette (< 0.8 mg nicotine/cig) the local concentration of formaldehyde in the lung will be 73 mg/m^3, this corresponds with the amount in mainstream smoke, i.e. 60-130 mg/m^3. The Dutch Health Council (1984) recommended a 120 μg/m^3 ceiling value (based on 30 min. means).

Conclusion

Smoking related formaldehyde exposure corresponds with high local concentrations in the respiratory tract and with a low systemic dose of formaldehyde. Formaldehyde in smoke is an important contributor in inhaled formaldehyde exposure. Smoking related formaldehyde exposure does not exceed the occupational limit values.

PHARMACODYNAMICS

Mechanism of action

In rats, which were exposed to 10 min inhalation of 15 ppm formaldehyde, the increase in vascular permeability induced by formaldehyde in the airways was mediated predominantly by NK1 receptor stimulation. Activation of bradykinin receptors and mast cells did not appear to play an important role in this airway response (13).

Pulmonary system

In humans the nasal mucous flow rate in the nose decreased during exposure to formaldehyde (0- 0.5 mg/m^3), but the response did not increase at concentrations ranging from 0.5 mg/m^3 to 2 mg/m^3 (0.415-1.66 ppm) or on prolongation of the exposure period from 3h to 5h. Formaldehyde decreases the mucus flow in the anterior two thirds of the ciliated epithelium, whereas no effect is seen in the posterior third. This suggests that formaldehyde is absorbed mainly in the anterior part of the nose (14). Rats exposed to 18 mg formaldehyde/m^3 (14.9 ppm) induced inhibition of mucociliary function in specific regions of the nose, and mucostasis was generally more extensive than ciliastasis. Inhibition of mucociliary function was much less severe with exposure to 7.2 mg/m^3 (6.0 ppm), minimal at 2.4 mg/m^3 (2.0 ppm), and

not detected in rats following exposure to 0.6 mg/m^3 (0.5 ppm) (4).
Formaldehyde-induced effects on human pulmonary function variables including forced capacity (FVC), forced expiratory volume in 1.0 seconds ($FEV_{1.0}$), peak expiratory flow rate (PEFR), and forced expiratory flowrate between 25 and 75 % FVC ($FEFR_{25-75}$) have not been found in several studies (7). In one study a small, but statistically significant, decrease in FEV_1 (2 % decrease) and $FEFR_{25-75}$ (7 % decrease) after 30 minutes of exposure to 3 ppm (3.7 mg/m^3) was found. No effect was found after 1 or 3 hours of exposure, in a group of 9 healthy subjects who performed intermittent exercise during exposure and who served as their own controls. In a different study small, but statistically significant, average deficits were measured, 2-3 % in FEV_1, FVC, and FEV_3 in a group of 22 exercising healthy subjects during and after 1 hour of exposure to 3 ppm. No significant deficits were found in a group of 16 asthmatic subjects similarly exposed (7).
Numerous assessments of pulmonary function variables in formaldehyde-exposed workers during workday shifts showed, similar to findings from controlled exposure studies, either no effects or only small and subtle effects from formaldehyde exposure (during a work period) (7). Small, but statistically significant average declines in FEV_1, FVC and $FEFR_{25-75}$ occurred during a workshift in a group of 11 non-smoking woodworkers, but not in 10 smokers, who were exposed to an estimated mean TWA formaldehyde concentration of 0.4-0.1 ppm (0.49-0.123 mg/m^3) (7).

- **breathing frequency**: With concentrations up to 4 ppm (4.9 mg/m^3), formaldehyde showed mainly sensory irritation effects of the upper airways in mice that decrease the respiratory rate from a trigeminal reflex. The no-effect level (NOEL) was about 0.3 ppm. This value is close to the human NOEL, which is about 0.08 ppm (0.10 mg/m^3) (15).
- **tidal volume**: Male Sprague-Dawley rats were exposed to 0, 0.5, or 15 ppm (0, 0.61, 18.45 mg/m^3) formaldehyde for 6 hours/day, 5 days/week, for 8 or 16 weeks. The pulmonary response of naive rats to formaldehyde tracheal challenge (30 ppm; 36.9 mg/m^3) involved the correlation of minute volume and tidal volume depression, while respiratory rate was either unaffected or slightly increased. This was also the response pattern for rats that received 8 weeks of repeated exposure to formaldehyde. The only significant difference in respiratory response patterns between naive and pre-exposed animals existed in a slight increase in the respiratory rate compensatory response in the rats pre-exposed for 16 weeks to 15 ppm (18.4 mg/m^3). There was substantial recovery of initially depressed respiratory parameters during the tracheal challenge in both naive and pre-exposed rats (16).
- **lung compliance**: To study the effects of formaldehyde on lung function and lung structures, 23 young pigs were automatically ventilated with defined formaldehyde concentrations during 6 hours. The concentrations used were 0.02 ppm, 0.2 ppm and 2.0 ppm (0.02, 0.25, 2.5 mg/m^3) (double of the maximum permissible concentration). No differences were found in lung function, as shown

by compliance measurements and arterial blood gas analysis (17).

- **airway resistance**: A significantly increased airway resistance was measured in guinea pigs exposed for 1 hour to formaldehyde concentrations as low as 0.3 ppm; the average increase in resistance was about 14, 29, and 43 % over control values at 0.3, 1.2, and 3.6 ppm (0.37, 1.5, 4.4 mg/m^3), respectively (7).

Cardiovascular system

- **blood pressure**: see heart rate.
- **heart rate**:

Blood pressure and heart rate were not affected in anesthetized rats exposed for 1 minute to 1.1 ppm (1.33 mg/m^3) formaldehyde (7).
Two hours of intermittent nasopharyngeal stimulation with formaldehyde vapour (the exact concentration of formaldehyde vapour was not determined) in the conscious rabbit caused apnoea, bradycardia and a rise in blood pressure known to be associated with vigorous vasoconstriction. Fos-positive neurons occurred in the spinal trigeminal nucleus, the nucleus tractus solitarius, the raphe nuclei and the ventrolateral medulla. In the rostral ventrolateral medulla, 68 % of the Fos-positive neurons were TH-positive C1 cells. These data indicate that nasopharyngeally-evoked peripheral vasoconstriction is associated with activation of C1 neurons (18).
In another study internal carotid and vertebral blood flow were measured during the nasopharyngeal reflex elicited by inhalation of formaldehyde vapour in conscious rabbits. The found delayed increases in cerebral blood flow contrasted with rapid decreases in ear flow and distal aortic flows, measured at the same time. This study indicates that forebrain vascular conductance increases in response to inhalation of formaldehyde vapour, possibly reflecting cerebrovascular events associated with hypoxemia (19).

Renal system

- **diuresis**: Anuria developed after intravesical formaldehyde instillation for the treatment of profuse hemorrhage due to inoperable bladder carcinoma. Renal biopsy showed focal tubular necrosis. Diuresis reappeared spontaneously after six days (20).
- **saluresis**: No data available.

Nervous system

- **central nervous system**: The investigation of low-level formaldehyde exposure on behaviour and neurochemistry in male Sprague-Dawley rats (3 h) showed at 5 ppm (6.1 mg/m^3) statistically significantly increased concentrations of 5-hydroxyindoleacetic acid, 3,4-dihydroxyphenylacetic acid, and dopamine in the hypothalamus, but did not affect the concentrations of norepinephrine or 5-hydroxytryptamine (7). Several other studies found no neurotoxicological effect of formaldehyde exposure (7).

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

Other

Critical assessment
Formaldehyde at high concentrations (18 mg formaldehyde/m^3) exerts some effects: mucostasis, ciliastasis, tidal volume depression, bradycardia and a rise in blood pressure. Through smoking short term concentrations of 73 mg/m^3 (45 μg/cig, inhalation volume 615 ml/cig) will be accomplished.

Conclusion
Formaldehyde exposure through smoking might induce an increased airway resistance. Further research is needed on smoking related exposures to formaldehyde.

PHARMACOKINETICS
Absorption
Formaldehyde is absorbed primarily in the upper respiratory tract (1).

Bioavailability
More than 93% of a dose of inhaled formaldehyde was adsorbed readily by the tissues of the respiratory tract of rats (3). Absorption from the nasal mucosa, trachea, and bronchi is expected to be near 100% in humans (7).

Distribution
Following a 6-h inhalation exposure of rats up to 18 mg/m^3 (14.9 ppm) ^{14}C-formaldehyde, radioactivity was extensively distributed in tissues, the highest concentrations occurring in the oesophagus, followed by the kidney, liver, intestine, and lung, indicating that the absorbed ^{14}C-formaldehyde and its metabolites were rapidly removed by the mucosal blood supply. Studies on the distribution and kinetics indicated that inhaled formaldehyde is extensively metabolized and incorporated (4). Given its rapid metabolism, the distribution of the intact formaldehyde molecule to more distant organs (kidney, fat, spleen, etc) in the body is not likely and is not considered a major factor in formaldehyde toxicity (7).

Metabolism
In humans, as in other animals, formaldehyde is an essential metabolic intermediate in all cells. It is produced endogenously from serine, glycine, methionine and choline,

and it is generated in the demethylation of N-, O-, and S-methyl compounds. It is an essential intermediate in the biosynthesis of purines, thymidine and certain amino acids (3). Formaldehyde is rapidly oxidized to formate, which is incorporated in biological macromolecules, excreted in the urine or oxidized to CO_2 and eliminated in expired air (3). Increases in blood concentrations of formaldehyde were not detected in rats or humans exposed to formaldehyde through inhalation, because of rapid metabolism (4). Several enzymes catalyze the oxidation of absorbed formaldehyde to formic acid. The most important enzyme is the NAD-dependent formaldehyde dehydrogenase, which requires reduced glutathione (GSH) as a cofactor. Thus exogenous formaldehyde becomes a source for the so-called one-carbon pool in intermediary metabolism. There are at least 7 enzymes that catalyze the oxidation of formaldehyde in animal tissue, namely aldehyde dehydrogenase, xanthinoxidase, catalase, peroxidase, glycerinaldehyde-3-phosphate dehydrogenase, aldehyde oxidase, and a speific DPN-dependent formaldehyde dehydrogenase (4). Oxidation takes place largely in the liver, but also in erythrocytes, brain, kidney and muscles (11).
Formaldehyde may be formed endogenously after contact with xenobiotics (11).

Excretion
There are two pathways of final elimination: via exhalation or renal elimination. The elimination of formate via the kidneys of rats is virtually negligible (4).
The fate of inhaled formaldehyde was studied in rats exposed to ^{14}C-formaldehyde (0.63 or 13.1 ppm) for 6 h. About 40 %of the inhaled ^{14}C-formaldehyde was eliminated as expired ^{14}C-carbon dioxideover a 70-h period; 17 % was excreted in the urine, 5 % was eliminated in the faeces and 35-39 % remained in the tissues and carcass (3).

Kinetic parameters
Formaldehyde half-life in plasma of rats, guinea pigs, rabbits and cats is approximately 1-1.5 minute (11). The terminal half-life of ^{14}C-formaldehyde was 55h (3).
Elimination of formate is slower than its formation from absorbed formaldehyde and depends on the species. Formate half-life in man is 55 min (4).

Critical assessment
The pharmacokinetics of formaldehyde is investigated in animal as well in human respiratory studies. Formaldehyde is well absorbed from nasal mucosa, trachea and bronchi. Formaldehyde is rapidly metabolized to formate. There are no indications for species differences.

Conclusion
The assessment of pharmacokinetic properties do not add to risk evaluation of

formaldehyde exposure via smoking which is based on well-established limit values.

TOXICOLOGY

Acute toxicity

Human

The clinical features of toxicity are weakness, headache, abdominal pain, vertigo, anaesthesia, anxiety, burning sensation in the nose and throat, thirst, clammy skin, central nervous system depression, coma, convulsions, cyanosis, diarrhoea, dizziness, dysphagia, irritation and necrosis of mucous membranes and gastrointestinal tract, vomiting, hoarseness, nausea, pallor, shock, and stupor. Respiratory system effects caused by high formaldehyde concentrations are pneumonia, dyspnoea, wheezing, laryngeal and pulmonary oedema, bronchospasm, coughing of frothy fluid, respiratory depression, obstructive tracheobronchitis, laryngeal spasm, and sensation of substernal pressure. Coagulation necrosis of the skin, dermatitis and hypersensitivity lachrymation and corrosion of the eyes, double vision, and conjuctivitis can occur (4).

Sensory reactions are apparently the most typical effects in the non-industrial indoor environment (11). A large number of observations of people in various settings support a conclusion that the generally observed range over which more than 95 % of people respond is 125-3,750 $\mu g/m^3$ (0.10-3.1 ppm). According to the Dutch Health Council (1984) and WHO (1989) the lowest statistically significant effect concentration for respiratory tract irritation is 240 $\mu g/m^3$ (LOAEL) (0.20 ppm) (11).

Animal

LC50 (30 min) rat 0.82 mg/L (1)
LC50 (30 min) rat 1020-1230 mg/m^3 (847-1021 ppm) (11)
LC50 (4 h) rat 310-720 mg/m^3 (257-598 ppm) (11)
LC50 (2 h) mouse 900 mg/m^3 (747 ppm) (11)
LC50 (4 h) mouse 620 mg/m^3 (515 ppm) (11)
LC50 (4 h) mouse 0.48 mg/L (1)
LD50 (oral) rat 800 mg/kg body weight (11)
LD50 (oral) rat 100-200 mg/kg body weight (11)
LD50 (oral) guinea pig 260 mg/kg body weight (11)
LD50 (subcutaneous) rat 420 mg/kg body weight (11)
LD50 (subcutaneous) mouse 300 mg/kg body weight (11)
LD50 (percutaneous) rabbit 270 mg/kg body weight (11)
LD50 (iv) rat 87 mg/kg body weight (11)

Typically inhalation causes increased airway resistance, decreased sensitivity of the nasopalatine nerve, irritation of eyes and respiratory system. High doses cause vomiting, cramps and death (1). Acute inhalation exposure of rats and mice to formaldehyde at very high concentrations (120 mg/m^3; 99.6 ppm) produced

salivation, dyspnoea, vomiting, spasms and death. At a concentration of 1.2 mg/m^3 (1.0 ppm), eye irritation, decreased respiratory rate, increased airway resistance, and decreased compliance appeared. Mice were more sensitive than rats (4).

Local tolerance

Human

Severely irritating to eyes, skin, and mucous membranes. It can cause hypersensitivity with a variety of manifestations (1). Eye irritation was reported for formaldehyde from a level of 0.05 mg/m^3 (0.07 ppm) and irritation of the respiratory tract, from 0.12 mg/m^3 (0.10 ppm). The irritation threshold was found to range between 1.2 and 2.4 mg/m^3 (1.0, 2.0 ppm). Clinical and epidemiological data showed substantial variations in individual irritant responses to formaldehyde (4). During 29-min chamber exposures, formaldehyde concentrations of 0.3 mg/m^3 (0.25 ppm) in a tobacco smoke environment resulted in moderate, strong, or very strong eye irritation (4).

In a study of 21 subjects exposed to formaldehyde (0.14-1.9 mg/m^3) in a mobile home trailer and 18 unexposed controls, no difference in lung function was found between the 2 groups. However, there were significantly more complaints of eye and throat irritation, headache, and fatigue among the exposed (4).

Allergic sensitisation of the skin is caused by formaldehyde in solution only, not by gaseous formaldehyde (4).

In the non-industrial indoor environment, sensory reactions are typical effects, but there are large individual differences in the normal population and between hyperreactive and sensitized people (4).

Animal

Formaldehyde is an eye irritant for rabbits.

Aqueous formaldehyde solution is a sensitizer for the skin (guinea pig).

At 0.6 mg formaldehyde/m^3 air, an irritant effect on the eyes, nose, and throat occurred, and tolerance to the irritant effects of formaldehyde did not develop (4).

Repeated dose toxicity

Subacute

Acute or subacte exposure of rats to a concentration of 2.5 mg/m^3 (2.1 ppm) appears to cause no detectable damage to the nasal epithelium and does not significantly increase rates of cell turnover (3). Rats exposed to 18 mg formaldehyde/m^3 (15 ppm) induced inhibition of mucociliary function in specific regions of the nose, and mucostasis was generally more extensive than ciliastasis. Inhibition of mucociliary function was much less severe with exposure to 7.2 mg/m^3, minimal at 2.4 mg/m^3, and not detected in rats following exposure to 0.6 mg/m^3 (6.0, 2.0, 0.5 ppm) (4).

Semichronic

Cell turnover rates in rat nose during subchronic or chronic exposure to formaldehyde do not increase at 2.5 mg/m^3, increase marginally at concentrations of 12.3-18.4 mg/m^3 (10.2-15.2 ppm). Concentration is more important than length of exposure

(total dose) in determining the cytotoxicity of formaldehyde (3).
Repeated exposures (7-25 mg/m^3; 5.8-20.7 ppm) of rats produced histological changes in the nasal epithelium, such as cell degeneration, inflammation, necrosis, squamous metaplasia, and increased cell proliferation (4). Concentrations below 1 mg/m^3 do not lead to cell damage and hyperplasia (4). In rats, morphological changes could not be proved at 0.6 and 2.4 mg/m^3 (0.0.5, 2.0 ppm) (4). Exposing rats inhalatory to formaldehyde at levels of 360 (LOAEL) and 1,200 μg/m^3 (0.3, 1.0 ppm respectively) challenged the nasal mucociliarly and regenerative defence systems at the beginning, but not at the end, of the study (11).
Chronic
In humans in the non-industrial indoor environment, sensory reactions are typical effects, but there are large individual differences in the normal population and between hyperreactive and sensitized people (4). Only nasal or nasopharyngeal tumours are likely to be causally related to formaldehyde exposure (4).
Male mice and rat exposed to 14.3 ppm (17.6 mg/m^3) for 6h/day for 2 years showed lesions and some squamous cell carcinoma's of the nasal cavity (1). Dose-related lesions observed in long-term, repeated inhalation exposure (2.4, 7.2 or 18 mg/m^3; 2.0, 5.5, 14.3 ppm) were dysplasia and squamous metaplasia of the respiratory and olfactory epithelia, which regressed to some extent after cessation of exposure (4). Several lesions were seen in the nasal cavities of mice exposed to concentrations of 7.2 or 18 mg/m^3 (6 or 15 ppm), including dysplasia and squamous metaplasia of the respiratory epithelium, purulent or seropurulent rhinitis, and atrophy of the olfactory epithelium. Three months after exposure was discontinued (27 months), the nasal lesions had regressed. In rats, several lesions occurred in the nasal cavities at the low concentration of 2.4 mg/m^3 (2 ppm) (4).
In rodents and monkeys, there is a no-observable-effect level (NOAEL= 2.5 mg/m^3; 2.1 ppm) of inhaled formaldehyde with respect to cell proliferation and tissue damage in otherwise undamaged nasal mucosa (3).
Several other studies found no neurotoxicological effect of formaldehyde exposure (7).

Carcinogenicity
Human
There is limited evidence for carcinogenicity to humans, and sufficient evidence for carcinogenicity to animals, IARC classification group 2A (1).
Although an excess for a number of cancers has been reported, the evidence for a causal role of formaldehyde is likely only for nasal and nasopharyngeal cancer. Some excess of nasal or nasopharyngeal cancer was reported in relation to formaldehyde exposure in 6 of the case-control studies reviewed by the WHO(1989). In 2 other case-control studies, the question of a relationship with formaldehyde was adressed either by primary design or by reporting formaldehyde exposure, but no excess risk was demonstrated (4). ECETOC concludes that cohort studies of formaldehyde

industry workers provide no convincing evidence of a link with cancer. There is no evidence of an excess of nasal cancer (12).
An increased relative risk for nasopharyngeal cancer was seen by the type of exposure to formaldehyde: 1.7 for occupation alone, 2.8 for living in mobile homes and 6.7 for both occupational and mobile home exposures. These risks were unaffected by potentially confounding factors such as smoking, alcohol use and socioeconomic status (11).
Animal
Several studies in which formaldehyde was administered to rats by inhalation showed evidence of carcinogenicity, particularly induction of squamous-cell carcinomas of the nasal cavities, usually only at the highest exposure. Similar studies in hamsters showed no evidence of carcinogenicity. Studies in mice either showed no effect or were inadequate for evaluation (3).
In an inhalation study on male rats with a severely damaged (by electrocoagulation) or undamaged nasal mucosa (exposures of 0, 0.12, 1.2, or 12 mg/m^3 (0, 0.10, 1.0, 10 ppm), 6h/day, 5 days/week, 28 or 3 months), a significant number of nasal squamous cell carcinomas (17/60) occurred only in rats with a damaged nose that had been exposed to 12 mg/m^3 for a period of 28 months (4).
The non-linear, steep concentration-response curve for squamous cell carcinomas of the nasal cavity is in accordance with the similar concentration-response curve observed for the formation of formaldehyde induced DNA adducts, also found in inhalation studies in rats. One explanation for the last-mentioned phenomenon is that the higher, cytotoxic formaldehyde concentrations result in DNA synthesis and cell proliferation, and thus in more single-stranded DNA which can react with formaldehyde. Furthermore, there is a greater chance that the repair mechanism may be insufficient to prevent a mutagenic/carcinogenic change prior to the ability of the cell to repair the damage. This theory is consistent with the findings that the toxicity of formaldehyde is much more dependent on concentration than on cumulative dose (11).

Reproduction toxicology
Human
There are no conclusive data showing that formaldehyde is toxic to the reproductive system or to developing fetuses in humans (3;4).
Animal
Mice receiving the compound intravenously (100 μL 1 of 37 % formaldehyde solution) on day 16 of pregnancy developed foetuses that demonstrated chromosome aberrations in cultured liver cells 24 days later (1).

Mutagenicity
Human
Formaldehyde induced DNA-protein cross-links, DNA single-strand breaks,

chromosomal aberrations, sister chromatid exchange and gene mutation in human cells *in vitro* (3). No detectable differences in the frequency of chromosome aberrations and sister chromatid exchange were found in six pathology workers compared with unexposed controls. Similarly, there were no increases in the incidence of chromosomal aberrations in workers exposed to formaldehyde during manufacture and processing, or in the incidence of sister chromatid exchanges in workers exposed to formaldehyde in a paper factory (11).

Animal

In general, the available data show that formaldehyde is mutagenic in different test systems, especially when high concentrations act directly on cells (gene and chromosome mutations). Addition of metabolizing systems to the assay system tends to reduce the activity of formaldehyde (4). Formaldehyde induced mutation, gene conversion, DNA strand breaks and DNA-protein cross-links in fungi and mutation and DNA damage in bacteria (3). Formaldehyde given by inhalation or gavage to rats *in vivo* induced chromosomal anomalies in lung cells, micronuclei in the gastrointestinal tract and sperm-head anomalies. It induced cell transformation, chromosomal aberrations, sister chromatid exchange, DNA strand breaks, DNA-protein cross-links and gene mutation in rodent cells *in vitro* (3). In rats depleted of gluthation a significant increase in the yield of formaldehyde-induced DNA protein cross-links was observed, suggesting that the formaldehyde dehydrogenase-catalyzed oxidation of formaldehyde is an important defence mechanism against the covalent binding of formaldehyde with nucleic acids in the nasal respiratory mucosa (11). DNA protein cross-links could not be detected in bone marrow of rats exposed by inhalation to formaldehyde, suggesting that these are formed only at the site of entry (11).

Other

Critical assessment

The acute toxicity of formaldehyde is low. The toxicity of formaldehyde appears to be dependent on concentration rather than on cumulative dose. Formaldehyde is irritating to the eyes, skin and mucous membranes. After sub-acute or (semi-)chronic inhalatory exposure of animals to relatively low concentrations the effects (e.g. inhibition of ciliary function, cell degeneration, inflammation, necrosis, squamous metaplasia and increased cell proliferation) are limited to the sites of initial contact (nasal cavity). The formaldehyde concentrations in main stream cigarette smoke are higher than of those used in the animal studies. There is evidence that formaldehyde may induce nasal or nasopharyngeal cancer in man and animals. Formaldehyde is mutagenic in bacteria, fungi and mammalian cells. In mammalian cells mutagenicity was also observed following in vivo exposure to formaldehyde.

Conclusion

Chronic inhalatory exposure to formaldehyde through cigarette smoking may lead to tissue damage and cancer in the tissues of initial contact, i.e. the upper respiratory tract.

INTERACTIONS

Chemical

Very reactive: undergoes self-condensation, particularly under alkaline conditions; condenses with numerous compounds to produce methylol or methylene derivatives (2). The gas is stable in the absence of water, incompatible with oxidizers, alkalics, acids, phenols and urea (3). Reacts explosively with peroxide, nitrogen oxide and performic acid. Can react with hydrogen chloride or other inorganic chlorides to form bis(chloromethyl) ether (3).

In vivo

Formaldehyde reacts with proteins and nucleic acids; it reacts with single-strand DNA, but not with double-stranded DNA. This link is reversible. Only formaldehyde cross-links of DNA and protein are stable (4). The formation of DNA-protein cross-links is a sublinear function of the formaldehyde concentration in inhaled air from 0.86-18.4 mg/m^3, and the yield of DNA-protein cross-links at a given concentration is approximately an order of magnitude lower in monkeys than in rats. There is no detectable accumulation of DNA-protein cross-links during related exposure (3). Simultaneous exposure to acrolein (2 ppm) and formaldehyde (6 ppm, 6h) enhanced formaldehyde-induced DNA-protein cross linking and that depletion of gluthatione by acrolein inhibited the metabolism of formaldehyde, thereby increasing formaldehyde-induced DNA-protein cross link formation (7).
The sensory irritant effect of formaldehyde at 1.2 mg/m^3 was shown to decrease when the chemical pyridine was injected into the chamber; such sensory interactions occur in environmentally realistic situations (4).

The toxicity studies with mixtures of aldehydes showed that histopathological changes and cell proliferation of the nasal epithelium induced by mixtures of formaldehyde, acetaldehyde and/or acrolein appeared to be more severe and more extensive, both in the respiratory and the olfactory part of the nose, than those observed after exposure to the individual aldehydes at comparable exposure levels. However the combined effect of the mixtures was at most the sum of the individual effects. Neither dose addition nor potentiating interactions occurred upon exposure to combinations of these aldehydes at exposure levels slightly below or around the minimal-observed-effect level (MOEL) (21).
Sensory irritation of (mixtures of) formaldehyde (10 ppm; 12 mg/m^3), acetaldehyde (13.8 ppm) and acrolein (9.2 ppm) (30 min) as measured by the decrease in breathing

frequency (DBF) studied in rats, appeared to be more marked than the sensory irritation expected for each of the individual aldehydes, but less marked than the sum of the irritant activities of the individual aldehydes. The irritant potencies of the mixtures could be accurately described by a mechanistic model for competitive agonism (21). The DBF due to exposure to irritants is caused by binding of a chemical to the trigeminal nerve receptor (21).
It was concluded that the combined exposure to these aldehydes (formaldehyde, acetaldehyde and acrolein) at the No-Observed-Effect-Levels is not associated with greater hazard than that associated with exposure to the individual chemicals.

Critical assessment
Chemical
Formaldehyde is a very reactive chemical.
In vivo
Formaldehyde reacts with proteins and single-stranded DNA. Mixtures of formaldehyde, acetaldehyde and acrolein cause stronger sensory irritation than that of the individual aldehydes but less than the sum of the individual potencies. This is a result of competition for a common receptor.

Conclusion
Chemical
Condenses easily with numerous compounds via nucleophilic addition.
In vivo
Additional systemic effects due to the simultaneous exposure to other aldehydes may occur during cigarette smoking.

DEPENDENCY
No data available.

Effects of smoking cessation
Several lesions were seen in the nasal cavities of mice exposed to concentrations of 7.2 or 18 mg/m^3 (6 or 15 ppm), including dysplasia and squamous metaplasia of the respiratory epithelium, purulent or seropurulent rhinitis, and atrophy of the olfactory epithelium. Three months after exposure was discontinued (27 months), the nasal lesions had regressed (4).

Critical assessment
After smoking cessation damage to the respiratory epithelium might regress.

Conclusion
After smoking cessation damage to the respiratory epithelium might regress. No data

were available on dependency of formaldehyde exposure through smoking.

COMMERCIAL USE

The widest use of formaldehyde is in the production of resins with urea, phenol and melamine and to a small extent, their derivatives. Formaldehyde-based resins are used as adhesives and impregnating resins in the manufacture of particle board, plywood, furniture and other wood products. They are also used for the production of curable moulding materials and as raw materials for surface coatings and controlled-release nitrogen fertilisers. They are used in the textile, leather, rubber, and cement industries. Further uses are as binders for foundry sand, stonewool and glasswool mats in insulating materials, abrasive paper and brake linings.
Another major use is as an intermediate for synthesising other industrial chemical compounds. Formaldehyde is also the basis for products used to manufacture dyes, tanning agents, dispersion and plastic precursors, extraction agents, crop protection agents, animal feeds, perfumes, vitamins, flavourings and drugs. Formaldehyde itself is used for preservation and disinfection. It is used as an antimicrobial agent in many cosmetics products, including soaps, shampoos, hair preparations, deodorants, lotions, make-up, mouthwashes and nail products (3).

BENEFICIAL EFFECTS

No data available.

Critical assessment

Not relevant.

Conclusion

Not relevant.

SUMMARY AND FINAL CONCLUSION

Formaldehyde 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 formaldehyde in tobacco products is not known.
Formaldehyde has been identified in mainstream cigarette smoke at levels of 60-130 mg/m^3. The reactivity of formaldehyde in the gas phase is very high and it can easily condense with numerous compounds. The typical reaction type is nucleophilic addition.
Risk assessment of formaldehyde in current framework is based on well-established

occupational limit values ranging from 1.5-3.7 mg/m^3, assuming an inhalation volume of 10 m^3/working day in workers. Smoking 20 cigarettes per day corresponds with an intake up to 2 mg/day through inhalation. It can be concluded that exposure via smoking does not exceed the occupational limit values. 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 to formaldehyde. Local respiratory tract exposures to formaldehyde are high (73 mg/m^3), while systemic concentrations are low (0.028 mg/ kg bodyweight). Formaldehyde in smoke is an important contributor in inhaled formaldehyde exposure.
The pharmacokinetics of formaldehyde is investigated in animal as well as in human respiratory studies. Formaldehyde is well absorbed from nasal mucosa, trachea and bronchi. Formaldehyde is rapidly metabolized to formate. There are no indications for species differences.
Formaldehyde exposure through smoking might induce an increased airway resistance. Chronic inhalatory exposure to formaldehyde may lead to tissue damage and cancer in the tissues of initial contact, i.e. the upper respiratory tract. Additional systemic effects due to the simultaneous exposure to other aldehydes may occur. There are no data on dependency available. After smoking cessation damage to the respiratory epithelium might regress. There are no known beneficial effects of formaldehyde exposure through smoking.
It can be concluded that intermittent peak exposure to formaldehyde needs further study to establish the effects of formaldehyde from cigarette smoke. Another point of concern is the exposure of formaldehyde together with other aldehydes in cigarette smoke and further study on this combined exposure is also needed. The need for such studies is supported by the found evidence that chronic exposure to formaldehyde may lead to tissue damage and cancer.

DATE THIS SHEET WAS GENERATED
Based on literature available in June 2001.

3.2.1 References

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

(2) formaldehyde. Some industrial Chemicals and Dyestuffs. Lyon: World Health Organization, Intenational agency for research on cancer, 1982: 345-389.

(3) formaldehyde. Wood dust and formaldehyde. Lyon: World Health Organization, Intenational agency for research on cancer, 1995: 217-362.

(4) Environmental Health Criteria 89, Formaldehyde. Geneva: World Health Organization, 1989.

(5) The hazardous Substance Data Bank (HSDB). through 2000/10 . 2001. The National Library of Medicine (NLM).
Ref Type: Electronic Citation

(6) Walder R, Franklin JL. Proton affinities of neutral molecules. International Journal of Mass Spectrometry and Ion Physics 1980; 36:85-112.

(7) Agency for Toxic Substances and Disease Registry. Toxicological profile for formaldehyde. 1999. Agency for Toxic Substances and Disease Registry.
Ref Type: Report

(8) Brandweerinformatiecentrum voor gevaarlijke stoffen (BIG). versie 9.0 . 2001. Belgium.
Ref Type: Electronic Citation

(9) IARC. Tobacco smoking. 38. 1986. Lyon, IARC. Evaluation of the carcinogenic risk of chemicals to humans.
Ref Type: Report

(10) Smith CJ, Perfetti TA, Rumple MA, Rodgman A, Doolittle DJ. "IARC group 2A Carcinogens" reported in cigarette mainstream smoke. Food Chem Toxicol 2000; 38(4):371-383.

(11) W.Slooff et al. Exploratory report formaldehyde. National Institute of Public Heatlh and Environmental, editor.RIVM report 710401018. 1992. Bilthoven.
Ref Type: Report

(12) Formaldehyde and human cancer risk. European Centre for Ecotoxicology and Toxicology of Chemicals ECETOC, editor. 65. 1995. Brussels. ECETOC technical report 65.

Ref Type: Report

(13) Ito K, Sakamoto T, Hayashi Y, Morishita M, Shibata E, Sakai K et al. Role of tachykinin and bradykinin receptors and mast cells in gaseous formaldehyde-induced airway microvascular leakage in rats. Eur J Pharmacol 1996; 307(3):291-298.

(14) Andersen I, Mollhave L. Controlled human studies with formaldehyde. In: Gibson JE, editor. Formaldehyde toxicity. Washington, New York, London: Hemisphere, 1983: 154-165.

(15) Nielsen GD, Hougaard KS, Larsen ST, Hammer M, Wolkoff P, Clausen PA et al. Acute airway effects of formaldehyde and ozone in BALB/c mice. Hum Exp Toxicol 1999; 18(6):400-409.

(16) Dallas CE, Theiss JC, Harrist RB, Fairchild EJ. Respiratory responses in the lower respiratory tract of Sprague-Dawley rats to formaldehyde inhalation. J Environ Pathol Toxicol Oncol 1986; 6(5-6):1-11.

(17) Frey G, Bock KH, Meister H, Haug HU, Kilian J, Ahnefeld FW. Auswirkungen einer Beatmung mit definierten Formaldehydkonzentrationen auf Lungenfunktion und Lungenstruktur Tierexperimentelle Untersuchungen uber die Schadlichkeit von Formaldehydruckstanden nach Aseptordesinfektion. [Effects of ventilation with defined formaldehyde concentrations on lung function and lung structures. Animal experiments on the noxiousness of formaldehyde residues after disinfection in the aseptor (author's transl)]. Anaesthesist 1979; 28(6):271-278.

(18) Gieroba ZJ, Yu YH, Blessing WW. Vasoconstriction induced by inhalation of irritant vapour is associated with appearance of Fos protein in C1 catecholamine neurons in rabbit medulla oblongata. Brain Res 1994; 636(1):157-161.

(19) Yu YH, Blessing WW. Cerebral blood flow in rabbits during the nasopharyngeal reflex elicited by inhalation of noxious vapor. J Auton Nerv Syst 1997; 66(3):149-153.

(20) Merimsky E, Blum M, Aviram A. Tubular necrosis complicating intravesical formaldehyde treatment. Int Surg 1982; 67(4 Suppl):504-505.

(21) Flemming RC. Upper respiratory tract toxicity of mixtures of aldehydes In vivo and in vitro studies. 1995. Wageningen, Ponsen en Looyen B.V.
Ref Type: Report

3.3 Acrolein

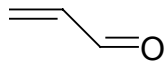
GENERAL

IUPAC systematic name: acrylaldehyde (1;2), 2-propenal (2)

Synonyms: acrylaldehyde, allyl-aldehyde, 2-propenal, prop-2-enal, ethylene-aldehyde, acrylic aldehyde (3); acraldehyde, propenal, prop-2-en-1-al (1), 2-prop-1-one, trans-acrolein (2)

Molecular formula: C_3H_4O (3)

Molecular structure



Molecular weight: 56.06 g/mol (3)

Alifatic: yes

Aromatic: no

N containing: no

Halogen containing: no

CAS registry no.: 107-02-8 (3)

Storage:

R/S classification: R11-25-26-34: S (1/2-)3/9/14-26-36/37/39-38-45 (4)

dangercode (transport): 663 (5)

Properties:

- melting point: -87 ºC (1;3)
- boiling point: 52 ºC (3)
- density: 0.843 (20 ºC) g/cm^3 (3)
- refractive index: 1.4017 (20 ºC) (6)
- solubility: 20.6 % at 20 ºC (3), soluble in: acetone, diethyl ether, ethanol (3).
- Substance description:
  - colourless (pure) or yellowish (commercial) (1).
  - liquid/gas/powder: volatile liquid, mobile liquid (2)
  - odor: burnt, sweet, pungent, choking, and disagreeable (1)
- volatility: vapour pressure, 220 mm Hg at 20 ºC (7)
- pK_a: no data available
- PA: 190.4 $kcal.mol^{-1}$ (8)
- flammability:
  - FP = -26 ºC (3), < -18 ºC (2)
  - FL Limits = 2.8-31.0 % by volume (1)
  - IT = 220 ºC (4)
- decomposition temperature: No data available.
- stability: very reactive compound (1).
- vapour pressure/ vapour tension (20 °C): 210 mmHg (3)

- ➢ vapour pressure (50 °C): no data available.
- ➢ relative density: 0.8427 (1)
- ➢ octanol water partition coefficient: log P, log K_{OW}: 1.2 (2), 0.101 (3)
- ➢ conversion factor: At 25 ºC and 101.3 kPa (760 mmHg), 1 ppm of acrolein = 2.29 mg/m^3 air and 1 mg of acrolein per m^3 air = 0.44 ppm (1).

Critical assessment

Acrolein is a volatile highly flammable liquid with a pungent, choking, disagreeable odour. It is a very reactive compound (1). Acrolein is an α,β-unsaturated Carbonyl compound, in which the available bonds are conjugated, implying that the compound has properties of both the carbon-carbon double bond and the carbonyl group, and that it possesses in addition properties due to the presence of the conjugated system. A carbon-carbon double bond can undergo electrophilic addition of acids and halogens, hydrogenation, hydroxylation, and cleavage, while at the carbonyl group the compound undergoes the nucleophilic substitition typical of an ester or the nucleophilic addition typical of a ketone. The mentioned conjugation system further adds to its reactivity (9).

Conclusion

Acrolein is a very reactive compound to a wide variety of compounds, it is a volatile and highly flammable liquid with a pungent, choking, disagreeable odour.

FUNCTION IN TOBACCO

No data available.

AMOUNT IN TOBACCO PRODUCTS

AMOUNT IN SMOKE

- **main stream**

Smoking one cigarette yields 3-228 µg acrolein, the amount depending on the type of cigarette and smoking conditions (1).

<0.01-0.14 mg/cigarette, the sales-weighted mean for the 74 tested brands was 0.11 mg acrolein per cigarette (10). The sales-weighted mean is the mean amount of acrolein per cigarette adjusted to the difference in composition of the most sold brands.

- **side stream**

Side stream smoke yields 723-1390 µg acrolein per cigarette (11). Smoking one cigarette per m^3 of room-space in 10-30 min was found to lead to acrolein vapour

concentrations of 450-840 μg/m^3. In one experiment it was observed that the presence of people in the room reduced the acrolein levels, probably by respiratory uptake and condensation onto hair, skin, and clothing. Evidence has also shown that acrolein is associated with smoke particles. The fraction thus associated can be deduced to be 20-75% of the total (1).

SOURCE

Acrolein emission arises from incomplete combustion or pyrolysis of organic materials such as tobacco (1).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Important acrolein emissions into the air arise from incomplete combustion or pyrolysis of organic materials such as fuels, synthetic polymers, food, and tobacco. Acrolein is also a product of photochemical oxidation of specific organic air pollutants. Acrolein is degraded in the atmosphere by reaction with hydroxyl radicals. Atmospheric residence times are about one day.

Exposure of the general population will predominantly occur via air. Oral exposure may occur via alcoholic beverages or heated foodstuffs (1). Acrolein has been detected as a volatile in beer (1.6-5 μg/L) (2), wines, “peppery” rums and whiskies, apple eau-de-vie, heated and aged bone grease (4.2 mg/kg), in white bread, cooked potatoes, ripe tomatoes, vegetable oils, turkey meat, sour salted pork, heated beef fat, cooked horse mackerel (1).

Average acrolein levels up to approximately 15 μg/m^3 have been measured in urban air. Near industries and close to exhaust pipes, levels that are ten to one hundred times higher may occur. Acrolein may make up 3-10% of total vehicle exhaust aldehydes (1). In the Netherlands an average concentration of 1.1 μg/m^3 acrolein in ambient air has been reported (2).

Extremely high air levels in the mg/m^3 range can be found as a result of fires. In indoor air, smoking one cigarette per m^3 of room-space in 10-30 min was found to lead to acrolein vapour concentrations of 450-840 μg/m^3 (1). The acrolein concentration in a cooking area, where sunflower oil was heated at 160-170 ºC, reached a value of 1100 μg/m^3 (2). Workplace levels of over 1000 μg/m^3 were reported in situations involving the heating of organic materials(1).

It is estimated that the dietary intake may be higher than 1 μg/kg body weight per day. Inhalation exposure will easily exceed 1 μg/m^3 in areas with a high traffic density, with a maximum concentration of about 10 μg/m^3. Inhalation exposure through indoor air may very well exceed 10 μg/m^3. In case of smoking in poorly ventilated rooms, exposure levels (for non-smokers) may be as high as several hundreds of μg/m^3 (2).

In summary, the main source of exposure of the general population to acrolein is via tobacco smoke. General environmental pollution by vehicle exhaust and the smoke of burning organic materials is the next most important source (1).

COMBUSTION PRODUCTS
No data available.

CONSENSUS REPORTS
The WHO (World Health Organisation) (1992) states that in animals and humans the reactivity of acrolein effectively confines the substance to the site of exposure, and pathological findings are also limited to these sites. Acrolein is a cytotoxic agent. Both respiratory tract function and histopathological effects were seen as toxicological effects in continuous inhalation studies in several laboratory animals. Acrolein has been shown to interact with nucleic acids *in vitro* and to inhibit their synthesis both *in vitro* and *in vivo* (1).
IARC (International Agency for Research on Cancer) (1984) states that there is inadequate evidence for the carcinogenicity of acrolein to experimental animals. There is inadequate evidence for the carcinogenicity of acrolein to humans (2).
The European Chemicals Bureau (1999) states that acrolein is very toxic after exposure by inhalation. No conclusions with regard to possible carcinogenicity upon exposure inhalation could be made (12).

STANDARDS AND RECOMMENDATIONS
ADI: 0.5 µg/kg body weight (2).
TWA_{NL} = MAC: 250 µg/m^3 (2)
TWA_D =MAK: 0.1 ppm (0.23 mg/m^3) (7)
TWA_{USA}: 0.1 ppm (0.23 mg/m^3) (7)
$STEL_{NL}$: 0.3 ppm (0.7 mg/m^3) (5)
$STEL_{USA}$: ceiling limit 0.1 ppm (3)
LTEL: 0.1 ppm (0.23 mg/m^3) (5)
TLV-C: 0.1 ppm (0.23 mg/m^3) (5)
TLV-CARCINOGENICITY: No data available
MAK-REPRODUCTION: No data available

Others:
With respect to inhalation and dietary exposure of humans to acrolein, a maximum permissible concentration (MPC) of 0.5 µg/m^3 and a tolerable daily intake of 0.5 µg/kg body weight has been derived. The MPC is considered to be the maximum acceptable risk level for humans at lifetime exposure (2).
The Health Council of the Netherlands has assessed the following limit values for acrolein, based on irritation after inhalation exposure:
Ceiling value (based on 30 min means): 25 µg/m^3;
98% value (based on 24 hr means): 8 µg/m^3;
95% value (based on 24 hr means): 6 µg/m^3 (2).
The 98-and 95-percentile values are derived for outdoor air and are not automatically valid for indoor air, because the factors influencing the distribution of the acrolein concentration in indoor air differ from those in outdoor air. The ceiling value (which is in fact the no-observed-effect-concentration for respiratory irritation in man) is

valid for both outdoor and indoor air (2).

Reference value:
No data available.

CLASS

EG Carc. Cat.: No data available.

IARC-category: 3 (7).

CEC: No data available.

Critical assessment

Comparison of daily acrolein consumption through cigarette smoking and environmental exposure:

	25 cigarettes	industrial TWA (8h)	residential (8h)
Acrolein exposure (mg)	2.75	2.5-7.0	0.011

Risk assessment of acrolein in current framework is based on well-established occupational limit values ranging from 0.25-0.7 mg/m^3, assuming an inhalation volume of 10 m^3/working day in workers. For acrolein exposure the concentration is more important than the dose. Therefore a comparison of concentration has been made. For a low yield cigarette (<0.8 mg nicotine/ cig) the local concentration of acrolein in the respiratory tract will be 179 mg/m^3 (0.11 mg/cig, inhalation volume 615 ml/cig (13)).

	Cigarette smoking	Ceiling value general population
Acrolein (mg/m^3)	179	0.025

Conclusion

Smoking related acrolein exposure corresponds with high local concentrations in the respiratory tract. Acrolein in smoke is the main source of exposure of the general population to acrolein. Smoking related acrolein exposures exceed the ceiling values for the general population.

PHARMACODYNAMICS

Mechanism of action

Acrolein exposure results in a respiratory rate depression from direct stimulation of the trigeminal nerve endings in the nasal mucosa (14).

Pulmonary system

- **breathing frequency**: The concentration that produces a 50% decrease in respiratory rate (RD_{50}) as a result of reflex stimulation of trigeminal nerve endings in the nasal mucosa (sensory irritation) has been used as an index of upper respiratory tract irritation. This effect reduces the penetration of noxious chemicals into the lower respiratory tract. The rate of respiration was measured in a body plethysmograph, only the animals' heads being exposed to the acrolein vapour. Depending on the strain, RD_{50} values for mice ranged from 2.4 to 6.6 mg/m^3. In rats a RD_{50} of 13.7 mg/m^3 was found (1).
- **tidal volume**: see below.
- **lung compliance**: see below.
- **airway resistance**: see below.

Contradictory findings have been reported on the effect of acrolein on the respiratory tract. First of all there are reports which subscribe the effects on direct stimulation of the trigeminal nerve endings in the nasal mucosa. A rapid reversible increase in respiratory rate was observed in intact guinea-pigs during exposure to 39 mg/m^3 for 60 min and in another study to 0.8 mg/m^3 or more for 2 h, was followed by a decrease in respiratory rate and an increase in tidal volume. No changes in pulmonary compliance were reported. These effects were not observed in tracheotomized animals which may indicate that they were caused by reflex stimulation of upper airway receptors and not by bronchoconstriction.
Secondly there are some authors who subscribe the effects of acrolein to bronchoconstriction mediated through a reflex cholinergic stimulation. Anticholinergic bronchodilatators (aminophylline and isoproterenol), but not antihistaminics, reduced the acrolein-induced increase in respiratory resistance.
And finally there are also studies that propose a bronchoconstriction mediated through the release of histamine. An increase in respiratory resistance was observed in anaesthetised tracheotomized guinea-pigs with transected medulla during exposure to 43 mg/m^3 for up to 5 min. The effect was not reversed by atropine. It was concluded by the authors that acrolein did not cause bronchoconstriction via reflex stimulation, but probably via histamine release (1).

Acrolein is a known inhibitor of respiratory tract ciliary movement *in vitro*. After a 20 min exposure to an acrolein concentration of 34-46 mg/m^3, the ciliary beating frequency of excised sheep trachea decreased by 30%. Exposure to 13 mg/m^3 for 1 h is the highest exposure level that does not stop ciliary activity in excised rabbit trachea. The no-observed-effect-level for longer exposure periods is expected to be lower than 13 mg/m^3. A decrease in respiratory rate in humans is evident from 0.7 mg/m^3 (1).

Cardiovascular system

- **blood pressure**: see below.
- **heart rate**: see below.

Rats anaesthetised by sodium pentobarbital and exposed only via the mouth and the nose to concentrations between 10 and 5000 mg/m^3 for 1 min showed an increase in blood pressure at all exposure levels. The heart rate was increased at concentrations from 50 mg/m^3 to 500 mg/m^3 but decreased at 2500 and 5000 mg/m^3. Intravenous experiments suggested that increased blood pressure resulted from the release of catecholamines from sympathetic nerve endings and from the adrenal medulla and that the decreased heart rate effect was mediated by the vagus nerve (1).

Renal system

No studies regarding renal effects in humans or animals after inhalation exposure to acrolein were located in the literature.

- **Diuresis**: no data available.
- **saluresis**: no data available.

Nervous system

- **central nervous system**: no data available.
- **autonomic system**: Concentrations of acrolein between 1858, and 5693 mg.min/m^3 for 10 minutes induced a dose-related decrease in substance P and calcitonin gene-related peptide in nerve terminals innervating the trachea of rats. No change was seen in total nerve distribution and number or in vasoactive intestinal peptide. These data indicate that acrolein may induce release of peptides that could play a role in the physiological response to irritants (15).

Other

In vivo studies have shown that rat liver alkaline phosphatase and tyrosine aminotransferase activities are increased markedly after inhalation of acrolein for 4 h at a concentration of 14.7 mg/m^3 or after a single intraperitoneal injection of acrolein in water at doses of 1.5-6 mg/kg body weight. The effects were reduced by prior adrenalectomy or hypophysectomy or by pretreatment with protein synthesis inhibitors such as actinomycin D, puromycin, and ethionine, suggesting that the irritant action of acrolein stimulates the pituitary-adrenal system to release glucocorticoids, which act to increase the synthesis of adaptive liver enzymes. Increased plasma and adrenal levels of corticosterone were measured in rats one hour after a single intraperitoneal injection (3 mg/kg body weight) of acrolein in water. The hypersecretion of glucocorticoids could also explain the observed increase in liver glycogen level following intraperitoneal exposure to acrolein at a dose of 1.5 mg/kg body weight.

There is limited evidence that acrolein can depress pulmonary host defences. In female Swiss mice, exposed to measured concentrations of 1.1, 6.9, and 14.2 mg/m^3 for 8 h, a concentration-related increase in the survival of *Staphylococcus aureus* was

seen at levels of 6.9 mg/m^3 or more. Similar findings have been reported for the survival of *Proteus mirabilis*, *Klebsiella pneumoniae* (exposed to 0.23 mg/m^3 acrolein for 3h per day over 5 days) and *Streptococcus zooepidemicus* (1).
It has been suggested that environmentally relevant concentrations of aldehydes can induce bronchial hyperreactivity in guinea pigs through a mechanism involving injury to cells present in the airways during exposure (rather than from subsequently recruited migratory cells) and that this response is dependent on leukotriene biosynthesis. Guinea pigs were exposed to acrolein, specific total pulmonary resistance and bronchial reactivity to intravenous acetylcholine were assessed. Bronchial hyperreactivity, assessed by the acetylcholine dose necessary to double resistance, increased and became maximal two to six hours after exposure to at least 1 ppm (2.29 mg/m^3) acrolein for two hours. Increases in three bronchoconstrictive eicosanoids, prostaglandin F2 α, thromboxane B2, and leukotriene C4, occurred immediately after exposure, whereas an influx of neutrophils into lavage fluid occurred 24 hours later (16).
There are several *in vitro* data on the role of acrolein in smoke-induced inflammatory processes in the lung. First of all, acrolein increases neutrophil recruitment and reduces neutrophil clearance by apoptosis *in vitro* (17). Secondly, two major volatile factors in cigarette smoke, acrolein and acetaldehyde, augmented IL-8 release. Four cell strains were tested and showed increased IL-8 release in response to cigarette smoke extract. In addition, bronchoalveolar lavage (BAL) was performed on 11 nonsmokers and 12 smokers. IL-8 concentration was greater in the proximal, bronchial samples than in distal, alveolar samples, and IL-8 in BAL from smokers was higher than in BAL from nonsmokers. There was a significant correlation between IL-8 concentration and neutrophil count in bronchial samples of BAL fluid. These data support the hypothesis that exposure to cigarette smoke may induce bronchial epithelial cells to release IL-8 and that this may contribute to airway inflammation in smokers (18).
Cigarette smoking is the major cause of pulmonary emphysema which is characterised by destruction of alveolar walls. Because tissue destruction represents a balance between injury and repair, it was hypothesized that cigarette smoke exposure may contribute to the development of emphysema through the inhibition of tissue contraction during the repair process. Inhibition of contraction was observed at 5 μmol/L acrolein. In conclusion, cigarette smoke inhibited fibroblast-mediated gel contraction, and this inhibition was due, at least in part, to the volatile components of cigarette smoke and may be mediated, at least in part, by a decrease in fibroblast fibronectin production. By inhibition of repair, these smoke components may contribute to the development of pulmonary emphysema (19).

Critical assessment

Through smoking short-term concentrations of 179 mg/m^3 (0.11 mg/cig, inhalation volume 615 ml/cig (13)) will be accomplished in the respiratory system. A decrease in respiratory rate in humans is evident from 0.7 mg/m^3. Acrolein is a known inhibitor of respiratory tract ciliary movement *in vitro* (>13 mg/m^3 acrolein). There is limited evidence that acrolein can depress pulmonary host defences and induce

bronchial hyperreactivity.

Conclusion

Acrolein exposure through smoking might induce an increased airway resistance. Further research is needed on smoking related exposures to acrolein to elucidate the pharmacodynamic effects on the pulmonary system.

PHARMACOKINETICS

Absorption

Controlled experiments on systemic absorption and kinetics have not been conducted, but there are indications that acrolein is not highly absorbed into the system since toxicological findings are restricted to the site of exposure (see toxicology). No reduction in liver glutathion following inhalation exposure, also suggests that inhaled acrolein does not reach the liver significantly (1).

The reactivity of acrolein (acrolein reacts directly with protein and non-protein sulfhydryl groups and with primary and secondary amines (1)) will effectively reduce transport of acrolein across membranes at the site of entry into organisms. Therefore, no important differences in acrolein kinetics are expected between humans and animals (2). A retention of 80-85% acrolein was found in the respiratory tract of dogs exposed to 400-600 mg/m^3 (1).

Bioavailability

The reactivity of acrolein towards free thiol groups, protein and non-protein sulfhydryl groups and towards primary and secondary amines, effectively reduces the bioavailability of the substance (1).

Distribution

There is no indication for significant transport to other tissues after inhalatory exposure (2). After oral exposure (10 mg/kg body weight) conjugates were found in the urine of rats, which indicates some distribution of acrolein to the liver and occurrence of hepatic metabolism (2).

Metabolism

Acrolein may be metabolised to mercapturic acids, acrylic acid, glycidaldehyde or glyceraldehyde. Evidence for the last three metabolites has only been obtained *in vitro*. There is evidence that the conjugation with glutathione forming mercapturic acid may dominate the metabolism of acrolein. Acrolein can also be a substrate for liver aldehyde dehydrogenase (forming acrylic acid) and lung or liver microsomal cytochrome P-450-dependent epoxidase (forming glyceraldehyde). Glyceraldehyde can be metabolised via the glycolytic pathways (1).

Acrolein is also formed endogenously by lipid peroxidation (20).

Excretion

In rat urine S-carboxylethyl-mercapturic acid has been identified after an oral dose of 10 mg/kg body weight acrolein in corn oil (1). Acrolein has not been found as parent

compound in urine or exhaled air. The major route of elimination appears to be excretion in the urine, as glutathion conjugate (2).

Kinetic parameters
No data available.

Critical assessment
It is not likely that acrolein is highly absorbed into the system since toxicological findings are restricted to the site of exposure. As a consequence of it's high reactivity the acrolein molecule will bind primarily at the application site, the respiratory tract in smoking exposure.

Conclusion
Bioavailability of acrolein after inhalation is low due to the high reactivity of acrolein. After inhalation acrolein retention in the respiratory tract is expected.

TOXICOLOGY
Acute toxicity
Human
Acrolein is a cytotoxic agent. *In vitro* cytotoxicity has been observed at levels as low as 0.1 mg/L. The substance is highly toxic to experimental animals and humans following a single exposure via different routes. The vapour is irritating to the eyes and respiratory tract (1). The lethal concentration for humans is 350 mg/m^3 during a period of 10 minutes. Acute toxic effects are burning sensation in the eyes, lachrymation, irritation of nose, throat and skin, fever, cough, frothy sputum, cyanosis and acute respiratory failure, oedema with haemorrhagic spots, increase of red and white blood cells, gastritis, ulceration, adverse effects on the respiratory tract, liver, cardiovascular system and possibly kidneys (2).
LCLo (10 min) inhalation human 350.4 mg/m^3 (3).
In a study, groups of human volunteer students of both sexes were exposed either for 60 minutes to acrolein at a concentration of 0.69 mg/m^3 or to gradually increasing acrolein concentrations from 0 up to 1.37 mg/m^3 over 35 min followed by a 5-min exposure to 1.37 mg/m^3. Increased incidence of subjective eye irritation, subjective nasal irritation, and subjective annoyance, increase in eye blink frequency, decrease in respiratory rate, and an increased incidence of general irritation of eyes, nose, and neck were the reported effects. In further experiments with side stream cigarette smoke instead of pure acrolein vapour, it was noted that the effects of pure acrolein vapour were small compared to those produced by side-stream smoke with the same acrolein vapour concentration. It was concluded that acrolein was only to a minor extent responsible for the effects observed. It must be noted, however, that a significant part of the acrolein in sidestream cigarette smoke may be associated with particulate matter and would not have been measured. This may have resulted in a underestimation of the acrolein concentration in the smoke (1).

The NOAEL for irritant dermatitis from ethanolic acrolein was found to be 0.1%. Experiments with human volunteers, exposed to acrolein vapour, show a lowest-observed-adverse-effect level (LOAEL) of 0.13 mg/m^3, at which level eyes may become irritated within 5 min. In addition, respiratory tract effects are evident from 0.7 mg/m^3 (decreased respiratory rate). At higher single exposure levels degeneration of the respiratory epithelium, inflammatory sequela, and perturbation of respiratory function develop. Oedematous changes in the tracheal and bronchial mucosa and bronchial obstruction can be expected after very high exposure to acrolein vapour (1). Acrolein has been identified as the major contributor to the irritant property of cigarette smoke (2).

Animal
LCLo (6 hr) inhalation rabbit 24 mg/m^3 (3).
LC50 inhalation (10 min) rat 750 mg/m^3 (1)
LC50 inhalation (30 min) rat 95-300 mg/m^3 (1)
LC50 inhalation (1h) rat 65 mg/m^3 (1)
LC50 inhalation (4h) rat 18-20.8 mg/m^3 (1)
LC50 inhalation (4h) hamster 58 mg/m^3 (1)
LC50 inhalation (6h) mouse 151 mg/m^3 (1)
LD50 oral rabbit, mouse 7-40 mg/kg (3).
LD50 dermal rabbit 562 mg/kg (3).
LD50 intraperitoneal rat, mouse 4-9 mg/kg (3).
In the LC50 studies, effects on the respiratory tract were clinically observed as nasal irritation and respiratory distress in rats, hamsters, mice, guinea-pigs, and rabbits at exposure levels of between 25 mg/m^3 for 4 h and 95 –150 mg/m^3 for 3 min. Rats exposed for 10 minutes to concentrations of 750 or 1000 mg/m^3 suffered asphyxiation. Histopathological investigations in experiments with vapour exposed rats, hamsters, guinea-pigs and rabbits revealed varying degrees of degeneration of the respiratory epithelium consisting of deciliation, exfoliation, necrosis, mucus secretion, and vacuolisation. Also observed were acute inflammatory changes consisting of infiltration of white blood cells into the mucosa, hyperaemia, haemorrhages, and intercellular oedema. Proliferative changes of the respiratory epithelium, in the form of early stratification and hyperplasia, were observed in hamsters 96 h after exposure to 13.7 mg/m^3 for 4 h (1).
Animal skin irritation tests have not been performed and skin irritation has not been mentioned as an effect in the acute inhalation tests reported. One special *in vivo* eye irritation test involved vapour-exposed and control rabbits. At analysed concentrations of acrolein between 4.3 and 5.9 mg/m^3, maintained over 4 h, slight chemosis was observed but no iritis. Eye irritation was observed clinically in rodents in several acute inhalation tests, but was not graded (1).

Local tolerance
Human: See acute toxicity.
Animal: See acute toxicity.

Repeated dose toxicity

Subacute

Acrolein inhalation in rats (3 wk, 0-6.9 mg/m^3 6 hr day-1 5 day/wk) induced exfoliation, erosion and necrosis of the respiratory epithelium and squamous metaplasia. Body and spleen weights decreased for rats exposed to 6.9 mg/m^3 (3). Histopathological examination of the respiratory tract of male Swiss-Webster mice was the object of a study involving groups of 16 to 24 male mice exposed to measured concentrations of 3.9 mg/m^3 for 6 h per day during 5 days. The lesions observed were restricted to the nose and were most severe in the anterior respiratory epithelium and on the free margins of the nasomaxillary and the adjacent nasal septum. They consisted of severe deciliation, moderate exfoliation, erosion, ulceration and necrosis, severe squamous metaplasia, moderate neutrofilic infiltration, and a slight serofibrinous exudate. Lesions in the olfactory epithelium were largely confined to the dorsal meatus and consists of moderate ulceration and necrosis, and slight squamous metaplasia. The nasal squamous epithelium was not affected (1).

Semichronic

Rats, guinea pigs, dogs and squirrel monkeys were exposed continuously to a vaporised acrolein-ethanol-water mixture for 90 days. The measured acrolein concentrations were 0, 0.5, 2.3, and 4.1 mg/m^3 and the ethanol concentrations were below 18.7 mg/m^3. Body weight gain reduction was only found in rats at 2.3 and 4.1 mg/m^3. Clinically ocular discharge and salivation were observed in dogs at 2.3 and 4.1 and in monkeys at 4.1 mg/m^3. No adverse effects on haematological or biochemical parameters were observed in any of the animals. At necropsy, occasional pulmonary haemorrhage and focal necrosis in the liver were found in three rats at 2.3 mg/m^3. Pulmonary inflammation and occasional focal liver necrosis were also observed in guinea pigs at this concentration. Sections of lung from two of the four dogs exposed at 0.5 mg/m^3 revealed focal vacuolisation, hyperaemia, and increased secretion of bronchiolar epithelial cells, slight bronchoconstriction, and moderate emphysema. At 2.3 mg/m^3, focal inflammatory reactions involved lung, kidney, and liver. Bronchiolitis and early bronchopneumonia were seen in one dog. At 4.1 mg/m^3, both dogs had confluent bronchopneumonia. All nine monkeys at 4.1 mg/m^3 showed squamous metaplasia in the trachea (1).

Chronic

The toxicological effects from continuous inhalation exposure at concentrations from 0.5-4.1 mg/m^3 have been studied in rats, dogs, guinea-pigs, and monkeys. Both effects on respiratory tract function and histopathological effects were seen when animals were exposed to acrolein at levels of 0.5 mg/m^3 or more for 90 days. The toxicological effects from repeated inhalation exposure to acrolein vapour at concentrations ranging from 0.39 mg/m^3 to 11.2 mg/m^3 have been studied in a variety of laboratory animals (rats, guinea pigs, syrian golden hamsters, mice, monkeys, dogs). Exposure duration ranged from 5 days to as long as 52 weeks. In general, body

weight reduction, decrement of pulmonary function, and pathological changes in nose, upper airways, and lungs have been documented in most species exposed to concentrations of 1.6 mg/m^3 or more for 8h/day for 6 weeks. Pathological changes include inflammation, metaplasia, and hyperplasia of the respiratory tract. Significant mortality has been observed following repeated exposures to acrolein vapour at concentrations above 9.7 mg/m^3. In experimental animals acrolein has been shown to deplete tissue glutathione and in *in vitro* studies, to inhibit enzymes by reacting with sulfhydryl groups at active sites. There is limited evidence that acrolein can depress pulmonary host defences in mice and rats (1).

Carcinogenicity

IARC concluded that there is no evidence for the carcinogenicity of acrolein to experimental animals and to humans and that no evaluation could be made of the carcinogenicity of acrolein to humans (2).

The European Chemicals Bureau (1999) states that concerns remain for carcinogenic and genotoxic effcets locally at the exposure site after long-term exposure by inhalation to non-cytotoxic concentrations. It is assumed that the risk for carcinogenic effects after inhalation will be low when irritation is avoided.

Human

No data available.

Animal

In hamsters which were exposed for 52 weeks to acrolein vapour at a level of 9.2 mg/m^3 for 7h/day and 5 days/week and were observed for another 29 weeks, no tumours were found. When hamsters were exposed to acrolein vapour similarly for 52 weeks, and, in addition, to intratracheal doses of benzo[*a*]pyrene weekly or to subcutaneous doses of diethylnitrosamine once every three weeks, no clear co-carcinogenic action of acrolein was observed (1). In rats and hamsters (2 yr) treated with an unspecified dose in drinking water showed a non-significant increase in the incidence of neoplasms. Target tissues included liver, uterus and thyroid gland (3). Oral exposure of rats to acrolein in drinking-water at doses of between 5 and 50 mg/kg body weight per day (5 days/ week for 104-124 weeks) did not induce tumours. In view of the limited nature of all these tests, the data for determining the carcinogenicity of acrolein to experimental animals are considered inadequate (1).

Reproduction toxicology

Human

No data available.

Animal

Acrolein can induce teratogenic and embryotoxic effects if administered directly into the amnion. However, the fact that no effect was found in rabbits injected intravenously with 3 mg/kg, suggests that human exposure to acrolein is unlikely to affect the developing embryo (1).

In an oral teratology study in rats (exposure by gavage), increased incidences of skeletal anomalies and delayed ossification and decreased mean fetal weight and total

litter weights were observed in the offspring of rats exposed to a dose level of 10 mg/kg body weight per day. This dose level also resulted in maternal mortality. At a dose level of 6mg/kg body weight per day, maternal toxicity was indicated by decreased maternal body weight gain; teratogenic or embryo-/fetotoxic effects were not observed at this dose level. No effects on fertility were found in a teratology study in which rabbits were exposed by gavage to 2 mg/kg body weight per day during pregnancy. However, in the preliminary range-finding study in rabbits preceding the final teratology study, a dose-related increase in foetal resorptions was reported at oral dose levels of 1 mg/kg body weight per day or more; a dose level of 0.5 mg/kg body weight per day was without effects. No explanation for the discrepancy between the range finding study and the final study was provided. In the range-finding study, no foetuses were found alive in the litters of dams that were exposed to 4 mg/kg body weight per day.
In a study in which acrolein was injected into the ear vein in rabbits at dose levels of 3, 4.5 and 6 mg/kg body weight on the 9th day of gestation, severe maternal toxicity at the highest two dose levels was indicated by maternal mortality; these two dose levels also resulted in embryotoxicity, as indicated by a dose-related increase in resorptions which was significant at 6 mg/kg body weight per day. It was also reported that the number of malformed and retarded foetuses increased in a dose-related manner, although the increase was statistically not significant. No maternal toxicity or embryo-foetotoxicity was observed at the dose level of 3 mg/kg body weight (2).

Mutagenicity

Human

When gingival tissue DNA from 11 smokers (4 males and 7 females; 30-58 years old) and 12 non-smokers (8 males and 4 females; 21-66 years old) was analysed, the mean acrolein derived 1,N2-propanodeoxyguanosine levels in smokers were significantly higher than those in non-smokers (1.36 +/- 0.90 µmol/mol guanine in smokers versus 0.46 +/- 0.26 µmol/mol guanine in nonsmokers; P = 0.003). In this study the detection of the potentially promutagenic 1,N2-propanoguanine adducts in human oral tissues was shown and for the first time an increase of structurally identified adducts in oral tissue DNA by cigarette smoking was demonstrated (21).

Animal

Acrolein has been shown to interact with nucleic acids *in vitro* and to inhibit their synthesis both *in vitro* and *in vivo*. Without activation it induced gene mutations in bacteria and fungi and caused sister chromatid exchanges in mammalian cells. In all cases these effects occurred within a very narrow dose range governed by the reactivity, volatility, and cytotoxicity of acrolein. A dominant lethal test in mice was negative. The available data show that acrolein is a weak mutagen to some bacteria, fungi, and cultured mammalian cells (1).
Among the cigarette smoke constituents, acrolein, but not formaldehyde and acetaldehyde, induced DNA damage *in vitro* although less intensely than cigarette smoke itself. At 50 and 100 µM concentrations, acrolein also inhibited repair of

gamma- irradiation-induced DNA damage. Inhibition of DNA synthesis by acrolein at 50 µM was demonstrated by an immunochemical assay for bromo-deoxyuridine incorporation; however, inhibition of a representative repair enzyme, 8-oxoguanosine hydrolase, by either cigarette smoke or acrolein was not observed. The present results further confirm the presence of direct-acting genotoxic components and inhibitors of DNA repair in the gas phase of tobacco smoke, that may contribute to DNA damage and smoking-associated cancers of the upper aerodigestive tract (22).

Other

A dose-related-non-protein sulfhydryl (reduced gluthatione) depletion was observed in the nasal respiratory mucosa of male Fischer rats after nose-only exposure for 3 h to acrolein vapour at concentrations of 0.23-11.4 mg/m^3. Depletion of glutathione in the liver was not observed at these exposure levels. The glutathione depletion in the nasal mucosa appears irreversible at 11.4 mg/m^3. A dose-related *in vitro* glutathione depletion has been observed in human bronchial fibroblasts, human bronchial epithelial cells, and human and rat phagocytic cells from the lowest acrolein concentration tested (56 µg/L).

When partially hepatectomized rats were exposed intraperitoneally to a single dose of 0.5, 1.6, 2.0 or 2.7 mg/kg body weight, a dose-related inhibition of the synthesis of DNA and RNA was measured in liver and lung cells.

In *in vitro* studies, acrolein has been shown to convert rat liver cytochrome P-450 to cytochrome P-420 and to inhibit rat liver NADPH-cytochrome-*c* reductase in a time and concentration related fashion. A concomitant decrease occurred in the activity of several monooxygenases. The lowest-observed-effect levels reported were 2 mg/L for inactivation of cytochrome P-450 and 25 mg/L for inhibition of NADPH-cytochrome-*c* reductase. It was also shown that the addition of sulfhydryl-containing agents, such as cysteine, acetylcysteine, glutathione, dithiothreitol, and semicarbazide, reduced the above effects, suggesting that acrolein produces them by reacting with sulfhydryl groups at the active sites (1).

Cigarette smoking is a risk factor for atherosclerosis. It is conceivable that reactive chemical components in cigarette smoke may adversely affect reverse cholesterol transport at the level of lecithin: cholesterol acyltransferase (LCAT) and promote atherogenesis. Among five aldehydes tested, acrolein was the strongest inhibitor of LCAT, with complete enzyme inhibition occurring at 1 mM. When plasma was incubated with 1 mM acrolein in the presence of 2.5 mM glutathione or dihydrolipoic acid, 100 and 57% of LCAT activity, respectively, remained after incubation. This finding suggests that reactive aldehydes may form adducts with certain free sulfhydryl groups functioning in the active site of LCAT to inhibit enzyme activity. It is concluded that reactive aldehydes are at least partially responsible for the reduction in LCAT activity in plasma treated with cigarette smoke extract (23). High doses (1.0-10 mM) of acrolein completely inhibited plasma lecithin:cholesterol acyltransferase activity *in vitro*, whereas platelet-activating factor acetylhydrolase was resistant to such exposures (24).

Acrolein, a component of tobacco smoke, potentiated platelet aggregation and

increased thromboxane A2 formation caused by thrombin and arachidonic acid. Acrolein produced these effects at concentrations in the range 50-5000 μM (25).

Critical assessment

Through smoking short-term concentrations of 179 mg/m^3 (0.11 mg/cig, inhalation volume 615 ml/cig (13)) will be accomplished in the respiratory system. The acute toxicity of acrolein consists mainly of irritation of the eyes and the respiratory tract. Respiratory tract effects, which consist of decreased respiratory rate, are evident from 0.7 mg/m^3. In chronic repeated dose toxicity studies, body weight reduction, decrement of pulmonary function, and pathological changes in nose, upper airways, and lungs have been documented in animals exposed to concentrations of 1.6 mg/m^3 or more for 8h/day. Acrolein can cause embryo-foetotoxic and teratogenic effects, but these effects only occurred at dose levels that also resulted in maternal toxicity or in studies in which acrolein was administered directly to the embryos or foetuses. There is no evidence for the carcinogenicity of acrolein to experimental animals or humans. Acrolein is capable of forming DNA adducts in oral tissue.

Conclusion

Smoking related acrolein exposures results in irritation of the respiratory tract and a decrease in pulmonary function.

INTERACTIONS

Chemical

Acrolein is a very reactive compound. The extreme reactivity can be attributed to the conjugation of a carbonyl group with a vinyl group within its structure. Reactions shown by acrolein include Diels-Alder condensations, dimerization and polymerization, additions to the carbon-carbon double bound, carbonyl additions, oxidation, and reduction. In the absence of an inhibitor, acrolein is subject to highly exothermic polymerization catalysed by light and air at room temperature to an insoluble, cross-linked solid. Highly exothermic polymerization also occurs in the presence of traces of acids or strong bases even when an inhibitor is present (1).
In the industry acrolein was produced formerly by vapour phase condensation of acetaldehyde and formaldehyde (2).
It has been suggested that the formation of a Schiff base between acrolein and sensitive amine groups is responsible for the observed inhibition *in vitro* of Salmonella typhimurium deoxyribose-5-phosphate-adolase at a concentration of approximately 14 mg/L and human plasma α_1-proteinase inhibitor (1).

In vivo

Apoptosis of alveolar epithelial cells found *in vitro* may be one of the mechanisms of lung injury induced by cigarette smoking. This cytotoxic effect might be due to an interaction between aldehydes and oxidants present in cigarette smoke extract or formed in cigarette smoke extract-exposed cells (26).

The toxicity studies with mixtures of aldehydes showed that histopathological changes and cell proliferation of the nasal epithelium induced by mixtures of formaldehyde, acetaldehyde and/or acrolein appeared to be more severe and more extensive, both in the respiratory and the olfactory part of the nose, than those observed after exposure to the individual aldehydes at comparable exposure levels. However the combined effect of the mixtures was at most the sum of the individual effects. Neither dose addition nor potentiating interactions occurred upon exposure to combinations of these aldehydes at exposure levels slightly below or around the minimal-observed-effect level (MOEL).
Sensory irritation of (mixtures of) formaldehyde (10 ppm; 12 mg/m^3), acetaldehyde (13.8 ppm; 24.8 mg/m^3) and acrolein (9.2 ppm; 21.1 mg/m^3) (30 min) as measured by the decrease in breathing frequency (DBF) studied in rats, appeared to be more marked than the sensory irritation expected for each of the individual aldehydes, but less marked than the sum of the irritant activities of the individual aldehydes. The irritant potencies of the mixtures could be accurately described by a mechanistic model for competitive agonism. The DBF due to exposure to irritants is caused by binding of a chemical to the trigeminal nerve receptor. It was concluded that the combined exposure to these aldehydes (formaldehyde, acetaldehyde and acrolein) at the No-Observed-Effect-Levels is not associated with greater hazard than that associated with exposure to the individual chemicals (14).
Cigarette smoking is a risk factor for atherosclerosis. It is conceivable that reactive chemical components in cigarette smoke may adversely affect reverse cholesterol transport at the level of lecithin: cholesterol acyltransferase (LCAT) and promote atherogenesis. Among five aldehydes tested, acrolein was the strongest inhibitor of LCAT, with complete enzyme inhibition occurring at 1 mM. Acetaldehyde was the weakest inhibitor of LCAT, with 85% enzyme inhibition at 50 mM. Hexanal, formaldehyde, and malondialdehyde completely inhibited LCAT activity at 10, 50, and 50 mM, respectively. When plasma was incubated with 1 mM acrolein in the presence of 2.5 mM glutathione or dihydrolipoic acid, 100 and 57% of LCAT activity, respectively, remained after incubation. This finding suggest that reactive aldehydes may form adducts with certain free sulfhydryl groups functioning in the active site of LCAT to inhibit enzyme activity. It is concluded that reactive aldehydes are at least partially responsible for the reduction in LCAT activity in plasma treated with cigarette smoke extract (23).
Acrolein is capable of alkylating free sulfhydryl groups in cytochrome P-450. The reactivity of acrolein makes the molecule a likely candidate for interactions with protein and non-protein sulfhydryl groups and with primary and secundary amine groups such as occur in proteins and nucleic acids. Co-exposure of organisms to acrolein and free sulfhydrylcontaining compounds protects against the biological effects of acrolein. Acrolein can inhibit enzymes containing free sulfhydrylgroups on their active site. Acrolein can cause or enhance the formation of complexes between DNA strands and between DNA and cellular proteins. However, no studies have demonstrated unequivocally the interaction of acrolein with DNA following *in vivo* administration to animals (1).

Exposures of Swiss mice to target concentrations of 10 mg/m^3 of carbon black and 5.7 mg/m^3 acrolein for 4 hr/day for 4 days suppressed the intrapulmonary killing of *Staphylococcus aureus* a day after exposure with a return to control levels by day 7. In contrast, the coexposure enhanced the intrapulmonary killing of *Proteus mirabilis* which correlated with a significant increase in accessory phagocytic PMNs recovered from the lungs. Combined exposure to carbon black and acrolein also resulted in impaired elimination of *Listeria monocytogenes* and influenza A virus from the lungs. These data demonstrate the effects of the toxicologic interaction of coexposures to an inert particle and acrolein on innate and acquired defenses of the lungs. The mechanism for the enhanced biologic effect may be that the carbon black particle acts as a carrier mechanism for acrolein to the deep lung (27).

Critical assessment

Chemical

Acrolein possesses features that make it ready for a wide variety of reactions with compounds of quite different character.

In vivo

Mixtures of formaldehyde, acetaldehyde and acrolein cause stronger sensory irritation (measured as a decrease in breathing frequency) than that of the individual aldehydes but less than the sum of the individual potencies. This may be a result of competition for a common receptor. A cytotoxic effect on alveolar epithelium might be due to an interaction between aldehydes and oxidants present in cigarette smoke. The combined exposure to formaldehyde, acetaldehyde and acrolein at the No-Observed-Effect-Levels is not associated with greater hazard than that associated with exposure to the individual chemicals.

Acrolein exposure in the deep lung may be possible due to a carrier mechanism of particles. Cigarette smoking is considered to be a risk factor for atherosclerosis. Reactive aldehydes are at least partially responsible for the reduction in lecithin: cholesterol acyltransferase activity in plasma treated with cigarette smoke extract.

Conclusion

Chemical

Acrolein is a very reactive compound, able to react with a wide variety of compounds.

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
In the manufacture of glycerol and glutaraldehyde. Acrolein is used as an aquatic herbicide and fungicide used in water and wastewater treatment. Used in military poison gas mixtures, manufacture of plastics, perfumes and warning agent in methyl chloride refrigerant. Acrolein is a toxic and reactive metabolite of the widely used anticancer drug and known teratogen cyclophosphamide (3). Acrolein is used for the fixation of tissues for electron microscopy.
And as a microbiocide (wastewater injection systems, liquid fuels, oil wells, cooling-water towers; prohibited in the Netherlands), and as a slimicide (manufacturing of paper and paperboard; prohibited in the Netherlands) (2).

BENEFICIAL EFFECTS
No data available.

Critical assessment
Not relevant.
Conclusion
Not relevant.

SUMMARY AND FINAL CONCLUSION
Acrolein 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. Acrolein is a very reactive compound to a wide variety of compounds, it is a volatile and highly flammable liquid with a pungent, choking, disagreeable odour. The function of acrolein in tobacco products is not known. Acrolein has been identified in cigarettes at a mean level of 0.11 mg per cigarette.
Risk assessment of acrolein in current framework is based on well-established occupational limit values ranging from 0.25-0.7 mg/m^3, assuming an inhalation volume of 10 m^3/working day in workers. Smoking 25 cigarettes per day corresponds

with an intake up to 2.75 mg/day through inhalation. Smoking related acrolein exposures may exceed the occupational limit values. However, it should be noted that for acrolein exposure the concentration is more important than the dose. Local respiratory tract exposures to acrolein are high (179 mg/m^3). Smoking related acrolein exposures exceed the ceiling values for the general population. Acrolein in smoke is the main source of exposure of the general population to acrolein.
The pharmacological effects of acrolein inhalation consist of a decrease in respiratory rate in humans (evident from 0.7 mg/m^3) and an inhibition of respiratory tract ciliary movement *in vitro* (>13 mg/m^3 acrolein). There is limited evidence that acrolein can depress pulmonary host defences and induce bronchial hyperreactivity.
Bioavailability of acrolein after inhalation is low due to the high reactivity of acrolein. After inhalation acrolein retention in the respiratory tract is expected.
The acute toxicity of acrolein consists mainly of irritation of the eyes and the respiratory tract. In chronic repeated dose toxicity studies, body weight reduction, decrement of pulmonary function, and pathological changes in nose, upper airways, and lungs have been documented in animals exposed to concentrations of 1.6 mg/m^3 or more for 8h/day. There is no evidence for the carcinogenicity of acrolein to experimental animals or humans. Acrolein is capable of forming DNA adducts in oral tissue. More research is needed to evaluate the hazards of smoking related exposure levels to a mixture of aldehydes. There are no data on dependency available and there are no known beneficial effects of acrolein exposure through smoking.

It can be concluded that smoking related exposure to acrolein needs further study because there are little or no data available on high concentrated peak exposures to acrolein. It is likely that these smoking related acrolein exposures result in damage to the respiratory tract and a decrease in pulmonary function. More research is needed to elucidate the pharmacodynamic effects on the pulmonary system of acrolein due to smoking related exposures.
Another point of concern is the exposure of acrolein 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 October 2001.

3.3.1 References

(1) Environmental Health Criteria 127, acrolein. Geneva: World Health Organization, 1992.

(2) W.Slooff, P.F.H.Bont, J.A.Janus, M.E.J.Pronk, J.P.M.Ros. Update of the exploratory report acrolein. RIVM report 601014001. 1994. Bilthoven, RIVM.
Ref Type: Report

(3) Dictionary of substances and their effects (DOSE). The Royal Society of Chemistry, editor. 10/2000 . 2001.
Ref Type: Electronic Citation

(4) Chemiekaarten®, Gegevens voor veilig werken met chemicaliën. 15e editie . 2000. Ten Hagen & Stam.
Ref Type: Electronic Citation

(5) Brandweerinformatiecentrum voor gevaarlijke stoffen (BIG). versie 9.0 . 2001. Belgium.
Ref Type: Electronic Citation

(6) Physical-chemical properties and environmental fate Handbook. D.Mackay, editor. CRC netBase . 1999.
Ref Type: Electronic Citation

(7) Acrolein. Allyl compounds, Aldehydes, Epoxides and Peroxides. Lyon: World Health Organization, International Agency for Research on Cancer, 1985: 133-161.

(8) R Walder, JL Franklin. *Proton Affinities of Neutral Molecules*. International Journal of Mass Spectrometry and Ion Physics 1980; 36:85-112.

(9) Morrison and Boyd. 3rd edition , 865. 2001.
Ref Type: Electronic Citation

(10) Phillips GF, Waller RE. Yields of tar and other smoke components from UK cigarettes. Food Chem Toxicol 1991; 29(7):469-474.

(11) Brunnemann KD, Kagan MR, Cox JE, Hoffmann D. Analysis of 1,3-butadiene and other selected gas-phase components in cigarette mainstream and sidestream smoke by gas chromatography-mass selective detection. Carcinogenesis 1990; 11(10):1863-1868.

(12) Acrolein, Risk assessment. 1999. European Chemicals Bureau.
Ref Type: Report

(13) Djordjevic MV, Stellman SD, Zang E. Doses of nicotine and lung carcinogens

delivered to cigarette smokers. Journal of the National Cancer Institute 2000; 92(2):106-111.

(14) Flemming RC. Upper respiratory tract toxicity of mixtures of aldehydes In vivo and in vitro studies. 1995. Wageningen, Ponsen en Looyen B.V. Ref Type: Report

(15) Springall DR, Edginton JA, Price PN, Swanston DW, Noel C, Bloom SR et al. Acrolein depletes the neuropeptides CGRP and substance P in sensory nerves in rat respiratory tract. Environ Health Perspect 1990; 85151-7:-7.

(16) Leikauf GD. Mechanisms of aldehyde-induced bronchial reactivity: role of airway epithelium. Res Rep Health Eff Inst 1992;(49):1-35.

(17) Finkelstein EI, Nardini M, van der Vliet A. Inhibition of neutrophil apoptosis by acrolein: a mechanism of tobacco-related lung disease? Am J Physiol Lung Cell Mol Physiol 2001; 281(3):L732-L739.

(18) Mio T, Romberger DJ, Thompson AB, Robbins RA, Heires A, Rennard SI. Cigarette smoke induces interleukin-8 release from human bronchial epithelial cells. Am J Respir Crit Care Med 1997; 155(5):1770-1776.

(19) Carnevali S, Nakamura Y, Mio T, Liu X, Takigawa K, Romberger DJ et al. Cigarette smoke extract inhibits fibroblast-mediated collagen gel contraction. Am J Physiol 1998; 274(4 Pt 1):L591-L598.

(20) Takeuchi K, Kato M, Suzuki H, Akhand AA, Wu J, Hossain K et al. Acrolein induces activation of the epidermal growth factor receptor of human keratinocytes for cell death. J Cell Biochem 2001; 81(4):679-688.

(21) Nath RG, Ocando JE, Guttenplan JB, Chung FL. 1,N2-propanodeoxyguanosine adducts: potential new biomarkers of smoking-induced DNA damage in human oral tissue. Cancer Res 1998; 58(4):581-584.

(22) Yang Q, Hergenhahn M, Weninger A, Bartsch H. Cigarette smoke induces direct DNA damage in the human B-lymphoid cell line Raji. Carcinogenesis 1999; 20(9):1769-1775.

(23) 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.

(24) Bielicki JK, Knoff LJ, Tribble DL, Forte TM. Relative sensitivities of plasma lecithin:cholesterol acyltransferase, platelet-activating factor acetylhydrolase, and paraoxonase to in vitro gas-phase cigarette smoke exposure. Atherosclerosis 2001; 155(1):71-78.

(25) Selley ML, Bartlett MR, McGuiness JA, Ardlie NG. Effects of acrolein on human platelet aggregation. Chem Biol Interact 1990; 76(1):101-109.

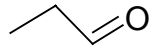
(26) Hoshino Y, Mio T, Nagai S, Miki H, Ito I, Izumi T. Cytotoxic effects of cigarette smoke extract on an alveolar type II cell-derived cell line. Am J Physiol Lung Cell Mol Physiol 2001; 281(2):L509-L516.

(27) Jakab GJ. The toxicologic interactions resulting from inhalation of carbon black and acrolein on pulmonary antibacterial and antiviral defenses. Toxicol Appl Pharmacol 1993; 121(2):167-175

3.4
Propionaldehyde

GENERAL
IUPAC systematic name: Propanal (1)
Synonyms: propanal, methylacetaldehyde; propaldehyde; n-propanal; propionic-aldehyde; propylaldehyde; propylic-aldehyde (2); propanaldehyde; propional (3), Methyl-acetaldehyde (4).
Molecular formula: C_3H_6O (2)

Molecular structure



Molecular weight: 58.08 g/mol (2)
Alifatic: yes
Aromatic: no
N containing: no
Halogen containing: no
CAS registry no.: 123-38-6 (2)
Storage:
R/S classification: R11, R36/37/38; S2, S9, S16, S29 (2)
dangercode (transport): 33 (5).
Properties:
➢ melting point: -81 ºC (2)
➢ boiling point: 49 ºC (2)
➢ density: 0.807 (20 ºC) (2)
➢ refractive index: 1.3695 (16.6 ºC/ 580 nm) (2)
➢ solubility: water: 200 g/L at 20 ºC (2)
organic solvent(s): miscible with ethanol, diethyl ether (2), soluble in chloroform (3).
➢ Substance description:
- colorless (3)
- liquid (3)
- odor: suffocating, pungent, unpleasant, fruity, characteristic odor similar to acetaldehyde (3)
- taste: cocoa, coffee (3).

➢ volatility: no data available.
➢ pK_a: no data available.
➢ PA: 187<PA<194.5 $kcal.mol^{-1}$ (6)
➢ flammability:
- FP = < -6 ºC (2)

- FL Limits = 2.6- 16.1 % (3)
- IT = 207 ºC (3)

➢ decomposition temperature: no data available.
➢ stability: stable under ordinary conditions of use and storage. Reacts with water to form propionic acid. May form explosive peroxides in air (7).
➢ vapour pressure/ vapour tension (20 °C): 235 mm Hg (2)
➢ vapour pressure (50 °C): no data available.
➢ relative density: 0.805 (5).
➢ octanol water partition coefficient: log P, log K_{OW}: 0.59 (2)
➢ conversion factor: ppmv=Mgas/24.45 milligrams/m^3 = 58.08/24.45 = 2,375 milligrams/m^3 (for gaseous form only). 1mg/m^3= 0.42 ppm.

Critical assessment
The main functional group is the aldehyde group, classifying the compound as a carbonyl compound; the backbone of the compound is a short aliphatic chain. The carbonyl group largely determines the chemical propertie(s): nucleophilic addition is the most pregnant.
Like all aldehydes propionaldehyde is oxidized quite easily (8).

Conclusion
Propionaldehyde is a rather volatile liquid, composed as an aliphatic compound with a carbonyl group as its marked functional group.

FUNCTION IN TOBACCO
No data available.

AMOUNT IN TOBACCO PRODUCTS
No data available.
AMOUNT IN SMOKE

- **main stream** According to information available on the internet the amount of propionaldehyde in main stream smoke ranges from 20.5-62.7 µg/cig (9).
- **side stream**

The amount of propionaldehyde in the vapour phase of cigarette smoke has been reported to vary between 25 and 116 µg (10).
SOURCE
It seems likely that propionaldehyde is formed during smoking from precursors such as polysaccharides, pectins, proteins and possible triglycerides in tobacco (10).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Propionaldehyde is a highly volatile compound and monitoring data indicate that it is a widely occurring atmospheric pollutant. Propionaldehyde is a product of wood, gasoline, diesel and polyethylene combustion.

The median urban atmospheric concentration of propionaldehyde in the USA according to the National Ambient Volatile Organic Compounds Database is 17.4 ppb (3). The median rural concentration reported of propionaldehyde is 0.350 ppb.

Propionaldehyde was identified as a component of coffee aroma. It also has been shown to occur in drinking waters. The most probable route of human exposure to propionaldehyde is by inhalation or ingestion.

Occupational exposure is likely to occur at sites were propionaldehyde is produced or used as a chemical intermediate in the manufacture of propionic acid, polyvinyl and other plastics, in the synthesis of rubber chemicals and as a disinfectant and preservative. Office workers are exposed to average atmospheric concentrations of 0.91 $\mu g/m^3$ propionaldehyde (3).

COMBUSTION PRODUCT

Carbon monoxide and carbon dioxide (5).

CONSENSUS REPORTS

No data available.

STANDARDS AND RECOMMENDATIONS

ADI: No data available.
TWA_{NL} = MAC: No value determined (11).
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 value determined (5).
TLV-CARCINOGENICITY: No data available.
MAK-REPRODUCTION: No data available.

Others:
No data available.
Reference value:
No data available.

CLASS

EG Carc. Cat.: not included (5).
IARC-category: not included (5).

CEC: no data available.

Critical assessment

It seems likely that propionaldehyde is formed during smoking from precursors such as polysaccharides, pectins, proteins and possible triglycerides in tobacco. There are some data available about the amount of propionaldehyde in the vapour phase of smoke. It remains unclear whether these amounts include main stream or side stream smoke or both.

Conclusion

More research is needed to determine the amount of propionaldehyde in main stream cigarette smoke. Based on information found on the internet 20.5-62.7 µg/cig propionaldehyde is expected in cigarette smoke.

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.

Propionaldehyde has been reported as ciliatoxic and mucus coagulating agent, but related exposure levels were not reported (3).

Cardiovascular system

- **blood pressure**: see below
- **heart rate**: see below

Propionaldehyde is thought to cause sympathomimetic effects by the release of noradrenaline from adrenergic neurons at <20 mg/kg body weight (iv) in rats. These sympathomimetic effects consist of an increase in blood pressure and an increase in heart rate. At higher doses (>20 mg/kg) a decrease in blood pressure and a decrease in heart rate are reported in rats, which are attributed to vagal stimulation. At intermediate dose (20 mg/kg), either effect may occur in a given animal.
The sympathomimetic effects can be slightly decreased by adrenalectomy and can be more strongly antagonized by pretreatment with reserpine or phentolamine (3;12).

Renal system

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

Nervous system

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

Other

Critical assessment
Sufficient inhalation data are missing to evaluate the pharmacodynamic effects of propionaldehyde due to cigarette smoking. Further research is needed to test the reported ciliatoxicity and its mucus coagulating properties.

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

PHARMACOKINETICS
Absorption
No data available.
Bioavailability
No data available.
Distribution
No data available.
Metabolism
Propionaldehyde is a product of lipid peroxidation. Propionaldehyde is a substrate for aldehyde dehydrogenase (13).
Excretion
No data available.
Kinetic parameters
No data available.

Critical assessment
Data on the pharmacokinetic properties of propionaldehyde are missing. For a critical assessment, research is needed, especially to obtain the amount of absorption and bioavailability after smoking related exposures to propionaldehyde. 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 propionaldehyde need further study.

TOXICOLOGY

Acute toxicity

Human

Irritating to eyes, pulmonary tract and skin. After inhalation headache, consciousness problems, breathing difficulties, sore throat, spasm, and/or edema of the larynx, and irritation of the nose mucosa have been reported (no concentrations reported) (5).

Animal

LCLo (4 hr) inhalation rat 8000 ppm (19 000 mg/m^3) (2).
LC50 inhalation rat 26000 ppm/30 min (3). (61750 mg/m^3)
LD50 oral rat 1.41 g/kg (2).
LD50 oral rat 0.8-1.6 g/kg (3).
LD50 dermal rabbit 5040 mg/kg (2).
LD50 subcutaneous mouse, rat ;680, 820 mg/kg, respectively (2).
Mice, guinea pigs and rabbits exposed to high levels of propionaldehyde by inhalation developed fatal pulmonary edema (3).

Local tolerance

Human

See acute toxicity data.

Animal

Dermal application to rabbit of 500 mg (72 hr) propionaldehyde caused mild irritation and 41 mg instilled into rabbit eye (72 hr) caused severe irritation (2).

Repeated dose toxicity

Subacute

No data available.

Semichronic

No data available.

Chronic

No data available.

Carcinogenicity

Human

No data available.

Animal

No data available.

Reproduction toxicology

Human

No data available.

Animal

Rat foetuses were injected intra-amniotically with 10, 100 and 1000 µg per foetus propionaldehyde on day 13 of gestation. Examination of embryos on day 20 of

gestation showed a dose-dependent increase in resorbed foetuses with significance at 1000 µg per foetus. One foetus was malformed, with a shortened tail (2).

Mutagenicity

Human

No data available.

Animal

The mutagenicity of propionaldehyde was measured in V79 cells as resistance to 6-thioguanine (2 h incubation period). Propionaldehyde was not mutagenic at 1 µM; it was toxic at 2 µM (14).

Propionaldehyde is able to form DNA-protein crosslinks *in vitro*, but is less potent than acrolein (15).

Propionaldehyde tested non-mutagenic, when using Salmonella typhimurium tester strains TA97a, TA100, TA102 and TA104, in the presence and absence of Aroclor-induced liver S9 mix from F344 rats and B6C3F1 mice, in either preincubation or vapour phase protocols (16).

Other

The effects of propionaldehyde (89 µmol/kg; terminated 0.5, 4, or 24 hr later) in male F-344 rats on hepatic glutathione, cytochrome P450, and NADPH-cytochrome c reductase activity were asssessed in time. Propionaldehyde changed none of these activities (17).

Critical assessment

The acute toxicity of propionaldehyde inhalation consists mainly of damage to the respiratory tract. No data were available on the repeated dose toxicity of propionaldehyde. *In vitro*, DNA-protein crosslinks were formed.

Conclusion

More data are needed on the repeated exposure toxicity through inhalation.

INTERACTIONS

Chemical

Propionaldehyde reacts vigorously with oxidizers. Polymerization may occur in presence of acids or caustics (3). Being an aldehyde, propionaldehyde 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
Nucleophilic addition and oxidizability are the most marked chemical features of propionaldehyde

In vivo
Not relevant.

Conclusion
Chemical
Propionaldehyde is a marked compound for nucleophilic addition reactions and for reactions with oxidizers.

In vivo
Not relevant.

DEPENDENCY
No data available.

Effects of smoking cessation
No data available.

Critical assessment
Not relevant.
Conclusion
Not relevant.

COMMERCIAL USE
Propionaldehyde is a manufacture of polyvinyl and other plastics; it is used in the synthesis of rubber chemicals; as a disinfectant and as a preservative.
Propionaldehyde is an intermediate in the manufactory of trimethylolethane for use in alkyd resin systems and in certain cases, it is oxidized to propionic acid and reduced to propyl alchohol; in medicinal and agricultural chemical preparations (3).

BENEFICIAL EFFECTS
No data available.

Critical assessment
Not relevant.
Conclusion
Not relevant.

SUMMARY AND FINAL CONCLUSION

Propionaldehyde 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. Propionaldehyde is a rather volatile liquid, composed as an aliphatic compound with a carbonyl group as its marked functional group. Propionaldehyde is a marked compound for nucleophilic addition reactions and for reactions with oxidizers.

The function of propionaldehyde in tobacco products is not known. The amount of propionaldehyde in the vapour phase of cigarette smoke has been reported to vary between 25 and 116 µg, but the exact amount in main stream smoke is unclear. According to information available on the internet the amount of propionaldehyde in main stream smoke ranges from 20.5-62.7 µg/cig. More research is needed to obtain the exposure levels to propionaldehyde due to cigarette smoking.

Sufficient inhalation data are missing to evaluate the pharmacodynamic effects of propionaldehyde due to cigarette smoking. Further research is needed to test the reported ciliatoxicity and mucus coagulating properties of propionaldehyde. Overall, the effect of smoking related exposure to propionaldehyde on the pulmonary system needs further study.

Data on the pharmacokinetic effects of propionaldehyde are missing. For a critical assessment, research is needed, especially to obtain the amount of absorption and bioavailability after smoking related exposures to propionaldehyde. Other aldehydes are known to induce mainly local effects at the site of exposure and little systemic effects. Expected effects according to other aldehydes are increased airway resistance and local damage to the respiratory tract.

The acute toxicity of propionaldehyde inhalation consists mainly of damage to the respiratory tract. No data were available on the repeated dose toxicity of propionaldehyde.

There are no data on dependency available and there are no known beneficial effects of propionaldehyde exposure through smoking.

No conclusions could be made based on the available information to assess the health risk of smoking related exposure to propionaldehyde. The health risks of the exposure to propionaldehyde 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 propionaldehyde 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 October 2001.

3.4.1 References

(1) A Guide to IUPAC Nomenclature of Organic Compounds (Recommendations 1993), Blackwell Scientific publications, Copyright 1993 IUPAC, 1993.

(2) Dictionary of substances and their effects (DOSE). The Royal Society of Chemistry, editor. 10/2000 . 2001.
Ref Type: Electronic Citation

(3) The hazardous Substance Data Bank (HSDB). through 2000/10 . 2001. The National Library of Medicine (NLM).
Ref Type: Electronic Citation

(4) The United States Coast Guard (USCG). The Chemical Hazards Response Information System (CHRIS). through 2000/10 . 2001.
Ref Type: Electronic Citation

(5) Brandweerinformatiecentrum voor gevaarlijke stoffen (BIG). versie 9.0 . 2001. Belgium.
Ref Type: Electronic Citation

(6) Int.J.Mass Spectrom.Ion Phys. 36, 85-112. 1980.
Ref Type: Electronic Citation

(7) http://www.jtbaker.com/msds/p6621.htm.
http://www.jtbaker.com/msds/p6621.htm . 2001.
Ref Type: Electronic Citation

(8) Morrison and Boyd. 3rd edition , 865. 2001.
Ref Type: Electronic Citation

(9) British Columbia Ministry of Health, Canadian Council for Tobacco Control. British Columbia Ministry of Health and Mnistry Responsible for Seniors; 1998 Reports on Cigarette Additives and Ingredients and Smoke Constituents. internet . 1998.
Ref Type: Electronic Citation

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

(11) Chemiekaarten®, Gegevens voor veilig werken met chemicaliën. 15e editie . 2000. Ten Hagen & Stam.
Ref Type: Electronic Citation

(12) Green MA, Egle JL. Effects of intravenous acetaldehyde, acrolein,

formaldehyde and propionaldehyde on arterial blood pressure following acute guanethidine treatment. Res Commun Chem Pathol Pharmacol 1983; 40(2):337-340.

(13) Canuto RA, Muzio G, Salvo RA, Maggiora M, Trombetta A, Chantepie J et al. The effect of a novel irreversible inhibitor of aldehyde dehydrogenases 1 and 3 on tumour cell growth and death. Chem Biol Interact 2001; 130-132(1-3):209-218.

(14) Smith RA, Cohen SM, Lawson TA. Acrolein mutagenicity in the V79 assay. Carcinogenesis 1990; 11(3):497-498.

(15) Kuykendall JR, Bogdanffy MS. Efficiency of DNA-histone crosslinking induced by saturated and unsaturated aldehydes in vitro. Mutat Res 1992; 283(2):131-136.

(16) 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.

(17) Cooper KO, Witz G, Witmer C. The effects of alpha, beta-unsaturated aldehydes on hepatic thiols and thiol-containing enzymes. Fundam Appl Toxicol 1992; 19(3):343-349.

4. General overview and discussion

4.1 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 such precursors as polysaccharides, pectin's, proteins, and possibly, triglycerides in tobacco. This is also the case for acetaldehyde, formaldehyde, acrolein and propionaldehyde. Beside the ones formed during combustion there are also aldehydes that are added to tobacco products. Aldehydes constitute a group of reactive compounds, which result in damage at the local site of entry, e.g. the respiratory tract. The function of aldehydes in tobacco products is not known, but it has been suggested that acetaldehyde has a role in smoking addiction (1) (2).

The main exposure to the four investigated aldehydes in mainstream cigarette smoke is listed in ***Table 1***. The exposure varies from 1.25 to 25 mg per 25 cigarettes. Reliable data on the exposure levels to propionaldehyde due to cigarette smoking are not available. It can be concluded that exposure 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.

Table 1 Exposure to acetaldehyde, formaldehyde, acrolein and propionaldehyde 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)
Acetaldehyde	25 (3) (4)	444-2160 (5) (4) (6)	-
Formaldehyde	1.25 (7-9)	15 (10)	1 (11)
Acrolein	2.75 (12)	2.5(13)	0.011 (13)
Propionaldehyde	1.56 (14)	-	0.011

-; currently no data available

These peak exposures of cigarette smoke result in high local respiratory tract concentrations. Local respiratory tract exposures to, for instance, formaldehyde are high (73 mg/m^3), while systemic concentrations are low (0.028 mg/kg bodyweight). The local respiratory tract exposures for the four investigated aldehydes are listed in ***Table 2***. In general, it can be concluded that exposure to aldehydes in cigarette smoke results in high local respiratory tract concentrations, exceeding the ceiling value for the general population. This is important to realise because aldehydes are usually not very well absorbed from the respiratory tract and result in local damage. It remains unclear if and in which amount inhaled aldehydes reach the bloodstream.

Table 2 Local concentration in the respiratory tract due to exposure to acetaldehyde, formaldehyde, acrolein and propionaldehyde compared to ceiling value for the general population

Local concentration respiratory tract (mg/m^3)	Cigarette smoking*	Ceiling value general population (30 minutes)
Acetaldehyde	1626	-
Formaldehyde	73	0.12 (11)
Acrolein	179	0.025 (13)
Propionaldehyde	101	-

**. Assuming an inhalation volume of 615 ml per cigarette (15) and based on the amount of aldehyde per cigarette (3;4;7-9;12;14).*
-; currently no data available

4.2 Effects

4.2.3 Acetaldehyde

In animals chronic inhalatory exposure to acetaldehyde leads to tissue damage in the respiratory tract and to the induction of bronchogenic cancer (16). Acetaldehyde is genotoxic and a confirmed animal carcinogen (3) (4) (17;18). Due to its reactivity and to rapid metabolism in the respiratory tract the systemic bioavailability of acetaldehyde from cigarette smoke will be low. However, the formation of several systemic active adducts can not be excluded. In smokers this phenomenon is poorly studied. A role of acetaldehyde in smoke in tobacco addiction, as suggested in some reports (1;2), seems unlikely but can not be excluded. Acetaldehyde originating from cigarette smoke might have direct damaging effects on the respiratory tract. The systemic pathophysiologic role of acetaldehyde from cigarette smoke is poorly understood and needs further study.

4.2.4 Formaldehyde

Formaldehyde in cigarette smoke is an important contributor to inhaled formaldehyde exposure in the general population (19). Formaldehyde is well absorbed from nasal mucosa, trachea and bronchi and is rapidly metabolized to formate (10;19). Formaldehyde exposure through smoking might induce an increased airway resistance. Chronic inhalatory exposure to formaldehyde may lead to tissue damage and cancer in the tissues of initial contact, i.e. the upper respiratory tract. Additional systemic effects due to the simultaneous exposure to other aldehydes may occur. After smoking cessation damage to the respiratory epithelium might regress.

4.2.5 Acrolein

Cigarette smoke is the main source of acrolein exposure to the general population. The pharmacological effects of acrolein inhalation consist of a decrease in respiratory rate in human subjects (evident from 0.7 mg/m^3) and an inhibition of respiratory tract ciliary movement *in vitro* (>13 mg/m^3 acrolein). There is limited evidence that acrolein can depress pulmonary host defences and can induce bronchial hyperreactivity (20).

Bioavailability of acrolein after inhalation is low due to the high reactivity of acrolein. After inhalation, acrolein retention in the respiratory tract is expected.
The acute toxicity of acrolein consists mainly of irritation of the eyes and the respiratory tract. In chronic repeated dose toxicity studies, body weight reduction, decrement of pulmonary function, and pathological changes in nose, upper airways, and lungs have been documented in animals exposed to concentrations of 1.6 mg/m^3 or more for 8h/day (20). There is no evidence for carcinogenicity of acrolein to experimental animals or humans (13). Acrolein is capable of forming DNA adducts in oral tissue.
It is likely that smoking related acrolein exposures result in damage of the respiratory tract and in a decrease in pulmonary function. More research is needed to elucidate the pharmacotoxic effects on the pulmonary system of acrolein due to smoking related exposures.

4.2.6 Propionaldehyde

Sufficient inhalation data are missing to evaluate the pharmacodynamic effects of propionaldehyde due to cigarette smoking. Further research is needed to test the reported ciliatoxicity and mucus coagulating properties of propionaldehyde. Overall, the effect of smoking related exposure to propionaldehyde on the pulmonary system needs further study. Also data on the pharmacokinetic effects of propionaldehyde are missing.
The acute toxicity of propionaldehyde inhalation consists mainly of damage to the respiratory tract (21). No data were available on the repeated dose toxicity of propionaldehyde.
No conclusions could be made based on the available information to assess the health risk of smoking related exposure to propionaldehyde. The health risks of the exposure to propionaldehyde due to cigarette smoking need to be studied.

4.3 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. Toxicity studies in rats (22), in which mixtures of formaldehyde, acetaldehyde and acrolein were tested, showed that the histopathological changes and cell proliferation of the nasal epithelium appeared to be more severe and more extensive, both in the respiratory and the olfactory part of the nose, than those observed after exposure to the individual aldehydes at comparable exposure levels. However, the combined effect of the mixtures was at most the sum of the individual effects. No dose addition or potentiating interactions occurred upon exposure to combinations of these aldehydes at exposure levels slightly below or around the minimal-observed-effect level (MOEL) (22).
Exposure to formaldehyde, acetaldehyde and acrolein mixtures resulted in a decrease in breathing frequency (DBF). The mean observed DBF of mixtures was significantly lower than the mean predicted by summation of the calculated DBFs of single compounds (22).

4.4 Conclusion

It can be concluded that cigarette smoking related exposures to aldehydes can be best characterised as high concentrated peak exposures. These exposures exceed ceiling values for the general population (see Table 2). Local damage to the respiratory tract, a decrease in breathing frequency, and ciliatoxic effects are likely to occur. The health effects of propionaldehyde exposure could not be assessed because sufficient inhalation data are missing. It remains unclear if and in which amount inhaled aldehydes reach the bloodstream.
Combined exposure to aldehydes is another point of concern. In rats the combined exposure of the mentioned aldehydes leads to a significant increase in damage to the respiratory tract and a decrease in breathing frequency. At low doses of combined exposure, no potentiation of the damage occurs. It remains unclear if potentiation of the damage will occur at high peak concentrations during cigarette smoking.
Addictive effects due to aldehyde exposure seem unlikely but can not be excluded for acetaldehyde. No addictive effects for formaldehyde, acrolein and propionaldehdye were found. More research will be needed to elucidate the possible role of acetaldehyde in smoking addiction.
It can be concluded that the existing data, described in this report, are conclusive about the toxicity of inhaled aldehydes. However, using these data to assess the health effects of aldehydes exposure due to cigarette smoking may lead to an underestimation of the toxicity. Moreover because in general the reported toxicity is based on 8 hours working exposure to relatively low concentrations. More research on the smoking-related high peak exposure would be necessary for a better estimation of the harmful effects of exposure to aldehydes due to cigarette smoking. In addition, the contribution of the added sugars and other ingredients of tobacco to the concentration of aldehydes in cigarette smoke needs to be thoroughly investigated.

4.5 References

(1) Bates C. Tobacco additives. 1999.
Ref Type: Internet Communication

(2) Singer GaMWD. Cigarettes and Alcohol: is there a common link. The Pharmacology of Nicotine. ICSU Press by IRL Oxford . Washingthon, 1988: 408-409.

(3) Environmental Health Criteria 167, Acetaldehyde. Geneva: World Health Organization, 1995.

(4) Acetaldehyde. Allyl compounds, Aldehydes, Epoxides and Peroxides. Lyon: World Health Organization, International Agency for Research on Cancer, 1985: 101-132.

(5) Chemiekaarten®, Gegevens voor veilig werken met chemicaliën. 15e editie . 2000. Ten Hagen & Stam.
Ref Type: Electronic Citation

(6) SAX Dangerous Properties of Industrial Materials. Richard J.Lewis Sr, editor. 10th edition, Version 2.0 . 1999. John Wiley & Sons, Inc.
Ref Type: Electronic Citation

(7) formaldehyde. Some industrial Chemicals and Dyestuffs. Lyon: World Health Organization, Intenational agency for research on cancer, 1982: 345-389.

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

(9) Smith CJ, Perfetti TA, Rumple MA, Rodgman A, Doolittle DJ. "IARC group 2A Carcinogens" reported in cigarette mainstream smoke. Food Chem Toxicol 2000; 38(4):371-383.

(10) formaldehyde. Wood dust and formaldehyde. Lyon: World Health Organization, Intenational agency for research on cancer, 1995: 217-362.

(11) W.Slooff PFHBJAJaBL. Exploratory report formaldehyde. National Institute of Public Heatlh and Environmental Protection, editor. RIVM Report 710401018. 1992. Bilthoven.
Ref Type: Report

(12) Phillips GF, Waller RE. Yields of tar and other smoke components from UK cigarettes. Food Chem Toxicol 1991; 29(7):469-474.

(13) W.Slooff, P.F.H.Bont, J.A.Janus, M.E.J.Pronk, J.P.M.Ros. Update of the exploratory report acrolein. RIVM Report 601014001. 1994. Bilthoven, RIVM.
Ref Type: Report

(14) British Columbia Ministry of Health, Canadian Council for Tobacco Control. British Columbia Ministry of Health and Mnistry Responsible for Seniors; 1998 Reports on Cigarette Additives and Ingredients and Smoke Constituents. internet . 1998.
Ref Type: Electronic Citation

(15) Djordjevic MV, Stellman SD, Zang E. Doses of nicotine and lung carcinogens delivered to cigarette smokers. Journal of the National Cancer Institute 2000; 92(2):106-111.

(16) Feron VJ, Kuper CF, Spit BJ, Reuzel PG, Woutersen RA. Glass fibers and vapor phase components of cigarette smoke as cofactors in experimental respiratory tract carcinogenesis. Carcinog Compr Surv 1985; 8:93-118.

(17) Acetaldehyde. Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1 to 42. Lyon: World Health Organization, International Agency for Research on Cancer, 1987: 77-78.

(18) Acetaldehyde. In: A.Berlin, M.Draper, J.Duffus, M.Th.van der Venne, editors. The toxicology of chemicals 1. Carcinogenicity, Summary review of the scientific evidence. Luxembourg: Commission of the European Communities, 1991: 95-100.

(19) Environmental Health Criteria 89, Formaldehyde. Geneva: World Health Organization, 1989.

(20) Environmental Health Criteria 127, acrolein. Geneva: World Health Organization, 1992.

(21) The hazardous Substance Data Bank (HSDB). through 2000/10 . 2001. The National Library of Medicine (NLM).
Ref Type: Electronic Citation

(22) Flemming RC. Upper respiratory tract toxicity of mixtures of aldehydes
In vivo and in vitro studies. Wageningen: Ponsen en Looyen B.V., 1995.

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).