# ACROLEIN

This substance was considered by previous Working Groups, in February 1978, June 1984 and March 1987 (IARC, 1979, 1985, 1987a). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

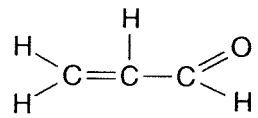
## 1. Exposure Data

### 1.1 Chemical and physical data

*1.1.1 Nomenclature*

*Chem. Abstr. Serv. Reg. No.*: 107-02-8
*Deleted CAS Reg. No.*: 25314-61-8
*Chem. Abstr. Name*: 2-Propenal
*IUPAC Systematic Name*: Acrolein
*Synonyms*: Acraldehyde; acrylaldehyde; acrylic aldehyde; allyl aldehyde; ethylene aldehyde; propenal; prop-2-en-1-al

*1.1.2 Structural and molecular formulae and relative molecular mass*



$C_3H_4O$ Relative molecular mass: 56.06

*1.1.3 Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless to yellowish liquid with extremely acrid, irritating odour (Verschueren, 1983; Budavari, 1989)

(*b*) *Boiling-point*: 52.5–53.5 °C (Lide, 1993)

(*c*) *Melting-point*: –86.9 °C (Lide, 1993)

(*d*) *Density*: 0.8410 at 20 °C/4 °C (Lide, 1993)

(*e*) *Spectroscopy data*: Infrared (prism [6646]; grating [29776]), ultraviolet [5-8], nuclear magnetic resonance (proton [9153]; C-13 [6242]) and mass [22] spectral data have been reported (Sadtler Research Laboratories, 1980; Weast & Astle, 1985).

(*f*) *Solubility*: Soluble in water (206 g/L at 20 °C), ethanol, diethyl ether and acetone (WHO, 1992; Lide, 1993)

(*g*) *Volatility*: Vapour pressure, 210 mm Hg [27.9 kPa] at 20 °C (Budavari, 1989); relative vapour density (air = 1), 1.9 (Union Carbide, 1993)

(*h*) *Stability*: Unstable; polymerizes, especially under light or in the presence of alkali or strong acid, to form disacryl, a plastic solid (Budavari, 1989)

(*i*) *Reactivity*: Reacts with air (oxygen), oxidizers, acids, alkalis and ammonia (United States National Institute for Occupational Safety and Health, 1994a)

(*j*) *Octanol/water partition coefficient (P)*: log (P) = – 0.01 (Hansch *et al.*, 1995)

(*k*) *Conversion factor*: $mg/m^3 = 2.29 \times ppm$[1]

### *1.1.4 Technical products and impurities*

Acrolein is available commercially with the following typical specifications: purity, 96.5%; water, 3.0%; hydroquinone (see IARC, 1987b), 0.10%; acetaldehyde (see IARC, 1987c), 0.30%; propionaldehyde, 0.002%; acetone, 0.07%; acetic acid, 0.07%; allyl alcohol, 0.005%; allyl acrylate, 0.03%; and benzene (see IARC, 1987d), 0.0003% (Union Carbide, 1993). Trade names for acrolein include Aqualin, Magnacide B and Magnacide H.

### *1.1.5 Analysis*

Methods for the analysis of acrolein in air, water, biological media, tissue and food have been reviewed (WHO, 1992). Selected methods for the analysis of acrolein in various media are presented in Table 1. A method similar to that of the United States Environmental Protection Agency (1988) has been described that can be used for ambient air, industrial emissions and automobile exhaust, with a limit of detection of 1.2 ppb [2.7 $\mu g/m^3$] (Lodge, 1989).

The methods generally used for the determination of acrolein are spectrophotometry, fluorimetry, liquid chromatography, gas chromatography (GC) with electron capture detection and high-performance liquid chromatography with fluorescence detection. The oxime derivatives used in determination of carbonyls by GC are methoximes, benzyloximes, *para*-nitrobenzyloximes and pentafluorobenzyloximes; in these methods, flame ionization and nitrogen-specific detection systems are used (Nishikawa *et al.*, 1987a).

A method for identifying carbonyl compounds, including acrolein, in environmental samples involves derivatization with *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine hydrochloride, followed by GC–mass spectrometry (Le Lacheur *et al.*, 1993). A similar method for the determination of low-relative molecular-mass aldehydes, including acrolein, formed by the ozonation of drinking-water involves derivatization with *O*-(2,3,4,5,6-pentafluorobenzyl)-hydroxylamine hydrochloride, followed by analysis by high-resolution capillary GC. The detection limits of methods involving GC–electron capture detection and GC–mass spectrometry with ion-selective monitoring are 3.5 and 16.4 µg/L, respectively (Glaze *et al.*, 1989).

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[1] Calculated from: $mg/m^3$ = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101 kPa)

Passive and active sampling methods for the assessment of personal exposures to airborne aldehydes, including acrolein, due to emissions from methanol-fuelled vehicles are based on derivatization of the aldehydes with 2,4-dinitrophenylhydrazine during collection. The adsorbent materials are extracted with toluene and analysed by GC with flame-ionization detection (Otson *et al.*, 1993).

**Table 1. Methods for the analysis of acrolein**

| Sample matrix | Sample preparation | Assay procedure | Limit of detection | Reference |
|---|---|---|---|---|
| Air | Adsorb on sorbent coated with 2-(hydroxymethyl)piperidine on XAD-2; desorb with toluene; analyse for oxazolidine derivative | GC/NSD | 2 µg/sample (6.1 µg/m$^3$) | Eller (1994); US Occupational Safety and Health Administration (1990) |
| | | GC/FID and GC/MS | 2 µg/sample | Eller (1994) |
| | Draw air through midget impinger containing acidified DNPH and isooctane; extract DNPH derivative with hexane:dichloromethane (70:30) solution; evaporate to dryness; dissolve in methanol | Reversed-phase HPLC/UV | NR | US Environmental Protection Agency (1988) |
| | Draw air through bubblers in series containing 4-hexylresorcinol in an alcoholic trichloroacetic acid solvent medium with mercuric chloride | Colorimetry | 10 ppb [22.9 µg/m$^3$] | Feldstein *et al.* (1989a) |
| | Draw air through midget impinger containing 1% sodium bisulfite; react with 4-hexylresorcinol in an alcoholic trichloroacetic acid solvent medium with mercuric chloride | Colorimetry | 10 ppb [22.9 µg/m$^3$] | Feldstein *et al.* (1989b) |
| Moist air | Collect in DNPH-impregnated adsorbent tubes (with CaCl, tubes); extract with acetonitrile | HPLC/UV | 0.3 µg/sample (0.01 mg/m$^3$) | Vainiotalo & Matveinen (1992) |
| Exhaust gas | Derivatize with *O*-benzyl-hydroxylamine to *O*-benzyloxime; brominate with sulfuric acid, potassium bromate and potassium bromide; reduce with sodium thiosulfate; extract with diethyl ether | GC/ECD | NR | Nishikawa *et al.* (1987a) |
| Aqueous solution | Derivatize with *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine | MIMS/EIMS | 10 ppb (µg/L) | Choudhury *et al.* (1992) |

**Table 1 (contd)**

| Sample matrix | Sample preparation | Assay procedure | Limit of detection | Reference |
|---|---|---|---|---|
| Rain-water | Derivatize with *O*-methoxylamine to *O*-methyloxime; brominate with sulfuric acid, potassium bromate and potassium bromide; reduce with sodium thiosulfate; elute with diethyl ether | GC/ECD | 0.4 µg/L | Nishikawa *et al.* (1987b) |
| Liquid and solid wastes | Purge (inert gas); trap on suitable adsorbent material; desorb as vapour onto packed gas chromatographic column | GC/FID | 0.7 µg/L[a] | US Environmental Protection Agency (1986) |
| Biological samples | Derivatize with DNPH; extract with chloroform; wash with hydrochloric acid; dry with nitrogen; dissolve in methanol | HPLC/UV | 1 ng | Boor & Ansari (1986) |

GC, gas chromatography; NSD, nitrogen selective detection; FID, flame ionization detection; MS, mass spectrometry; HPLC/UV, high-performance liquid chromatography/ultraviolet detection; DNPH, 2,4-dinitrophenylhydrazine; ECD, electron capture detection; MIMS/EIMS, membrane introduction mass spectrometry/electron impact mass spectrometry; NR, not reported

[a] Practical quantification limits for other matrices: 7 µg/L for groundwater; 7 µg/kg for low-level soil samples; 350 µg/L for water-miscible liquid waste samples; 875 µg/kg for high-level soil and sludge samples; 875 µg/L for non-water-miscible waste samples

## 1.2 Production and use

### *1.2.1 Production*

Acrolein was first prepared in 1843 by Redtenbacher by the dry distillation of fat (Prager *et al.*, 1918). Commercial production of acrolein began in Germany in 1942, by a process based on the vapour-phase condensation of acetaldehyde and formaldehyde (see IARC, 1995). This method was used until 1959, when a process was introduced for producing acrolein by vapour-phase oxidation of propylene (see IARC, 1994) (Ohara *et al.*, 1985). Several catalysts have been used in the vapour-phase oxidation of propylene, including cuprous oxide, bismuth molybdate and antimony oxide (Hess *et al.*, 1978). All commercial production of acrolein is currently based on propylene oxidation (Ohara *et al.*, 1985).

In 1975, global production of acrolein was about 59 000 tonnes (Hess *et al.*, 1978). The worldwide capacity for production of refined acrolein is about 113 000 tonnes per year (Etzkorn *et al.*, 1991).

Acrolein is produced by three companies each in Japan and the United States of America and by one company each in France and Germany (Chemical Information Services, Inc., 1994).

### *1.2.2 Use*

The principal use of acrolein is as an intermediate in the synthesis of acrylic acid (see IARC, 1987e), which is used to make acrylates, and of DL-methionine, an essential amino acid used as an animal feed supplement. Other important derivatives of acrolein are glutaraldehyde, pyridines, tetrahydrobenzaldehyde, allyl alcohol and glycerol, 1,4-butanedial and 1,4-butenediol, 1,3-propanediol, DL-glyceraldehyde, flavours and fragrances, polyurethane and polyester resins (Ohara *et al.*, 1985; Sax & Lewis, 1987).

The most important direct use of acrolein is as a biocide: It is used as a herbicide and to control algae, aquatic weeds and molluscs in recirculating process water systems. It is further used to control the growth of microorganisms in liquid fuel, the growth of algae in oil fields and the formation of slime in paper manufacture. Acrolein has been used in leather tanning and as a tissue fixative in histological work (Hess *et al.*, 1978; Ohara *et al.*, 1985; United States Environmental Protection Agency, 1985; Etzkorn *et al.*, 1991; WHO, 1992).

Acrolein has also been used as a warning agent in methyl chloride refrigerants and other gases, in poison gas mixtures for military use, in the manufacture of colloidal forms of metals (Budavari, 1989) and as a test gas for gas masks (Neumüller, 1979).

## 1.3 Occurrence

### *1.3.1 Natural occurrence*

Acrolein has been identified as a volatile component of essential oils extracted from the wood of oak trees (Egorov *et al.*, 1976), in biogenic emissions from pine (0.49 μg/m$^3$) and deciduous (0.27 μg/m$^3$) forests in Europe and in remote, high-altitude areas with scarce vegetation (e.g. Nepal; 0.08–0.25 μg/m$^3$) (Ciccioli *et al.*, 1993). Acrolein occurs in a wide variety of food and food components (Feron *et al.*, 1991) (see also section 1.3.5).

### *1.3.2 Occupational exposures*

The National Occupational Exposure Survey conducted between 1981 and 1983 indicated that 1298 employees in four industries (a total of 37 plants) in the United States were potentially exposed occupationally to acrolein (United States National Institute for Occupational Safety and Health, 1994b). The estimate is based on a survey of companies and did not involve measurements of actual exposures. Exposure to acrolein can occur in a wide variety of occupations, as indicated in Table 2.

### *1.3.3 Air (including emissions and combustion)*

The levels of acrolein in ambient air and various emission rates have been reviewed (IARC, 1985; WHO, 1992).

Acrolein can be formed *in situ* in the atmosphere by photochemical oxidation of hydrocarbons (Atkinson & Arey, 1993). Concentrations of acrolein in ambient air have been reported to be 2–7 pbb [4.58–16 μg/m$^3$] in the United States, 0.5 pbb [1.15 μg/m$^3$] in the Netherlands and 0.13–0.56 pbb [0.30–1.28 μg/m$^3$] in Brazil (Grosjean, 1990).

## Table 2. Occupational exposure of acrolein

| Country | No. of plants | Job, task or industry | No. of samples | Concentration in air ($mg/m^3$) | | Reference |
|---|---|---|---|---|---|---|
| | | | | Mean | Range | |
| Finland (1980–92) | | Various industries, e.g. manufacture of plastics products, pulp, paper, paperboard, metal, glass products, electronic equipment | 257 (A and P) | 96.9% of measurements < 0.25 | | Finnish Institute of Occupational Health (1994) |
| Finland | 5 | Restaurant kitchen | (A) | | 0.06–0.59 | Vainiotalo & Matveinen (1993) |
| | 2 | Bakery | | 0.02 | | |
| | 1 | Food factory | | 0.01 | | |
| Finland | 3 | Bakery | 11(A) | 0.12 | < 0.03–0.59 | Linnainmaa *et al.* (1990) |
| USA | | Bakery | (A) | – | 0.02–0.32 mg/batch | Lane & Smathers (1991) |
| China | | Emission from rapeseed oil | | Qualitative identification | | Shields *et al.* (1993) |
| Former USSR | | Emission from sunflower oil (160–170 °C) | (A) | ≤ 1.1 | | Izmerov (1984) |
| Finland | 1 | Shipyard | 82(A) | 0.01–0.07 (median) | 0.04–1.4 (max) | Engström *et al.* (1990) |
| Denmark | 3 | Engine workshops | (A) | | ND–0.61 | Rietz (1985) |
| USA | | Wildland fire fighters | 1(P) | | 0.05 | Materna *et al.* (1992) |
| USA | 1 | Truck maintenance shop | | 0.005 | | Castle & Smith (1974) |
| Russian Federation | 1 | Rubber vulcanization | | | 0.44–1.5 | Volkova & Bagdinov (1969) |
| Russian Federation | | Workshop, welding of metals coated with anti-corrosive primers | | | 0.11–1.0 | Protsenko *et al.* (1973) |

**Table 2 (contd)**

| Country | No. of plants | Job, task or industry | No. of samples | Concentration in air ($mg/m^3$) | | Reference |
|---|---|---|---|---|---|---|
| | | | | Mean | Range | |
| Former Czechoslovakia | 1 | Pitch-coking plant<br>Coal-coking plant | 10<br>20 | 0.27<br>0.05 | 0.1–0.6<br>0.002–0.55 | Mašek (1972) |
| USA | 1 | Workshop, repair and service (diesel exhaust) | | | < 0.1 | Apol (1973) |
| Russian Federation | | Quarries, exhaust from diesel engines | | | 2.1–7.2 | Klochkovskii *et al.* (1981) |
| Russian Federation | 1 | Production of acrolein and methyl mercaptopropionic aldehyde | (A) | | 0.1–8.2 | Izmerov (1984) |
| Russian Federation | 1 | Press shops in oil seed mills | | | 2–10 | WHO (1992) |
| Finland | 14 | Manufacture of thermoplastics (17 different processes) | 67(A) | | < 0.02 | Pfäffli (1982) |

A, area sample; P, personal air sample (breathing zone)

In the former USSR, acrolein was measured at concentrations of 2 mg/m$^3$ in the air 100 m from oil chemical plants and 0.64 mg/m$^3$ at 1000 m; it was also measured at 0.4 mg/m$^3$ in the air 100 m from an oil mill and at 0.1–0.2 mg/m$^3$ 1000 m from the mill. The concentrations of acrolein 150–800 m from an imitation-leather cloth and oil-cloth factory were 0.088–0.02 mg/m$^3$, and those 50 m from a perfume factory were 0.04–0.48 mg/m$^3$ (Izmerov, 1984). In the Netherlands, the annual emission of acrolein in 1989–90 was estimated to be 1.4 tonnes from the production of acrylonitrile and 0.03 tonnes from the metal and metallurgical industry (Sloof *et al.*, 1991).

Acrolein has been measured in smoky indoor air. In a tavern in the United States, the concentrations were 21–24 μg/m$^3$ (Löfroth *et al.*, 1989). In Germany, concentrations of 30–100 ppb [68.7–229 μg/m$^3$] were measured in five cafes, 3–13 pbb [6.87–29.8 μg/m$^3$] in two restaurants, 20–120 ppb [45.8–275 μg/m$^3$] in a train, 5–18 ppb [11.5–41.2 μg/m$^3$] in a tavern and 1–10 pbb [2.29–22.9 μg/m$^3$] in a cafeteria (Triebig & Zober, 1984).

Acrolein has been detected in exhaust gases from both gasoline engines, at 0.02–12.1 ppm [0.05–27.7 mg/m$^3$], and diesel engines, at 0.05–0.09 ppm [0.12–0.21 mg/m$^3$]. It has also been measured in exhaust from a diesel truck, at 6.9 ppm [15.8 mg/m$^3$], and a two-stroke motorcycle, at 6.5 ppm [14.9 mg/m$^3$] (Kuwata *et al.*, 1979; Lipari & Swarin, 1982; Nishikawa *et al.*, 1987a; Sigrist, 1994). The emission rate of acrolein from gasoline-fuelled vehicles with different emission control systems varied from undetectable to 1.7 mg/km (Victorin *et al.*, 1988). The emission rate from gasoline-fuelled light-duty vehicles operated under different driving conditions ranged from 0.004 to 0.17 mg/km (Westerholm *et al.*, 1992) and from undetectable to 0.4 mg/mile [0.25 mg/km] (Warner-Selph, 1989). In a study of light-duty vehicles fuelled with natural gas, the emission rate of acrolein was 0.0121 g/kg fuel (Siewert *et al.*, 1993). The emission from heavy-duty engines run with natural gas was 0.32 mg/kW h [0.09 mg/MJ], and that of diesel engines was 0.30 mg/kW h [0.08 mg/MJ] (Gambino *et al.*, 1993). In another study of diesel engines, the acrolein emissions were 7 mg/bhp h [2.59 mg/MJ] from base fuel, 3 mg/bhp h [1.11 mg/MJ] from fuels with ethylhexyl nitrate-containing additives and 3 mg/bhp h [1.11 mg/MJ] from fuels with peroxide-containing additives (Liotta, 1993). In Japan, acrolein was measured at concentrations of 0.9–1.3 ppb [2.06–3.00 μg/m$^3$] in urban air, 1.4–1.8 ppb [3.21–4.12 μg/m$^3$] in a road tunnel and 1.5–3.6 ppb [3.44–8.24 μg/m$^3$] in automobile exhaust (Nishikawa *et al.*, 1986). In the former USSR, acrolein concentrations of 0.6–22 μg/m$^3$ were measured on a highway and from undetectable to 13 μg/m$^3$ in a neighbouring residential area (Izmerov, 1984). The estimated annual emissions of acrolein from road traffic in 12 European countries (Bouscaren *et al.*, 1987) are summarized in Table 3.

Acrolein has been determined as an odorous constituent in aircraft emissions. In the United States, it was emitted by model jet engines operating at idling power at concentrations of 0.80–2.23 ppm [1.83–5.11 mg/m$^3$] (Rossi, 1992). In Japan, concentrations of 0.009–0.052 ppm [0.02–0.12 mg/m$^3$] were measured about 50 m behind a low-smoke combustor jet engine at idling power (Miyamoto, 1986).

Acrolein concentrations associated with residences where wood stoves were used were 0.7–6.0 μg/m$^3$ in indoor air and 1.6–4.9% outdoors (Highsmith *et al.*, 1988). The rate of emission of acrolein from wood-burning fireplaces varied from 0.021 to 0.132 g/kg (Lipari *et al.*, 1984).

Acrolein was identified in oil combustion products in a hospital at a level of 166 μg/m$^3$ (Götze & Harke, 1989).

**Table 3. Estimated annual emissions of acrolein (tonnes/year) from road traffic in 12 European countries**

| Country | Acrolein emission (tonnes/year) | |
|---|---|---|
| | Gasoline engines | Diesel engines |
| Belgium | 70 | 60 |
| Denmark | 30 | 30 |
| Germany | 550 | 450 |
| France | 450 | 400 |
| Greece | 40 | 70 |
| Ireland | 20 | 10 |
| Italy | 400 | 400 |
| Luxembourg | 4 | 2 |
| Netherlands[a] | 90 | 70 |
| Portugal | 20 | 60 |
| Spain | 140 | 200 |
| United Kingdom | 500 | 250 |

From Bouscaren *et al.* (1987)
[a]Plus 30 tonnes per year from the chemical industry

Acrolein has been identified among the decomposition products of cellophane (Feron *et al.*, 1991) and polyvinyl chloride (Boettner & Ball, 1980) used for food wrapping. It has also been identified in Chinese incense smoke (Lin & Wang, 1994).

### *1.3.4 Water*

The levels of acrolein in water from various sources have been reviewed (WHO, 1992). Acrolein was detected in surface water in an irrigation canal downstream from its application as a slimicide or herbicide at concentrations of 30–100 μg/L (WHO, 1992). It has also been detected in raw sewage in treatment plants at concentrations of 216–825 ppb [μg/L] and in municipal effluents at 20–200 ppb (United States Environmental Protection Agency, 1985).

Acrolein has not been detected in drinking-water (WHO, 1992). It was detected at concentrations of 1.5–3.1 μg/L in samples of rainwater in Japan (Nishikawa *et al.*, 1987b); it was not detected in rainwater in the Po Valley, Italy, but was found in fog at levels varying from undetectable (< 1 μmol [56 μg]/L) to 120 μg/L (Facchini *et al.*, 1986, 1990).

### *1.3.5 Food and beverages*

Acrolein has been detected in a wide variety of fruits (apples, grapes, raspberries, strawberries, blackberries) at concentrations of < 0.01–0.05 ppm [mg/kg] and in vegetables (cabbage, carrots, potatoes, tomatoes) at ≤ 0.59 ppm. It has also been detected in caviar, lamb, hops, sour

salted pork, the aroma of cooked horse mackerel and of white bread and in raw chicken breast (Feron *et al.*, 1991). It was detected in doughnuts fried at 182 °C at concentrations of 0.1–0.9 ppm and in the coating of codfish fillets fried at 182 °C and 204 °C at a concentration of 0.1 ppm (Lane & Smathers, 1991).

Acrolein has been detected in cheese at levels of 290–1300 ppb [μg/kg] (Collin *et al.*, 1993). It was found in whisky at 0.67–11.1 ppb [μg/L] (Miller & Danielson, 1988), in red wine at 3.8 ppm [mg/L] and in fresh lager beer at 0.0011–0.002 ppm [mg/L]. It has also been identified in coffee and tea (Feron *et al.*, 1991) and in the emissions from heated animal fat and vegetable oils (Umano & Shibamoto, 1987; Yasuhara *et al.*, 1989).

#### *1.3.6 Tobacco smoke*

The occurrence of acrolein in tobacco smoke has been reviewed. The acrolein concentrations in the smoke from various cigarettes were 3–220 μg/cigarette (IARC, 1985, 1986). Levels as high as 463–684 μg/cigarette were reported in Japan (Kuwata *et al.*, 1979). The mean acrolein concentrations detected in 75 brands of cigarettes in the United Kingdom during 1983–90 varied from < 10 to 140 μg/cigarette (Phillips & Waller, 1991).

#### *1.3.7 Humans*

Acrolein was detected in the urine of a bone-marrow recipient after intravenous administration of cyclosphamide (Al-Rawithi et al., 1993).

### 1.4 Regulations and guidelines

Occupational exposure limits and guidelines for acrolein in several countries are given in Table 4. In the Russian Federation, the maximal acceptable background concentration of acrolein in ambient air is 0.03 mg/m$^3$ (Environmental Chemicals Data and Information Network, 1993). In the United States, acrolein may be used as a slimicide in the manufacture of paper and paperboard that will come into contact with food (United States Food and Drug Administration, 1994). An Expert Panel of the European Commission recommended a time-weighted average occupational exposure limit of 0.12 mg/m$^3$, with a short-term exposure limit of 0.23 mg/m$^3$ (European Commission, 1994).

## 2. Studies of Cancer in Humans

Epidemiological studies of exposure to acrolein in complex mixtures originating from the combustion of organic products, such as indoor cooking and occupations related to motor exhaust, were available but were considered to be insufficiently specific for use in evaluating the carcinogenicity of acrolein. Only one study in which individual exposure to acrolein was assessed was available to the Working Group.

**Table 4. Occupational exposure limits and guidelines for acrolein**

| Country | Year | Concentration ($mg/m^3$) | Interpretation |
|---|---|---|---|
| Australia | 1991 | 0.25 | TWA |
| | | 0.8 | STEL |
| Belgium | 1991 | 0.23 | TWA |
| | | 0.69 | STEL |
| Canada | 1994 | 0.25 | TWA |
| | | 0.8 | STEL |
| Denmark | 1991 | 0.25 | TWA |
| Finland | 1993 | 0.25 | STEL |
| France | 1991 | 0.25 | STEL |
| Germany | 1993 | 0.25 | TWA |
| Hungary | 1991 | 0.25 | TWA |
| | | 0.5 | STEL |
| Italy | 1994 | 0.25 | TWA |
| | | 0.75 | STEL |
| Japan | 1991 | 0.23 | TWA |
| Netherlands | 1994 | 0.25 | TWA |
| Poland | 1991 | 0.5 | TWA |
| Romania | 1994 | 0.3 | TWA |
| | | 0.5 | STEL |
| Russian Federation | 1991 | 0.2 | STEL |
| Sweden | 1993 | 0.2 | TWA |
| | | 0.7 | STEL |
| Switzerland | 1994 | 0.25 | TWA |
| | | 0.5 | STEL |
| United Kingdom | 1993 | 0.25 | TWA |
| | | 0.8 | STEL |
| United States | | | |
| ACGIH (TLV) | 1994 | 0.23 | TWA |
| | | 0.69 | STEL |
| NIOSH (REL) | 1994 | 0.25 | TWA |
| | | 0.8 | STEL |
| OSHA (PEL) | 1994 | 0.25 | TWA |

From ILO (1991); United States National Institute for Occupational Safety and Health (NIOSH) (1994a); Arbetarskyddsstyrelsens (1993); Deutsche Forschungsgemeinschaft (1993); Environmental Chemicals Data and Information Network (1993); Työministeriö (1993); United Kingdom Health and Safety Executive (1993); Arbeidsinspectie (1994); American Conference of Governmental Industrial Hygienists (ACGIH) (1994); Schweizerische Unfallversicherungsanstalt (1994); United States Occupational Safety and Health Adminitration (OSHA) (1994)

TWA, time-weighted average; STEL, short-term exposure limit; PEL, permissible exposure limit; REL, recommended exposure limit; TLV, threshold limit value

In the case–control study of Ott *et al.* (1989), described in the monograph on vinyl acetate, p. 450, exposure to acrolein was reported for two men who had died with non-Hodgkin's lymphoma (odds ratio, 2.6), one with multiple myeloma (odds ratio, 1.7), three with non-lymphocytic leukaemia (odds ratio, 2.6) and none who had died with lymphocytic leukaemia.

## 3. Studies of Cancer in Experimental Animals

### 3.1 Oral administration

#### *3.1.1 Mouse*

Four groups of 70–75 male and 70–75 female Swiss albino CD-1 mice, eight weeks of age, received 0, 0.5, 2.0 or 4.5 mg/kg bw acrolein (purity, 94.9–98.5%; containing 0.25–0.3% hydroquinone as a stabilizer) per day by gavage in deionized water for 18 months, at which time all surviving mice were killed. Treated mice had decreased body weight gain, and treated males had an increased mortality rate, particularly at the high dose. All mice killed at the end of treatment and those found dead or moribund were necropsied, and tissues from major organs were examined histologically. No treatment-related increase in tumour frequency was observed (Parent *et al.*, 1991a).

#### *3.1.2 Rat*

Groups of 20 male and 20 female Fischer 344 rats, seven to eight weeks of age, received 0 or 625 mg/L acrolein ([purity unspecified] stabilized with hydroquinone) per day in the drinking-water on five days a week for 124 or 104 weeks and were killed at 132 weeks. Additional groups of 20 males received 100 or 250 mg/L acrolein for 124 weeks, and surviving rats were killed at 130 weeks. Survival was comparable in treated and control groups. No significant, dose-related increase in the frequency of tumours at any site was observed (Lijinsky & Reuber, 1987; Lijinsky, 1988). [The Working Group noted the small number of animals used.]

Groups of 50 male and 50 female Sprague-Dawley rats, about six weeks of age, received 0, 0.05, 0.5 or 2.5 mg/kg bw acrolein (purity, 94.9–98.5%; containing 0.25–0.3% hydroquinone as a stabilizer) in deionized water by gavage daily for 102 weeks, at which time all surviving rats were killed. Survival was significantly reduced among males and females at the high dose during the first year, and this trend continued among females throughout the treatment period. All rats, including those that were found dead, were necropsied, and tissues from major organs were examined histologically. There was no significant increase in the incidence of neoplastic or non-neoplastic lesions in treated rats in comparison with controls (Parent *et al.*, 1992a).

### 3.2 Inhalation and/or intratracheal administration

*Hamster*: Two groups of 18 male and 18 female Syrian golden hamsters, six weeks old, were exposed to 0 or 4 ppm (0 or 9.2 mg/m$^3$) acrolein vapour [purity unspecified] for 7 h per day on five days per week for 52 weeks. Six animals per group were killed at 52 weeks and the remainder at 81 weeks. Survival was similar in treated and control groups. All animals were

subjected to necropsy, and all tissues from the respiratory tract and gross or suspect lesions were examined histologically. A single papilloma of the respiratory tract was found in a treated female. Inflammation and epithelial metaplasia of the respiratory tract were observed in about 20% of animals killed at 81 weeks, even after a withdrawal period of six months (Feron & Kruysse, 1977). [The Working Group noted the short exposure period and the small number of animals used.]

### 3.3 Skin application

*Mouse*: A group of 15 S strain mice [sex and age unspecified] received 10 weekly skin applications of a 0.5% solution of acrolein [purity unspecified] in acetone (total dose of acrolein, 12.6 mg per animal). Starting 25 days after the first application of acrolein, the mice received weekly skin applications of 0.17% croton oil for 18 weeks; for the second and third applications, the concentration was reduced to 0.085%. When croton oil and acrolein were administered together, each compound was given alternately at three- or four-day intervals. At the end of the treatment with croton oil, all 15 mice were still alive, and two had a total of three skin papillomas; 4/19 controls that received the croton oil treatment alone had four skin papillomas (Salaman & Roe, 1956). [The Working Group noted the small number of animals used and the short duration of the experiment.]

### 3.4 Administration with known carcinogens

#### *3.4.1 Rat*

In a two-stage initiation–promotion assay in rat urinary bladder, male Fischer 344 rats, five weeks of age, were divided into eight groups. During the initial phase, groups 1, 3 and 5 (30 rats per group) received intraperitoneal injections of 2 mg/kg bw acrolein (purity, 97%) in distilled water twice a week for six weeks; groups 2, 6 and 7 (30, 30 and 40 rats per group, respectively) were fed 0.2% *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) in the diet for six weeks; group 4 (30 rats) received injections of distilled water and the control diet; and group 8 (40 rats) received no treatment and the control diet. In the second phase, groups 1, 2 and 4 received 3.0% uracil in the diet for 20 weeks, followed by six weeks of control diet; group 3 received the control diet only; groups 5 and 6 received intraperitoneal injections of 2 mg/kg bw acrolein twice a week for two weeks, 1.5 mg/kg bw once in week 10, then 1.5 mg/kg bw twice a week for seven weeks (weeks 11–17) and 1.0 mg/kg bw once in week 18, twice in week 19 and once in weeks 20 and 21; group 7 received intraperitoneal injections of distilled water and the control diet; and group 8 received control diet only. In the group receiving acrolein followed by uracil (group 1), 18/30 animals developed urinary bladder papillomas, in comparison with 8/30 in the group receiving distilled water followed by uracil (group 4) ($p < 0.05$, Fisher's exact test). The group receiving FANFT followed by uracil (group 2) developed 9/30 urinary bladder papillomas and 21/30 bladder carcinomas. No bladder tumour was observed in the rats receiving acrolein alone (group 5) (Cohen *et al.*, 1992).

*3.4.2 Hamster*

Groups of 30 male and 30 female Syrian golden hamsters, about six weeks of age, were exposed by inhalation to 0 or 4.0 ppm [0 or 9.2 mg/m$^3$] acrolein [purity unspecified] for 7 h per day on five days per week for 52 weeks, together with either weekly intratracheal instillations of 0.175 or 0.35% benzo[*a*]pyrene (purity, > 99%) in 0.9% saline (total doses, 18.2 or 36.4 mg/animal) or subcutaneous injections of 0.0675% *N*-nitrosodiethylamine in saline once every three weeks (total dose, 2 µl/animal). The experiment was terminated at 81 weeks, and all survivors were killed and autopsied. Papillomas, adenomas, adenocarcinomas and squamous-cell carcinomas of the respiratory tract were found in male and female hamsters treated with benzo[*a*]pyrene and *N*-nitrosodiethylamine. Exposure to acrolein vapour did not increase the incidence of these tumours (Feron & Kruysse, 1977).

### 3.5 Carcinogenicity of possible metabolites

Acrolein is metabolized *in vitro* by liver and lung microsomes to glycidaldehyde, which is carcinogenic to mice after skin application and to mice and rats after subcutaneous injection, producing tumours at the site of application (IARC, 1987f).

## 4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

### 4.1 Absorption, distribution, metabolism and excretion

*4.1.1 Humans*

No data were available to the Working Group.

*4.1.2 Experimental systems*

Exposure of dogs to acrolein by inhalation results in extensive retention in the respiratory tract (Egle, 1972), probably because of its strong reactivity with tissues (Beauchamp *et al.*, 1985; WHO, 1992). There seems to be limited, if any, distribution to other organs under these circumstances. After exposure of rats to concentrations of 0.1–5 ppm [0.23–11.5 mg/m$^3$], the amount of reduced glutathione (GSH) in respiratory mucosa was reduced in a dose-dependent manner; even at 5 ppm, however, there was no change in the amount of GSH in liver (McNulty *et al.*, 1984). In rats and guinea-pigs, exposure to acrolein by inhalation for 24 h/day for 90 days at concentrations of 0.22, 1 and 1.8 ppm [0.51, 2.3 and 4.1 mg/m$^3$] resulted in some changes to the liver (Lyon *et al.*, 1970), suggesting that it may also be distributed to sites distant from the respiratory tract after exposure by this route. The effects could be due to a locally produced metabolite. Subcutaneous (Kaye, 1973) and oral (Draminski *et al.*, 1983; Sanduja *et al.*, 1989) administration resulted in urinary metabolites of acrolein, indicating absorption of the parent molecule.

Acrolein reacts rapidly with thiols such as GSH, and conjugation is complete within seconds in nonenzymatic incubations *in vitro* with millimolar concentrations of GSH (Esterbauer *et al.*, 1975; Beauchamp *et al.*, 1985). This pathway seems to dominate the metabolism of acrolein (Berhane & Mannervik, 1990). The formation of GSH adducts may be catalysed in part by glutathione *S*-transferase (Beauchamp *et al.*, 1985). Acrolein may also bind to the enzyme itself, which would result in some elimination of the parent molecule (Haenen *et al.*, 1988; Berhane & Mannervik, 1990). Acrolein also binds to other proteins at sulfydryl and amino groups (Beauchamp *et al.*, 1985; Esterbauer *et al.*, 1991).

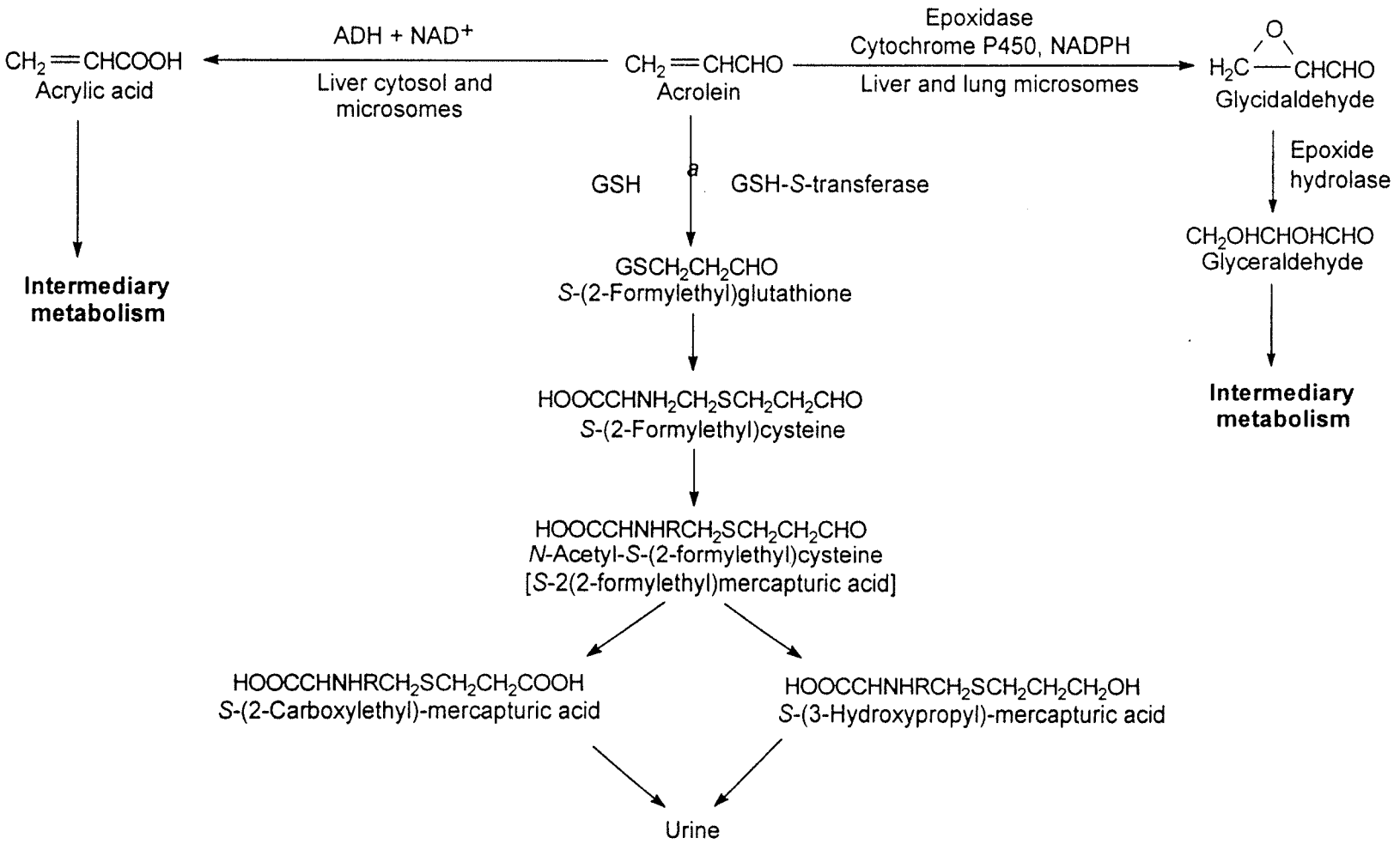
The urinary metabolites that have been identified include *S*-(2-carboxylethyl)mercapturic acid and *S*-(3-hydroxypropyl)mercapturic acid (Draminski *et al.*, 1983). Other metabolic products have been identified *in vitro*, including acrylic acid and glyceraldehyde. Acrylic acid was formed during $NAD^+$- or $NADP^+$-dependent incubation of acrolein with cytosol or microsomes from rat liver, but not from rat lung (Patel *et al.*, 1980). No evidence was found for formation of acrylic acid from acrolein by rat liver mitochondrial or cytosolic aldehyde dehydrogenases, but acrolein was a potent inhibitor of these enzymes, suggesting that the GSH adduct of acrolein is the substrate (Mitchell & Petersen, 1988). The epoxide glycidaldehyde is generated from acrolein by cytochrome P450 epoxidase, which is then subjected to the action of epoxide hydrolase to form glyceraldehyde. Acrylic acid and glyceraldehyde may then be incorporated into normal cellular metabolism (WHO, 1992). [Owing to the very efficient conjugation of acrolein with glutathione, it is unlikely that this pathway is significant *in vivo*.]

The metabolism of acrolein (summarized in Figure 1) has been studied extensively because acrolein is probably the toxic metabolite of cyclophosphamide, a chemotherapeutic agent (see IARC, 1987g). The mercapturic acid adduct of acrolein has been detected in the urine of humans after intravenous administration of cyclophosphamide. Acrolein and its glutathione adduct have also been shown to produce oxygen radicals through interaction with aldehyde dehydrogenase and xanthine oxidase (Adams & Klaidman, 1993). The depletion of GSH does not, however, involve generation of active oxygen species (Grafström *et al.*, 1988).

The 1:1 acrolein:glutathione adduct *S*-(3-oxopropyl)glutathione is nephrotoxic in rats when administered intravenously; however, this activity can be inhibited by acivicin, a γ-glutamyl-transpeptidase inhibitor, suggesting that *S*-(3-oxopropyl)glutathione is further metabolized before it becomes toxic (Horvath *et al.*, 1992). In primary cultures of rat kidney proximal tubule cells, the mercapturic acid that can be derived from the adduct, *S*-(3-oxopropyl)-*N*-acetyl-L-cysteine, is cytotoxic and can release acrolein (Hashmi *et al.*, 1992).

The results of such experiments with acrolein *in vitro* must be interpreted with caution (Beauchamp *et al.*, 1985), because the main route of exposure is inhalation and the distribution of tolerable levels is likely to be negligible. Thus, while consideration of such pathways is important for understanding the toxicity of cyclophosphamide, they are of lesser importance for the effects of acrolein itself at distant sites.

**Figure 1. Possible metabolic pathways of acrolein**




Modified from Draminski *et al.* (1983)
GSH, glutathione or glutamylcysteinylglycine; ADH, aldehyde dehydrogenase; R, COCH,
[a] A spontaneous reaction occurs rapidly

## 4.2 Toxic effects

### *4.2.1 Humans*

The toxic effects of acrolein to humans have been reviewed (WHO, 1992). It causes intense eye and respiratory irritation, the irritation threshold being about 0.1–0.2 mg/m$^3$, with no effects reported below 0.05 mg/m$^3$. This intense irritation may limit the amount of exposure to acrolein, even at low concentrations. For example, exposure to 1 ppm [2.29 mg/m$^3$] for 5 min results in intolerable eye irritation (Beauchamp *et al.*, 1985).

Skin burns and dermatitis occur after prolonged or repeated exposures (Beauchamp *et al.*, 1985). Sensitization has been reported (Key *et al.*, 1983).

### *4.2.2 Experimental systems*

Acrolein was reported to be ciliostatic in rabbit tracheal slices exposed to > 13 mg/m$^3$ for 1 h (Dalhamn & Rosengren, 1971). It did not induce sensitization in the guinea-pig maximization test (Susten & Breitenstein, 1990).

Acrolein inhibited the respiratory rate in mice at a concentration as low as 0.7 ppm [1.6 mg/m$^3$] ( Steinhagen & Barrow, 1984). A level of 6 ppm [13.8 mg/m$^3$] was required to inhibit respiration in rats (Babiuk *et al.*, 1985).

The effects of repeated exposure have been reviewed (Beauchamp *et al.*, 1985; WHO, 1992). Exposure of rats, guinea-pigs, monkeys and dogs by inhalation, the most relevant route, causes reductions in body weight gain, interference with pulmonary function and a variety of histopathological changes in the nose, airways and lungs. After groups of rats, Syrian hamsters and rabbits were exposed to acrolein at concentrations of 0, 0.4, 1.4 or 4.9 ppm [0, 0.92, 3.21 or 11.2 mg/m$^3$] for 6 h per day, five days per week for 13 weeks, squamous metaplasia and neutrophilic infiltration of the nasal mucosa were observed in rats at ≥ 0.9 mg/m$^3$; Syrian hamsters had similar nasal effects at 4.9 ppm but minimal inflammatory changes at 1.4 ppm. Rats exposed to 4.9 ppm also had squamous metaplasia in the larynx and trachea and hyperplasia in the bronchi and bronchioli. Syrian hamsters exposed to the same concentration had slight thickening of the larynx and focal hyperplasia and metaplasia of the trachea. Effects were seen on the airways of rabbits only at 4.9 ppm (Feron *et al.*, 1978).

Groups of Fischer 344 rats were exposed to acrolein at concentrations of 0, 0.4, 1.4 or 4.0 ppm [0, 0.92, 3.21 or 9.16 mg/m$^3$] for 6 h per day, five days per week for 62 days. Studies of lung mechanics and diffusion suggested airway obstruction only at the highest dose, at which severe peribronchiolar and bronchiolar damage was apparent. Similar damage was observed in a few rats at 1.4 ppm, but lung function was unaffected. In contrast, air flow dynamics were significantly enhanced in the rats exposed to 0.4 ppm, with no observed changes in histological appearance or composition. The lack of an apparent effect at 1.4 ppm was considered to be due to a cancellation of the effects observed at the higher and lower levels (Costa *et al.*, 1986).

Exposure of rats for one day or for three consecutive days to acrolein at 0.2 or 0.6 ppm [0.46 or 1.37 mg/m$^3$] increased cell proliferation in the respiratory tract (Roemer *et al.*, 1993).

Groups of Sprague-Dawley rats, guinea-pigs, beagle dogs and squirrel monkeys (*Saimiri scuirea*) were exposed to acrolein at concentrations of 0, 0.22, 1.0 or 1.8 ppm [0, 0.50, 2.29 and 4.12 mg/m$^3$] for 24 h per day, continuously for 90 days. Both dogs and monkeys showed eye and respiratory irritation at the highest concentration. Significant histological changes considered to be related to the exposure consisted of squamous metaplasia and basal-cell hyperplasia of the trachea in monkeys and confluent bronchopneumonia in dogs at the highest concentration. While no effects were noted in guinea-pigs and rats at the lowest concentration, animals of both species showed focal liver necrosis and guinea-pigs showed pulmonary inflammation at 1.0 ppm. In dogs exposed continuously, emphysema, acute congestion and focal vacuolization of bronchiolar epithelial cells with increased secretory activity occurred at 0.50 mg/m$^3$ (Lyon *et al.*, 1970).

In dogs given acrolein in gelatin capsules at 0.1, 0.5 or 1.5 mg/kg bw per day (the high dose being increased to 2 mg/kg bw per day after four weeks) orally for one year, the main effect at the two higher doses was vomiting, the frequency of which decreased with time. The levels of serum albumin, calcium and total protein were decreased at the highest dose, with some variability in red blood cell parameters and coagulation times (Parent *et al.*, 1992b).

Male and female Sprague-Dawley rats treated with acrolein in water at 0.05, 0.5 or 2.5 mg/kg bw per day by gavage for two years showed depression of creatinine phosphokinase activity and a dose-related increase in the frequency of early mortality. No histopathological effects were observed (Parent *et al.*, 1992b). [The results obtained after exposure orally cannot be compared directly with those obtained after inhalation, especially as there are local effects in the respiratory tract. The breakdown of acrolein in water may contribute to the lack of local effects after treatment by gavage.]

In an effort to understand the mechanism of the pulmonary toxicity of acrolein, plasma $\alpha_1$-proteinase inhibitor, which is inactivated by acrolein, probably by adduct formation with lysine and histidine, has been studied, as it would reduce protection against leukocyte elastase activity in the lungs (Gan & Ansari, 1987, 1989). It has also been suggested that acrolein-induced bronchial hyperresponsiveness is mediated by sulfidopeptide leukotrienes, since an immediate increase in leukotriene $C_4$ and cyclooxygenases is seen in bronchoalveolar lavage fluid from guinea-pigs before bronchial hyperreactivity. Cultured bovine airway epithelial cells exposed to 100 µmol/L [5.6 mg/L] acrolein released both cyclooxygenases and lipoxygenases (Leikauf *et al.*, 1989; Doupnik & Leikauf, 1990).

There is some evidence that acrolein interferes with aspects of the immune system, including macrophages (Sherwood *et al.*, 1986; Witz *et al.*, 1987; Jakab & Hemenway, 1993), lymphocytes (Wood *et al.*, 1992), thymocytes (Comment *et al.*, 1992) and polymorphonuclear leukocytes (Bridges *et al.*, 1980; Bridges, 1985; Witz *et al.*, 1987). Defense against pulmonary infection due to carbon black was impaired by co-exposure to acrolein, but neither substance alone had this effect (Jakab, 1993).

Acrolein has been reported to decrease cytochrome P450 enzyme activity and to inhibit microsomal cytochrome c reductase *in vitro* (Cooper *et al.*, 1987). Treatment of male Fischer 344 rats with a single intraperitoneal dose of 89 µmol /kg bw [5 mg/kg bw] did not inhibit the reductase, but both cytochrome P450 activity and ethylmorphine *N*-demethylation were decreased after 24 h, to 61 and 35% of the control levels, respectively (Cooper *et al.*, 1992). Acrolein has also been reported to inhibit aldehyde dehydrogenases (Mitchell & Petersen, 1988).

## 4.3 Reproductive and prenatal effects

### *4.3.1 Humans*

No data were available to the Working Group.

### *4.3.2 Experimental systems*

Acrolein was both embryolethal and teratogenic in rats treated by intraamnionic injection *in vivo* on day 13 of gestation, with doses as low as 0.1 μg/fetus for embryolethality and 5 μg/fetus for malformations. The defects reported included tail abnormalities, microencephaly and prosencephalic hypoplasia (Slott & Hales, 1985). No significant reproductive toxicity was seen after acrolein was administered by gavage to two generations of rats at ≤ 6 mg/kg per day (Parent *et al.*, 1992c), and no developmental toxicity was reported in rabbits administered acrolein by gavage at ≤ 2 mg/kg bw per day on days 7–19 of gestation (Parent *et al.*, 1993).

## 4.4 Genetic and related effects

### *4.4.1 Humans*

Acrolein-modified DNA was detected by an antibody reaction in the peripheral blood lymphocytes of patients receiving cyclophosphamide. No untreated cancer patients had detectable adducts. There was, however, no clear association between the total drug dose and acrolein–DNA adduct formation (McDiarmid *et al.*, 1991)

### *4.4.2 Experimental systems* (see also Table 5 and Appendices 1 and 2)

#### *(a) Adducts*

Acrolein binds to proteins, thus inhibiting critical enzymes involved in replicative DNA synthesis, RNA transcription and cell membrane integrity, although inactivation of enzymes associated with sister chromatid exchange and DNA excision repair could not be established (Wilmer *et al.*, 1986).

Acrolein reacts chemically with proteins and DNA constituents (Nelsestuen, 1980; Chung *et al.*, 1984), but DNA binding has not been demonstrated in acrolein-treated animals. Acrolein-derived adducts were observed in DNA from livers of unexposed mice, rats and humans by a very sensitive procedure (Nath & Chung, 1994).

#### *(b) Mutagenic effects*

Acrolein induced SOS repair in *Escherichia coli* PQ37, but only when ethanol was used as the solvent. DNA–histone cross-links were detected in *E. coli* HB101pUC13.

## Table 5. Genetic and related effects of acrolein

| Test system | Result[a] | | Dose[b] LED/HID | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| PRB, SOS (*umu*) induction assay, *Salmonella typhimurium* TA1535 pks 1002 | – | 0 | 5.6 | Benamira & Marnett (1992) |
| PRB, *Escherichia coli* PQ37, SOS repair | + | 0 | 0.00 | Eder *et al.* (1993) |
| ECB, *Escherichia coli* HB101pUC13, DNA–histone cross-links | + | | 3 | Kuykendall & Bogdanffy (1992) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation (spot test) | – | – | 17 | Florin *et al.* (1980) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | – | 43 | Lijinsky & Andrews (1980) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | – | 28 | Loquet *et al.* (1981) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | (+) | 38 | Haworth *et al.* (1983) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | + | – | 2.1 | Lutz *et al.* (1982) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | – | 0.00 | Basu & Marnett (1984) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | + | | 224 | Foiles *et al.* (1989) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | + | Toxic | 0.00 | Eder *et al.* (1993) |
| SA2, *Salmonella typhimurium* TA102, reverse mutation | – | 0 | 0.00 | Marnett *et al.* (1985) |
| SA4, *Salmonella typhimurium* TA104, reverse mutation | + | 0 | 8 | Marnett *et al.* (1985) |
| SA4, *Salmonella typhimurium* TA104, reverse mutation | + | 0 | 224 | Foiles *et al.* (1989) |
| SA5, *Salmonella typhimurium* TA1535, reverse mutation (spot test) | – | – | 17 | Florin *et al.* (1980) |
| SA5, *Salmonella typhimurium* TA1535, reverse mutation | – | – | 43 | Lijinsky & Andrews (1980) |
| SA5, *Salmonella typhimurium* TA1535, reverse mutation | – | – | 28 | Loquet *et al.* (1981) |
| SA5, *Salmonella typhimurium* TA1535, reverse mutation | – | (+) | 0.005 | Hales (1982) |
| SA5, *Salmonella typhimurium* TA1535, reverse mutation | – | – | 13 | Haworth *et al.* (1983) |
| SA7, *Salmonella typhimurium* TA1537, reverse mutation (spot test) | – | – | 17 | Florin *et al.* (1980) |
| SA7, *Salmonella typhimurium* TA1537, reverse mutation | – | – | 43 | Lijinsky & Andrews (1980) |
| SA7, *Salmonella typhimurium* TA1537, reverse mutation | – | – | 13 | Haworth *et al.* (1983) |

**Table 5 (contd)**

| Test system | Result[a] | | Dose[b] LED/HID | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| SA8, *Salmonella typhimurium* TA1538, reverse mutation | – | – | 43 | Lijinsky & Andrews (1980) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation | – | – | 17 | Florin *et al.* (1980) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation | + | – | 8.4 | Lijinsky & Andrews (1980) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation | – | – | 28 | Loquet *et al.* (1981) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation | – | – | 13 | Haworth *et al.* (1983) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation | – | – | 0.00 | Basu & Marnett (1984) |
| SA9, *Salmonella typhimurium* TA98, reverse mutation | + | + | 0.00 | Claxton (1985) |
| SAS, *Salmonella typhimurium his*D3052/*nop*KM101, reverse mutation | – | – | 0.00 | Basu & Marnett (1984) |
| ECW, *Escherichia coli* WP2 (*uvr*A), reverse mutation | + | 0 | 560 | Hemminki *et al.* (1980) |
| SSB, *Saccharomyces cerevisiae*, DNA strand breaks and interstrand cross-links | – | 0 | 5.6 | Fleer & Brendel (1982) |
| SCR, *Saccharomyces cerevisiae* S211 and S138, reverse mutation | – | 0 | 100 | Izard (1973) |
| DMM, *Drosophila melanogaster*, SMART eye spot mutation | + | | 280 feed | Sierra *et al.* (1991) |
| DMM, *Drosophila melanogaster*, SMART wing spot mutation | + | | 280 feed | Sierra *et al.* (1991) |
| DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation | – | | 280 feed | Sierra *et al.* (1991) |
| | + | | 168 inj | |
| DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation | – | | 3000 feed | Zimmering *et al.* (1985) |
| | – | | 200 inj | |
| DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation | – | | 800 feed | Zimmering *et al.* (1989) |
| DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation | + | | 168 inj | Barros *et al.* (1994a,b) |
| | – | | 560 feed | |
| DMN, *Drosophila melanogaster*, sex chromosome loss | – | | 280 feed | Sierra *et al.* (1991) |
| | – | | 280 inj | |
| DIA, DNA–protein cross-links, rat nasal mucosal cells *in vitro* | + | 0 | 168 | Lam *et al.* (1985) |
| DIA, DNA–strand breaks (alkaline elution), mouse leukaemia L1210 cells *in vitro* | + | 0 | 56 | Eder *et al.* (1993) |
| DIA, DNA–strand breaks (alkaline elution), Chinese hamster ovary K1 cells *in vitro* | + | 0 | 1.2 | Deaton *et al.* (1993) |

**Table 5 (contd)**

| Test system | Result[a] | | Dose[b] LED/HID | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| GCL, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro* | + | 0 | 0.06 | Smith *et al.* ((1990a) |
| GCO, Gene mutation, Chinese hamster ovary (CHO) cells, *hprt* locus *in vitro* | – | 0 | 5.6 | Foiles *et al.* (1990) |
| GCO, Gene mutation, Chinese hamster ovary (CHO) cells, *hprt* locus *in vitro* | – | – | 5 | Parent *et al.* (1991b) |
| SIC, Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro* | – | – | 0.56 | Au *et al.* (1980) |
| SIC, Sister chromatid exchange, Chinese hamster ovary (CHO) cells *in vitro* | (+) | – | 1.0 | Galloway *et al.* (1987) |
| CIC, Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro* | – | (+) | 2.24 | Au *et al.* (1980) |
| CIC, Chromosomal aberrations, Chinese hamster ovary (CHO) cells *in vitro* | – | – | 1.0 | Galloway *et al.* (1987) |
| TCM, Cell transformation, C3H 10T½ mouse cells *in vitro* | – | 0 | 0.00 | Abernethy *et al.* (1983) (abstract) |
| DIH, DNA cross-links, human bronchial epithelial cells *in vitro* | – | 0 | 5.6 | Grafström *et al.* (1986) |
| DIH, DNA strand breaks (alkaline elution), human bronchial epithelial cells *in vitro* | – | 0 | 5.6 | Grafström *et al.* (1986) |
| DIH, DNA single-strand breaks, human myeloid leukaemia K562 cells *in vitro* | + | 0 | 0.3 | Crook *et al.* (1986) |
| DIH, DNA–protein cross-links, human bronchial epithelial cells *in vitro* | + | 0 | 5.6 | Grafström *et al.* (1986) |
| GIH, Gene mutation, human xeroderma pigmentosum fibroblasts, 6-thioguanine resistance *in vitro* | + | 0 | 0.1 | Curren *et al.* (1988) |
| SHL, Sister chromatid exchange, human lymphocytes *in vitro* | + | 0 | 0.84 | Wilmer *et al.* (1986) |
| DVA, DNA–protein cross-links in rat nasal mucosa *in vivo* | – | | 1.0 inh 6 h | Lam *et al.* (1985) |
| DLM, Dominant lethal mutation, mice *in vivo* | – | | 2.2 ip × 1 | Epstein *et al.* (1972) |
| BID, Binding (covalent) to calf thymus DNA *in vitro* | + | 0 | 58 | Chung *et al.* (1984) |
| ***, Binding to poly dC *in vitro* | + | 0 | 1960 | Smith *et al.* (1988) |
| ***, Cyclic binding to adenine *in vitro* | + | 0 | 1275 | Sodum & Shapiro (1988) |
| ***, Cyclic binding to cytosine *in vitro* | + | 0 | 2125 | Sodum & Shapiro (1988) |
| ***, Binding to poly dA *in vitro* | + | 0 | 2.0 | Smith *et al.* (1990b) |
| BID, Binding (covalent) to DNA (dG) of *Salmonella typhimurium in vitro* | + | 0 | 224 | Foiles *et al.* (1989) |

**Table 5 (contd)**

| Test system | Result[a] | | Dose[b] LED/HID | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| BID, Binding (covalent) to DNA (dGuo), Chinese hamster ovary (CHO) cells *in vitro* | + | 0 | 5.6 | Foiles *et al.* (1990) |
| BID, Binding (covalent) to calf thymus DNA *in vitro* | + | 0 | 5.6 | Wilson *et al.* (1991) |
| BID, Binding (covalent) to DNA, human fibroblasts *in vitro* | + | 0 | 5.6 | Wilson *et al.* (1991) |

[a]+, considered to be positive; (+), considered to be weakly positive in an inadequate study; –, considered to be negative; 0, not tested
[b]LED, lowest effective dose; HID, highest effective dose. In-vitro tests, µg/ml; in-vivo tests, mg/kg bw; 0.00, dose not reported; inh, inhalation; ip, intraperitoneally
***, Not included on the profile
dC, deoxycytosine; dA, deoxyadenine; dG, deoxyguanine; dGuo, deoxyguanosine

Acrolein caused gene mutation in *E. coli* and *Salmonella typhimurium* in the absence of an exogenous metabolic system. The high toxicity of the compound led to conflicting results when the standard protocol was not modified.

No interstrand cross-links or mutations were seen in yeast after exposure to acrolein. In *Drosophila melanogaster*, it induced somatic mutations and (after injection) sex-linked recessive lethal mutations. No sex chromosome loss was detected .

Acrolein induced DNA–protein cross-links and DNA strand breaks in cultured mammalian cells. It induced gene mutations at the *hprt* locus in one study with Chinese hamster V79 cells but not in two other studies with Chinese hamster ovary cells. Acrolein induced sister chromatid exchange and chromosomal aberrations in Chinese hamster ovary cells *in vitro*. As reported in an abstract, it did not transform C3H10T$^{1}/_{2}$ cells, but it showed some initiating activity in a two-stage assay in which treatment with acrolein was followed by application of 12-*O*-tetradecanoylphorbol 13-acetate. It induced gene mutations (6-thioguanine resistance) in human xeroderma pigmentosum fibroblasts *in vitro*.

Acrolein did not induce DNA–protein cross-links in nasal mucosa of rats exposed by inhalation *in vivo*. It did not induce dominant lethal mutations in mice after males were treated on a single occasion by intraperitoneal injection.

# 5. Summary and Evaluation

## 5.1 Exposure data

Acrolein has been produced commercially since the 1940s. It is used mainly in the production of acrylic acid, a starting material for acrylate polymers. It is also used in the production of DL-methionine and as a herbicide and slimicide.

Acrolein occurs naturally in foods and is formed during the combustion of fossil fuels (including engine exhausts), wood and tobacco and during the heating of cooking oils. Human exposure occurs from these sources and during its production and use.

## 5.2 Human carcinogenicity data

The available data were inadequate to form the basis for an evaluation of the carcinogenicity of acrolein to humans.

## 5.3 Animal carcinogenicity data

Acrolein was tested for carcinogenicity in one experiment in mice and in two experiments in rats by oral administration. No increase in tumour incidence was observed in mice or in rats in the one adequate study.

An increased incidence of urinary bladder papillomas was observed in rats receiving intraperitoneal injections of acrolein in combination with uracil in the diet.

### 5.4 Other relevant data

Acrolein is retained irreversibly in the respiratory tract after exposure by inhalation, probably because of its high tissue reactivity. Consequently, there is little, if any, distribution to other organs. Subcutaneous and oral exposure and long-term inhalation result in some systemic distribution and urinary excretion. Acrolein reacts readily with reduced glutathione, and this is the dominant detoxification pathway.

Acrolein is an intense irritant, and its irritancy may limit exposure to this substance. Repeated inhalation results in changes in the upper and lower respiratory tract. In dogs, acute congestion, changes in bronchiolar epithelial cells and emphysema were found after inhalation of the lowest dose tested.

No data were available on the effects of acrolein on human reproduction. No reproductive toxicity was seen in rats or rabbits treated with acrolein by gavage.

In single studies, acrolein did not induce DNA damage in rats or dominant lethal mutations in mice treated *in vivo*.

In cultured mammalian cells, acrolein induced gene mutation, sister chromatid exchange and DNA damage; weak induction of chromosomal aberrations was observed in one study.

Acrolein induced both somatic and germinal mutations in insects and DNA mutation and DNA damage in bacteria. DNA binding *in vitro* was observed in several studies.

### 5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of acrolein.

There is *inadequate evidence* in experimental animals for the carcinogenicity of acrolein.

#### Overall evaluation

Acrolein *is not classifiable as to its carcinogenicity to humans (Group 3).*

## 6. References

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[1] For definition of the italicized terms, see Preamble, pp. 22–26.

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