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Concise International Chemical Assessment Document 74

2-BUTENAL

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**World Health
Organization**

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are published by the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs have been developed from the Environmental Health Criteria documents (EHCs), more than 200 of which have been published since 1976 as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are usually based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all

possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170.¹

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart on page 2 shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Coordinator, IPCS, on the selection of chemicals for an IPCS risk assessment based on the following criteria:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, it is typical of a priority chemical that:

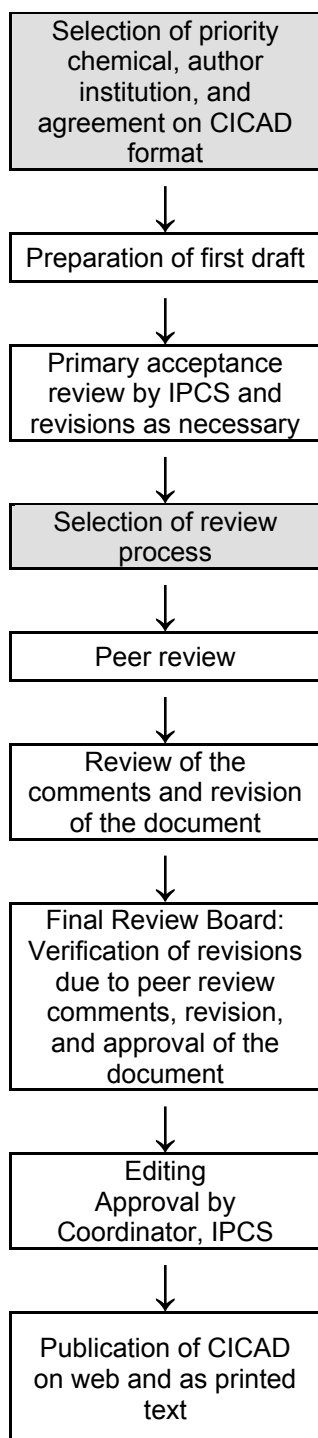
- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- there is significant international trade;
- it has high production volume;
- it has dispersive use.

The Steering Group will also advise IPCS on the appropriate form of the document (i.e. a standard CICAD or a de novo CICAD) and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

The first draft is usually based on an existing national, regional, or international review. When no appropriate source document is available, a CICAD may be produced de novo. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The

¹ International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits*. Geneva, World Health Organization (Environmental Health Criteria 170) (also available at <http://www.who.int/pcs/>).

CICAD PREPARATION FLOW CHART



Advice from Risk Assessment Steering Group

Criteria of priority:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, it is typical of a priority chemical that:

- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- there is significant international trade;
- the production volume is high;
- the use is dispersive.

Special emphasis is placed on avoiding duplication of effort by WHO and other international organizations.

A usual prerequisite of the production of a CICAD is the availability of a recent high-quality national/regional risk assessment document = source document. The source document and the CICAD may be produced in parallel. If the source document does not contain an environmental section, this may be produced de novo, provided it is not controversial. If no source document is available, IPCS may produce a de novo risk assessment document if the cost is justified.

Depending on the complexity and extent of controversy of the issues involved, the steering group may advise on different levels of peer review:

- standard IPCS Contact Points;
- above + specialized experts;
- above + consultative group.

first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments. At any stage in the international review process, a consultative group may be necessary to address specific areas of the science. When a CICAD is prepared *de novo*, a consultative group is normally convened.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This CICAD¹ on 2-butenal was prepared by the Fraunhofer Institute for Toxicology and Experimental Medicine, Hanover, Germany, and the German MAK Commission. It is based primarily on the BUA (1993) report and the German MAK Commission reports (MAK, 1981, 2007) on this compound. A comprehensive literature search of relevant databases was also conducted up to August 2006 to identify any relevant references published subsequent to those incorporated in these three reports. Information on the source documents and their peer review is presented in Appendix 2. Information on the peer review of this CICAD is presented in Appendix 3. This CICAD was considered and approved as an international assessment at a meeting of the 14th Final Review Board, held in Helsinki, Finland, on 26–29 March 2007. Participants at the Final Review Board meeting are presented in Appendix 4. The International Chemical Safety Card for 2-butenal (ICSC 0241), produced by IPCS (2003), has also been reproduced in this document.

This document is on 2-butenal. However, to enable an understanding and evaluation of this aldehyde in the context of environmental health, other aldehydes, such as formaldehyde, acetaldehyde, and acrolein, are mentioned for comparison, where necessary, in the relevant sections.

2-Butenal is an α,β -unsaturated aldehyde and consequently a very reactive compound. It is a chemical intermediate used chiefly in the manufacture of sorbates, solvents, and, to a lesser extent, pharmaceutical products and aroma chemicals.

2-Butenal is produced endogenously and is found in many food products up to the lower milligram per kilogram range as a result of enzymatic and abiotic (autoxidative, thermal) processes. Emissions into the atmosphere are from combustion — in particular, combustion of vehicle fuels, wood combustion, and tobacco smoking.

There were no studies specifically investigating the absorption and distribution of 2-butenal in experimental animals after its exogenous administration by any route. 2-Butenal is endogenously formed during lipid peroxidation. DNA and protein adducts have been found endogenously and after exogenous administration of 2-butenal in almost all investigated tissues (skin, liver, lung, kidney, intestinal epithelial cells) from rats and mice. Human DNA adducts have also been detected in human oral tissue.

¹ For a complete list of acronyms and abbreviations used in this report, the reader should refer to Appendix 1.

A general route of metabolism of 2-alkenals is oxidation to the corresponding acids by cytosolic and microsomal liver enzymes. However, 2-butenal is not easily oxidized by aldehyde dehydrogenase. The major detoxification pathway of 2-butenal is with glutathione to form glutathione conjugates. 3-Hydroxy-1-methylpropylmercapturic acid and small amounts of 2-carboxy-1-methylethylmercapturic acid were found in rat urine 24 h after subcutaneous injection of 2-butenal.

2-Butenal is acutely toxic (rat: oral LD₅₀ 200–300 mg/kg body weight; inhalation LC₅₀ 200–290 mg/m³; rabbit: dermal LD₅₀ 128–324 mg/kg body weight). After acute inhalation exposure, rats and mice exhibited respiratory and neurotoxic symptoms. At autopsy, effects on the lungs, heart, liver, and kidney were noted.

2-Butenal causes irritation and inflammation of the skin, respiratory tract, and eyes in humans and experimental animals. Its strong odour and irritancy may limit exposure to this substance.

Most studies identified a genotoxic potential of 2-butenal. 2-Butenal has given positive results in a range of *in vitro* tests for genotoxicity (gene mutation in bacteria, chromosomal aberrations in CHO cells, comet assay in mammalian cells). *In vivo* data on mutagenicity are limited. Negative results were obtained in a bone marrow micronucleus test in mice.

2-Butenal is a highly reactive compound. It reacts with cellular macromolecules and can form protein adducts and histone–DNA crosslinks. Like other α,β -unsaturated compounds, 2-butenal can form DNA adducts both *in vitro* and *in vivo* and therefore can be a source of DNA damage.

After long-term oral administration to rats, liver damage and induction of liver tumours were reported. However, the increases of hepatic neoplastic nodules and altered liver cell foci were not dose related, and only two doses were tested.

There is only limited information on the effects of 2-butenal on fertility. There is some suggestive evidence that 2-butenal reaches the germ cells. No studies on developmental toxicity were available.

The only epidemiological study available is a study of cancer incidence in a cohort of aldehyde production workers. The data were too limited, however, to permit any conclusions to be drawn with respect to 2-butenal.

In the evaluation of acrolein, also an α,β -unsaturated aldehyde and a highly reactive compound, non-neoplastic effects in the respiratory tract of experimental animals were considered critical for the derivation of a tolerable concentration. In the murine respiratory tract,

2-butenal was only slightly less irritating than acrolein and formaldehyde and comparable to these aldehydes in an *in vitro* test on inhibition of tracheal ciliary activity. The lowest concentration producing irritation of the mucous membranes of the respiratory tract and the eyes was specified as being 0.5 mg/m³ for humans, although other studies give higher values. No histopathological studies were reported for the respiratory tract for 2-butenal. There were no further short-term inhalation studies available, nor have there been any medium- or long-term inhalation studies.

Therefore, owing to a lack of reliable data, it is not possible to adequately evaluate the toxicity of 2-butenal in humans or to derive a tolerable concentration.

Concerning the ecotoxicological evaluation, in the aquatic compartment, 2-butenal is reported to be toxic to bacteria, freshwater and marine algae, water fleas (*Daphnia magna*), and fish.

2-Butenal is unlikely to partition out of the air when released into that medium, based on its physicochemical properties. The presence of 2-butenal in water or soil has rarely been reported. 2-Butenal is intrinsically biodegradable under aerobic and anaerobic conditions. There are no studies on bioaccumulation available. However, from its log *K*_{ow} of 0.63, no bioaccumulation of 2-butenal is expected. 2-Butenal is relatively stable in pure water but undergoes hydrolysis in the presence of water with low or high pH.

Therefore, the ecotoxicological assessment of 2-butenal should be focused on terrestrial organisms exposed to air. In the atmosphere, rapid photodegradation takes place by reaction with hydroxyl radicals and more slowly by reaction with nitrate radicals or ozone. Decomposition by direct photolysis does not occur. Since 2-butenal is not persistent in air, environmental effects are expected to be greatest in urban areas where traffic volume is high and continuous.

2-Butenal is fungicidal, with EC₅₀s given in one experiment of about 80 mg/m³. The parasitic fungi were about 5 times more sensitive than the respective host plants, wheat and barley (EC₅₀s about 400 mg/m³). Other types of plants (bean, tomato, cucumber, and begonia) were reported to be more sensitive, but no details were provided. Exposure of 10-day-old oat seedlings and 30-day-old alfalfa, endive, sugar beet, and spinach plants to 2-butenal at a concentration of 2.9 mg/m³ did not cause any damage to the leaves of these plants. Owing to the uncertainty of the other values, the value of 2.9 mg/m³ is taken as the NOEC.

Reported concentrations of 2-butenal in air are at maxima of 1 µg/m³ in tunnel studies and 10 µg/m³ in polluted cities. Considering the above data, these

concentrations of 2-butenal alone would not be expected to cause damage to plants. However, in environmental scenarios, this compound is always present together with other saturated aldehydes (e.g. formaldehyde and acetaldehyde) at higher (e.g. 30-fold) concentrations, as well as with unsaturated aldehydes (e.g. acrolein), so the effects due to 2-butenal are only a part of the combined effect.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

2-Butenal (also known as crotonaldehyde) is a clear, colourless to straw-coloured liquid with a strong, suffocating odour. Its empirical formula is C₄H₆O, and its structural formula is CH₃-CH=CH-CHO. Its molar mass is 70.09 g/mol. It is present to 96% in the *trans* configuration (D-*trans*-2-butenal) and 4% in the *cis* configuration (D-*cis*-2-butenal) (Figure 1) (Hoechst AG, 1984). The market product (CAS No. 4170-30-3) consists of more than 95% of the *trans* form (CAS No. 123-73-9). The *cis* form (CAS No. 15798-64-8) has hardly been characterized toxicologically (BUA, 1993). The technical product has a purity of 99.8%.

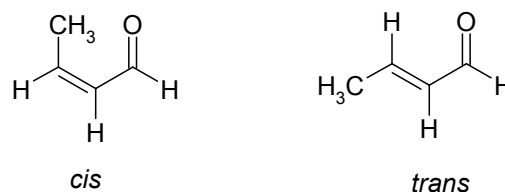


Figure 1: Structure of 2-butenal

The physicochemical properties of 2-butenal are summarized in Table 1. Additional physicochemical properties for 2-butenal are presented in the International Chemical Safety Card (ICSC 0241) reproduced in this document. Amoores & Hautala (1983) give the odour threshold as 0.35 mg/m³. The conversion factors¹ for 2-butenal in air (101.3 kPa and 20 °C) are as follows: 1 ppm = 2.91 mg/m³; 1 mg/m³ = 0.344 ppm.

¹ In keeping with WHO policy, which is to provide measurements in SI units, all concentrations of gaseous chemicals in air will be given in SI units in the CICAD series. Where the original study or source document has provided concentrations in SI units, these will be cited here. Where the original study or source document has provided concentrations in volumetric units, conversions will be done using the conversion factors given here, assuming a temperature of 20 °C and a pressure of 101.3 kPa. Conversions are to no more than two significant digits.

Table 1: Physical and chemical properties of 2-butenal.

Property	Value	Reference
Solidification point	-76.6 °C	Dolliver et al. (1938)
Boiling point (at 101.3 kPa)	102.4	Hoechst AG (1991b)
Vapour density	2.41 (air = 1)	Sax et al. (1984)
Vapour pressure at 20 °C	4 kPa	Rinehart (1967)
Solubility in water at 20 °C	150 g/l	Coulson & Crowell (1952)
	181 g/l	Fernandez & Solomons (1962)
Solubility in water at 5 °C	192 g/l	Fernandez & Solomons (1962)
Solubility of water in 2-butenal at 20 °C	95 g/kg	Fernandez & Solomons (1962)
Henry's law constant at 25 °C	1.983 Pa·m ³ /mol	Buttery et al. (1971)
Log <i>n</i> -octanol/water partition coefficient (log <i>K</i> _{ow})	0.63 (calculated)	Hoechst AG (1991b)

With water at normal pressure, 2-butenal forms an azeotrope with 24.8% water (by weight), which boils at 84 °C (Schulz et al., 2000). 2-Butenal dissolves well in organic solvents, such as alcohols, benzene, and diethyl ether (Hoechst AG, 1991a).

2-Butenal is an α,β -unsaturated aldehyde and consequently a very reactive compound. The wide spectrum of reactions comprises those on the carbonyl group and on the carbon-carbon double bond, with formation of 1,2-adducts as well as 1,4-adducts, on the basis of the conjugation with the carbonyl function. Reactions also occur on the methyl group, activated by the carbonyl group via the carbon-carbon double bond (BUA, 1993).

3. ANALYTICAL METHODS

3.1 Ambient air

The traditional method to measure carbonyls relies on derivatization with DNPH followed by separation and detection of hydrazones with HPLC and UV-visible absorption. These methods are of limited use for unsaturated compounds owing to the formation of unstable derivatives, co-elution of similar compounds, long sample collection times, and ozone interferences that result in poor sensitivity, selectivity, and reproducibility (Seaman et al., 2006). Therefore, it is expected that the DNPH method underestimates acrolein, 2-butenal, and other carbonyls of environmental concern. Methods are being refined to overcome these limitations — for example, using water-soluble carbonyl-bisulfite adducts, *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine, and *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine/bis(trimethylsilyl)trifluoroacetamide together with GC ion trap MS (Destailats et al., 2002; Seaman et al., 2006).

In the two highway tunnels study described in section 6.1.1.1, air downstream of potassium iodide oxidant scrubbers was sampled on silica gel cartridges coated with DNPH. Carbonyls were identified as their DNPH derivatives by LC with detection by diode array, UV-visible spectroscopy and atmospheric pressure negative ion chemical ionization MS (Grosjean et al., 1999; Grosjean & Grosjean, 2002).

3.2 Emission studies

The determination of carbonyl compounds in exhaust gas samples is usually accomplished by enrichment methods in which DNPH as a derivatization reagent has become established to a large extent. However, DNPH derivatives as well as DNPH are also decomposed by nitrogen dioxide, and the hydrazones of unsaturated carbonyl compounds are particularly sensitive. An HPLC method or modified procedure of handling enriched DNPH cartridges was described that would make GC analysis of hydrazones possible (Lange & Eckhoff, 1996).

Carbonyl compounds in mainstream cigarette smoke were measured after derivatization with DNPH followed by GC/MS (Dong & Moldoveanu, 2004).

In the series of studies on emissions (Schauer et al., 1999a, 1999b, 2001, 2002a, 2002b; see section 4.2.3), samples were collected on two DNPH-impregnated C₁₈ cartridges operating in series. Identification and quantification were by GC/MS (Grosjean & Grosjean, 1995; Schauer et al., 1999a).

3.3 Passive sampling

In the last few years, passive samplers for 2-butenal and other regulated workplace aldehydes using, for example, DNPH and HPLC have been evaluated (Otson et al., 1993; Liu et al., 2001), and new ones have been developed. These include passive samplers employing *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine methods

(Tsai & Hee, 1999) and those employing dansyl-hydrazine-coated solid sorbent (Zhang et al., 2000). The latter give a detection limit for 2-butenal of 13 pg (with a concentration range of 3.6–110 $\mu\text{g}/\text{m}^3$) compared with 577 pg using the DNPH method (Zhang et al., 2000).

3.4 Dust

2-Butenal was measured in dust samples using GC–UV spectrometry (Nilsson et al., 2005) or headspace sampling together with GC/MS analysis (Wolkoff & Wilkins, 1994).

3.5 Water

A method described for the determination of low-relative-molecular-mass aldehydes formed by the ozonation of drinking-water, including 2-butenal, involves derivatization with *O*-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine and analysis by high-resolution capillary GC. The limits of detection with GC–electron capture detection and GC/MS with ion selective monitoring were 1.2 and 11.2 $\mu\text{g}/\text{l}$, respectively (Glaze et al., 1989).

3.6 Biological samples

2-Butenal has been detected (1 in 12 samples) in human milk using capillary GC/MS after enrichment on Tenax and thermal desorption onto the GC column. No detection limit was given (Pellizzari et al., 1982).

Zlatkis et al. (1980) reported the detection of 2-butenal in human sera using a transelevator procedure to obtain sample extracts followed by GC. Identification was by MS. Fluorescence derivatization has been developed as a method for the determination of the Michael adducts of α,β -unsaturated aldehydes in pharmaceutical preparations and in biological material. It is based on the reaction of the carbonyl groups with dansylhydrazine using thin-layer chromatography with subsequent fluorodensitometric evaluation. The detection limit in blood is given as 20 $\mu\text{g}/\text{ml}$.

Scherer et al. (2006) developed an LC/MS/MS method for the detection of the 2-butenal metabolite 3-hydroxy-1-methylpropylmercapturic acid in human urine. The limit of detection and limit of quantification were 28 and 92 ng/ml, respectively.

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

4.1 Natural sources

2-Butenal is produced endogenously from lipid peroxidation, a process involving the oxidation of polyunsaturated fatty acids, which are basic components of biological membranes. It occurs naturally in many fruits, vegetables, and other foods (see section 6.1.4).

4.2 Anthropogenic sources

4.2.1 Production

2-Butenal is generally produced in a closed unit by the aldol condensation of acetaldehyde with a catalyst to aldol (3-hydroxybutanal) and subsequent cleavage of water and then purification by rectification (Blau et al., 1987).

4.2.2 Uses

2-Butenal is used mainly in the manufacture of sorbic acid (*trans,trans*-2,4-hexadienoic acid), which is a food preservative. Most producers use 2-butenal as an intermediate, so the market for this compound is small (Blau et al., 1987; ATSDR, 2002). According to the German manufacturer, the pattern of use in Germany is as follows: for the manufacture of sorbic acid, ~50%; trimethylhydroquinone, ~30%; 3-methoxybutanol, ~20%; and other products, 1% (mostly for processing quinoline derivatives, pharmaceutical products, and aroma chemicals) (BUA, 1993). According to the German manufacturer, <10 000 t of 2-butenal was produced in Germany in 1990, and <500 t of this amount was exported.

It is estimated that the world production of sorbic acid is about 38 000 t. Most of the production capacity is located in Europe, China, and Japan. The only producer in the USA closed its production factory in 2000 (Anonymous, 2002).

2-Butenal has been used as a warning agent in fuel gases, for locating breaks and leaks in pipes. It has been used as an alcohol denaturant, as a stabilizer for tetraethyl lead, in the preparation of rubber accelerators, and in leather tanning (IARC, 1995).

4.2.3 Other anthropogenic sources

2-Butenal is formed during incomplete combustion and pyrolysis of organic substances, in particular during combustion of fuels in gasoline- and diesel-powered engines, wood combustion, and tobacco smoking.

Table 2: Carbonyl emission profiles from gasoline and diesel vehicle tailpipe emissions.

Compound	Emission profile, mg/km (% of carbonyls)					
	Non-catalyst-equipped gasoline-powered motor vehicle ^a	Catalyst-equipped gasoline-powered motor vehicle ^b	Diesel-powered medium-duty truck emissions ^c	Heavy-duty diesel engine ^d	Catalyst-equipped light-duty diesel vehicle ^e	Spark ignition engine ^f
Formaldehyde	884 (44)	8.7 (42)	22.3 (16)	44.5 (48)	9.2 (54)	(31.5)
Acetaldehyde	301 (15)	3.9 (19)	41.8 (31)	15.5 (17)	3.5 (20)	(9.4)
2-Butenal	114 (5.7)	1.8 (1.8)	13.4 (10)	1.9 (2)	0.65 (3.8)	(1.9)
Acrolein	3.8 (2)	0.06 (0.3)	3.4 (2.5)	1.3 (1.4)	Not given	(8.9)
Total carbonyls (aldehydes + ketones)	2009 (100)	20.5 (100)	136 (100)	92 (100)	17 (100)	(100)

^a Using California reformulated gasoline; on-road fleet of two automobiles (1969, 1970) (Schauer et al., 2002a).

^b Using California reformulated gasoline; on-road fleet of three light-duty trucks and six automobiles (1981–1994) (Schauer et al., 2002a).

^c Using California reformulated diesel fuel; 1995 model truck (Schauer et al., 1999b).

^d Using European diesel fuel (Westerholm et al., 2001).

^e Using European diesel fuel; 1992 model (Siegl et al., 1999).

^f Using nine synthetic fuels and eight oxygenated fuels (Zervas et al., 2002).

4.2.3.1 Formation during combustion of fuels in gasoline- and diesel-powered engines

The emission of 2-butenal (together with other aldehydes) through the exhaust gases of motor vehicles with gasoline- and diesel-powered engines is well documented. The emission values for cars with gasoline engines (production years 1960–1982) were in the range of 0.26–3.87 mg/m³ exhaust gas and <0.125–40.5 mg/km (BUA, 1993).

The emission values for cars with diesel engines (production years 1972–1982) were in the range of 0.02–3.2 mg/m³ exhaust gas and 0.625–6.2 mg/km. For trucks, values up to 17 mg/m³ and 7 mg/km were determined under fuel economy test conditions (BUA, 1993). Emissions determined under the United States federal test procedure conditions for Volkswagen automobiles as of model year 1987 were 0.03–0.125 mg/km for cars with a gasoline-fuelled engine and a catalyst and 0.5–1.56 mg/km for cars with a diesel engine (BUA, 1993). Details of older studies on emissions of 2-butenal from vehicle engines are given in BUA (1993).

In an effort to reduce the emissions of air pollutants, both motor vehicle designs and gasoline formulations changed during the 1980s and 1990s. Studies more recent than those cited in the BUA report are summarized in Table 2.

Formaldehyde, acetaldehyde, and aromatic aldehydes are by far the most abundant carbonyls in regular gasoline exhaust. Acetaldehyde dominates for all ethanol-blended fuels, and formaldehyde dominates for gasoline. Higher emission rates of 2-butenal (20–90%

higher) are seen for regular gasoline compared with aliphatic gasoline, suggesting that olefins or aromatics (1-hexene, cyclohexane, *n*-hexane, and *n*-octane) are the main sources of formation of these carbonyls (Magnusson et al., 2002; Schauer et al., 2002a; Zervas et al., 2002).

Table 2 shows the results of an experiment in which gas- and particle-phase organic compounds were determined in the tailpipe emissions from an in-use fleet of gasoline-powered automobiles and light-duty trucks. Catalyst-equipped vehicles were compared with non-catalyst-equipped vehicles, showing, for example, a 100-fold reduction in carbonyl compounds (see Table 2; Schauer et al., 2002a). A previous study quantified tailpipe emissions from late-model medium-duty diesel trucks. When all C1–C13 carbonyls are combined, they account for 60% of the gas-phase organic compound mass emissions (Schauer et al., 1999b).

In all these studies, 2-butenal is emitted in the gas phase at much lower concentrations than formaldehyde or acetaldehyde, but in general at higher concentrations than acrolein.

2-Butenal not only is present in the vapour phase of vehicle exhaust but has also been detected (0–67 ng/mg) in fine particulate matter (PM_{2.5} particles) emitted from heavy-duty trucks and light-duty automobiles from the Caldecott tunnel, California, USA (Rao et al., 2001).

4.2.3.2 Formation during wood combustion

2-Butenal was detected in the smoke formed by the incomplete combustion of wood that was also, in many cases, used for the smoke preservation of foods (BUA,

1993). 2-Butenal emissions of 6–116 mg/kg wood were calculated during the combustion of cedar, oak, and ash wood (with water contents of <5–20%) in an open fireplace (Lipari et al., 1984). The results of Schauer et al. (2001) (see Table 3) give somewhat higher values (177–276 mg/kg wood). 2-Butenal is emitted at lower concentrations than formaldehyde or acetaldehyde but at higher concentrations than acrolein.

Table 3: Rates of emission of organic compounds from the combustion of wood in fireplaces.^a

Compound	Emission rate (mg/kg wood burned)		
	Pine	Oak	Eucalyptus
Formaldehyde	1165	759	599
Acetaldehyde	1704	823	1021
2-Butenal	276	177	198
Acrolein	63	44	56

^a From Schauer et al. (2001).

4.2.3.3 Formation during cooking processes

Organic compound emission rates were measured from hamburger meat charbroiling over a natural gas-fired grill in the USA (Schauer et al., 1999a). For the carbonyls formaldehyde, acetaldehyde, and 2-butenal, values of 1382, 1092, and 495 mg/kg meat cooked were given. Table 4 shows emissions of carbonyls from cookstoves.

In the study of Zhang & Smith (1999), background indoor concentrations were 3.2 µg/m³ for formaldehyde, 2.0 µg/m³ for acetaldehyde, and below the detection limit for all other measured carbonyls.

Stir frying of vegetables in soybean oil or canola oil released 29.1 mg and 24.1 mg 2-butenal, respectively, into the gas phase per kilogram of vegetables cooked. Deep frying of potatoes in hydrogenated oil released 5.2 mg 2-butenal/kg potatoes cooked (Schauer et al., 2002b).

Table 4: Carbonyl emission factors reported in a summary of a survey of 22 types of fuel/stove combinations in China.^a

Compound	Carbonyl emission factors (mg/kg)						
	Crop residue	Wood	Coal	Kerosene	LPG	Coal gas	Natural gas
Formaldehyde	78.3	135	18.5	94.3	118	28.3	66.3
Acetaldehyde	85.1	141	19.7	85.8	166	14.7	36.7
Acrolein	101	12.6	–	14.4	27.1	–	5.5
2-Butenal	18.1	32.3	16.1	31.1	60.2	3.4	13.0
Total carbonyls	399	525	43.3	344	573	46.2	150

LPG, liquefied petroleum gas.

^a From Zhang & Smith (1999).

4.2.3.4 Formation during tobacco smoking

The presence of 2-butenal in tobacco smoke is well documented. It is one of the 44 “Hoffmann analytes” in mainstream smoke that are believed to be relevant to smoking-related disease (Borgerding & Klus, 2005). The amount of 2-butenal formed during smoking ranged from 17 to 77 mg/kg tobacco (BUA, 1993).

2-Butenal concentrations of 40 mg/m³ (Newsome et al., 1965) and 60 mg/m³ (Mold & McRae, 1957) were measured in mainstream tobacco smoke. A cellulose acetate filter with activated charcoal reduced the 2-butenal concentration from 40 to 7.5 mg/m³, whereas a filter without charcoal did not cause any reduction (Newsome et al., 1965).

The results of more recent studies on carbonyl compounds in mainstream cigarette smoke are given in Table 5. In these studies, the predominant saturated aldehyde was acetaldehyde, and the predominant unsaturated aldehyde was acrolein (Dong & Moldoveanu, 2004; Lambert et al., 2005).

Yields of 2-butenal were reduced by over 25% in all six varieties of “light” cigarettes compared with regular cigarettes (Gendreau & Vitaro, 2005). Lambert et al. (2005) found that levels of aldehydes emitted were reduced 10-fold between high-tar and ultralow-tar extracts (Table 5).

4.3 Estimated global release

4.3.1 Emissions to the atmosphere

According to the German producer, about 4 kg of 2-butenal were emitted during the production and shipment of 2-butenal in 1990 (production volume <10 000 t). It was estimated that there was no release of 2-butenal during the production of sorbic acid, 3-methoxybutanol, or trimethylhydroquinone (BUA, 1993).

Table 5: Average concentrations of carbonyl compounds in mainstream cigarette smoke.

Compound	Reference cigarette (µg/cigarette) ^a	High tar cigarette (µmol/l) ^b	Ultralow tar cigarette (µmol/l) ^b
Acetaldehyde	620	1352	111
Acrolein	47	503	34
2-Butenal	18.5	101	2
Formaldehyde	23	Not given	Not given

^a Dong & Moldoveanu (2004).

^b Mean level from 10 experiments detected in extracts prepared from 1 cigarette bubbled through 10-ml phosphate-buffered saline (Lambert et al., 2005).

A traffic emission of 300–460 t of 2-butenal in the former Federal Republic of Germany was calculated for 1989 on the basis of the values from test engines given in the BUA (1993) report.

An emission of 140–2700 t could be projected for 1983 based on emissions of 0.006–0.116 g/kg wood and the annual wood fuel consumption in the USA (Lipari et al., 1984).

The worldwide production of tobacco in 1989 was about 7 million tonnes (BUA, 1993). Assuming a 2-butenal formation of 17–77 µg/g tobacco, the amount of 2-butenal emitted by tobacco smoking would be in the range of 120–540 t in 1989 (BUA, 1993).

4.3.2 Emissions to the hydrosphere

According to the German producer, the 2-butenal load in sewage treatment plant influent was 2.15 t in 1990 (BUA, 1993). According to simulation tests regarding biodegradability or elimination, 2-butenal can be more than 90% eliminated in an industrial sewage treatment plant. Therefore, it was calculated that <215 kg were discharged into the environment in 1990 during 2-butenal production in Germany (BUA, 1993).

In 1990, the 2-butenal load in wastewater resulting from sorbic acid production was 21 t prior to treatment in a biological wastewater treatment plant. On the basis of an elimination rate of >90%, <2.1 t was therefore released into the environment during processing of 2-butenal in Germany. No detectable emissions into wastewater were reported for both 3-methoxybutanol and trimethylhydroquinone.

The main introduction into the hydrosphere of <17 t 2-butenal takes place during the manufacture of acetaldehyde, from which 2-butenal is formed as a by-product according to its technical manufacturing process.

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, TRANSFORMATION, AND ACCUMULATION

5.1 Transport and distribution between media

Buttery et al. (1971) experimentally determined an air/water partition coefficient of 8×10^{-4} at 25 °C, which corresponds to a Henry's law constant of 1.98 Pa·m³/mol. Other calculated values range from 1.87 to 2.92 Pa·m³/mol at 20 °C. 2-Butenal is considered to be a moderately volatile substance from aqueous solution.

The log K_{ow} is calculated to be 0.63 (BUA, 1993).

Only a low sorption of 2-butenal onto soils is expected on the basis of its physicochemical properties.

5.2 Transformation

There are indications of ready biodegradability of 2-butenal at concentrations atoxic to bacteria. Under aerobic conditions, 2-butenal is first oxidized to *trans*-2-butenic acid, which is then further degraded at a lower rate. Under anaerobic conditions, the first products of biotransformation are 2-butenol or butanol (BUA, 1994).

2-Butenal is relatively stable in pure water but undergoes hydrolysis in water at low or high pH until attaining equilibrium with 3-hydroxybutanal, which is in turn in equilibrium with acetaldehyde (BUA, 1994). 2-Butenal in an aqueous solution is hardly or only very slowly degraded photochemically with light of wavelength >290 nm (Hirschberg & Farkas, 1937).

In the atmosphere, decomposition by direct photolysis does not occur (BUA, 1993). However, rapid photodegradation takes place by reaction with photochemically produced hydroxyl radicals. The half-life is calculated to be 11 h (BUA, 1993) and, more recently, 8 h (Thévenet et al., 2000) from measured reaction rate constants and typical tropospheric concentrations of the species (see Table 6). Likewise, for reactions with nitrate radicals or ozone, atmospheric half-lives were calculated from measured reaction rate constants to be 1.6 and 13 days, respectively (BUA, 1993), and 4.5 and 5.5 days, respectively (Thévenet et al., 2000) (see Table 6). The lifetime of 2-butenal with respect to chlorine was calculated to be 44 days (Thévenet et al., 2000).

Table 6: Rate constants and lifetimes of 2-butenal with potential atmospheric oxidants.^a

Potential atmospheric oxidants (X)	Rate constants (k) at 298 K (cm ³ /molecule per second)	Typical tropospheric concentrations of X (/cm ³)	Calculated lifetimes for 2-butenal with respect to X
Hydroxyl radicals	3.35×10^{-11}	1×10^6	8 h
Nitrate radicals	5.1×10^{-15} ^b	5×10^8	109 h (4.5 days)
Chlorine	2.6×10^{-10}	1×10^3	44 days
Ozone	1.74×10^{-18} ^c	1.25×10^{12}	133 h (5.5 days)

^a Data from Thévenet et al. (2000).

^b From Atkinson et al. (1987).

^c From Grosjean & Grosjean (1998).

5.3 Accumulation

There are no studies available on the bioaccumulation of 2-butenal. Bioaccumulation is not expected on the basis of the (calculated) log K_{ow} of 0.63.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

6.1.1 Atmosphere

6.1.1.1 Ambient air

Acetaldehyde, formaldehyde, and acetone, the most abundant carbonyls generated by vehicle emissions, were present in ambient air at concentrations nearly 1 order of magnitude higher than concentrations of acrolein or 2-butenal (Grosjean & Grosjean, 2001). Formaldehyde is the most abundant carbonyl in ambient air in cities worldwide. However, in some countries (e.g. Brazil), there has been, in the past, extensive use of ethanol in vehicle fuels. The combustion of ethanol leads to acetaldehyde as a major product. As a result, acetaldehyde is often the most abundant carbonyl in urban air in these countries.

The α,β -unsaturated aldehydes 2-butenal and acrolein are both highly reactive and capable of being subjected to relatively rapid physical and chemical degradation (see section 5.2). This is one of the reasons that these unsaturated carbonyls are typically present at lower concentrations in the atmosphere. The reactive nature of these compounds also makes measurements more difficult (Zhang et al., 2003).

In 1983, measurements of air samples in the USA taken for 1 h during the rush-hour on 4 days at six sites along a six-lane municipal highway showed that 3–3.7% of the carbon from the aldehyde fraction originated from 2-butenal. Average concentrations of 2-butenal in the direct vicinity of the highway (1 m from the roadside at a height of 1.5 m) were 1.1–2.1 $\mu\text{g}/\text{m}^3$ (Zweidinger et al., 1988).

2-Butenal was one of 221 organic compounds detected in a roadway tunnel in Los Angeles, California, USA, in 1993 (emission rate 20 mg/l; cf. formaldehyde 128 mg/l, acetaldehyde 29 mg/l) (Fraser et al., 1998).

Air samples were collected at the inlet and outlet of two highway tunnels — Caldecott tunnel, near San Francisco, California, USA, in July–August 1999 (mostly light-duty vehicles using reformulated gasoline), and the Tuscarora Mountain tunnel in Pennsylvania, USA (light-duty and heavy-duty diesel trucks), in May 1999 (see Table 7). About 100 carbonyls were identified. 2-Butenal was one of the 10 most abundant carbonyls measured. Formaldehyde was the most abundant carbonyl measured (e.g. 45.4% in Caldecott tunnel) (Grosjean & Grosjean, 2001, 2002).

Table 7: Concentrations of carbonyls in air samples at the inlet and outlet of the Tuscarora Mountain tunnel in Pennsylvania, USA, in May 1999 (light-duty and heavy-duty diesel trucks) and the Caldecott tunnel near San Francisco, California, USA, in July–August 1999 (mostly light-duty vehicles).

Carbonyl	Concentrations ($\mu\text{g}/\text{m}^3$)		
	Inlet	Outlet	Outlet minus inlet
Tuscarora Mountain tunnel			
Formaldehyde	1.72	4.6	2.99
Acetaldehyde	1.12	2.25	1.18
2-Butenal	0.12	0.44	0.32
Acrolein	0.10	0.31	0.22
Caldecott tunnel			
Formaldehyde	5.0	20.5	15.5
Acetaldehyde	1.5	5.5	3.99
2-Butenal	0.23	0.76	0.54
Acrolein	0.08	0.60	0.52

Acrolein, 2-butenal, and other airborne carbonyls were detected in ambient air at the Oakland–San Francisco Bay Bridge (California, USA) toll booth plaza in 2001 during three periods of rush-hour traffic: 3:00 pm to 7:00 pm (23 April), 6:00 am to 10:00 am (24 April), and 3:00 pm to 7:00 pm (24 April) (Table 8) (Destailats et al., 2002). The concentrations measured reflect the emission of these compounds in vehicle traffic and their possible photochemical degradation during the daytime in the presence of nitrogen oxides and ozone (see section 5.2).

Table 8: Measurements of acrolein and 2-butenal detected in ambient air at the Oakland–San Francisco Bay Bridge toll booth plaza^a

Time period	Mean concentration ($\mu\text{g}/\text{m}^3$)	
	Acrolein	2-Butenal
3:00–7:00 pm, 23 April 2001	0.032	0.061
6:00–10:00 am, 24 April 2001	0.100	0.147
3:00–7:00 pm, 24 April 2001	0.058	0.093

^a From Destailats et al. (2002).

Table 9 summarizes the levels of 2-butenal and other carbonyls measured in some urban environments.

2-Butenal was one of the aldehydes and ketones studied in a long-term study at urban (Leipzig) and rural (Melpitz) sites in Saxony, (eastern) Germany. Until 1990, this was the most polluted region in Germany (Müller, 1997). Increased levels of formaldehyde together with 2-butenal demonstrate the influence of traffic on aldehyde levels in the air. In Leipzig, in winter 1993–94, mixing ratios (ratio of the mass of a variable atmospheric constituent to the mass of dry air) of a maximum 0.55 ppb were measured for 2-butenal (compared with nearly 30 ppb for formaldehyde). Daily variations in 2-butenal concentrations were also measured, giving peaks during the day, especially at rush-hour times.

Table 10 shows the mean concentrations of some carbonyls measured outside 87 residences in Elizabeth, New Jersey, USA, throughout 1999–2001. Only 55.1% of the samples for 2-butenal and 59.4% for acrolein were above the method detection limits (using the passive aldehydes and ketone sampler and analysed using an HPLC fluorescence method). In contrast to the other carbonyls, 2-butenal showed no apparent secondary production or losses. Traffic sources contributed significantly to the ambient levels of 2-butenal measured (Liu et al., 2006).

6.1.1.2 Indoor air

2-Butenal was detected in samples of household floor dust (quantitative values not given; Wolkoff & Wilkins, 1994). 2-Butenal was detected in 310 samples of household dust in 389 residences in Sweden (0.01–10 $\mu\text{g}/\text{g}$; mean 0.9 $\mu\text{g}/\text{g}$) (Nilsson et al., 2005).

6.1.1.3 Workplace air

In a 2-butenal production and processing plant (sorbic acid) in Germany, 2-butenal was not detectable in 15 personal samples (detection limit 1.5 mg/m^3) from 1987 to 1990. 2-Butenal was occasionally measured in dispatch facilities for 2-butenal and in an acetaldehyde production plant at a time-weighted average concentration (8 h) of $\leq 0.6 \text{ mg}/\text{m}^3$ (BUA, 1993).

In a dye and pigment plant in the USA, concentrations of 2-butenal up to 3.2 mg/m^3 in workplace air were measured in 1982 (NIOSH, 1982).

In a study carried out on 37 subjects, including 22 garage workers (9 smokers and 13 non-smokers) and 15 non-garage workers as controls (4 smokers and 11 non-smokers), daily exposure was estimated using 48-h integrated measurements of breathing-zone concentrations (passive carbonyl sampler and HPLC fluorescence analysis technique). Breathing-zone concentrations were observed for a wide variety of chemicals, including the following carbonyls: formaldehyde (14.1–80.1 $\mu\text{g}/\text{m}^3$), acetaldehyde (8.41–80.3 $\mu\text{g}/\text{m}^3$), acrolein (<0.14 –3.71 $\mu\text{g}/\text{m}^3$), and 2-butenal (<0.13 –2.80 $\mu\text{g}/\text{m}^3$). The garage workers were exposed to significantly higher levels of formaldehyde and acetaldehyde in the breathing zone compared with the controls, and the smokers were similarly exposed to significantly higher levels of acetaldehyde than were the non-smokers ($P < 0.10$). Both garage employment and

Table 9: Recent measurements of 2-butenal and other carbonyls in select cities.

Compound	Concentrations ($\mu\text{g}/\text{m}^3$)			
	Range of values at three sites (November 2002) in Santiago de Chile, Chile (Rappenglück et al., 2005)	Averages of maxima during 6 spring days (November 2003) at downtown Santiago de Chile, Chile (Rubio et al., 2006)	Three-hour samples averaged over 1 year (October 1999 – October 2000) in Rio de Janeiro, Brazil (Grosjean et al., 2002)	Range of values at three sites (June–December 2000) in Athens, Greece (Bakeas et al., 2003)
Formaldehyde	1.7–15	11.3	10.84	0.05–39
Acetaldehyde	3.5–21	8.7	10.43	4.3–49
Acrolein	Not identified	Not identified	0.82	Not analysed
2-Butenal	0.32–1.89	1.6	0.30	0.9–8.7

Table 10: Mean concentrations of some carbonyls measured outside 87 residences in Elizabeth, New Jersey, USA, throughout 1999–2001.

Carbonyl	Mean concentration ($\mu\text{g}/\text{m}^3$)			
	Spring	Summer	Autumn	Winter
Formaldehyde	7.1	5.2	6.3	7.6
Acetaldehyde	9.3	9.1	11.6	4.8
Acrolein	1.9	1.0	0.4	0.7
2-Butenal	0.2	0.5	0.3	0.4

smoking appeared to increase the breathing-zone concentrations of 2-butenal. The authors noted that the method was not optimal for measuring acrolein and 2-butenal, so the concentrations of these carbonyls may have actually been higher (Zhang et al., 2003).

6.1.2 Hydrosphere

There were no quantitative data available on 2-butenal levels in the hydrosphere.

6.1.3 Geosphere

There were no data available on 2-butenal levels in the geosphere.

6.1.4 Biosphere

6.1.4.1 Occurrence in plants

The natural formation of 2-butenal was qualitatively detected in various fresh parts of numerous plants and after their treatment (drying, roasting) (BUA, 1993) (see also Table 11).

6.1.4.2 Occurrence in food

In many studies, 2-butenal could be qualitatively and, in some reports, quantitatively detected in untreated and, especially, prepared muscle meat and in autoxidized fish oil (BUA, 1993) (see also Table 11).

2-Butenal occurs naturally in many fruits and foods (BUA, 1993; Table 11). In another food survey, the following values were given: fruits (e.g. apples, guavas, grapes, strawberries, and tomatoes), concentrations below 0.01 mg/kg; vegetables (e.g. cabbage, carrots, celery leaves, cauliflower, and Brussels sprouts), concentrations ranging from 0.02 to 0.1 mg/kg; bread, cheese, meat, and fish, 0–0.04 mg/kg; milk and beer, 0–0.04 mg/l; and wine, 0–0.7 mg/l (Feron et al., 1991).

6.1.4.3 Occurrence in humans

2-Butenal has been identified in normal human serum by GC/MS analysis (Zlatkis et al., 1980).

2-Butenal has been qualitatively detected (1 in 12 samples) in human milk samples of women living in four cities in the USA (Pellizzari et al., 1982).

After inhalation of air purified by activated charcoal, 2-butenal was qualitatively detected in the expired air of 20 of 62 examined male and female test individuals who were non-smokers living in Chicago, Illinois, USA, or its suburbs (Krotoszynski & O'Neill, 1982).

6.2 Human exposure

Humans are exposed to 2-butenal through a number of routes, which are summarized in Table 11, together

Table 11: Human exposure to 2-butenal and estimated daily intake.^a

Source	Concentration	Estimated daily intake, $\mu\text{g}/65\text{-kg}$ body weight (intake assumption)	References
Air 1 m from highway	1–2 $\mu\text{g}/\text{m}^3$	0.5 (24-h inhalation)	Zweidinger et al. (1988)
Air, workplace ^b (production)	300–600 $\mu\text{g}/\text{m}^3$	22–44	BUA (1993)
Tobacco smoke	72–228 $\mu\text{g}/\text{cigarette}$	33–105 (30 cigarettes/day)	Vickroy (1976); Kuwata et al. (1979)
Fruit and vegetables	1.4–100 $\mu\text{g}/\text{kg}$	0.01–0.77 (500 g/day)	Winter & Willhalm (1964); Linko et al. (1978)
Fish	71.4–100 $\mu\text{g}/\text{kg}$	0.28–3 (200 g/day)	Yurkowski & Bordeleau (1965); Yoshida et al. (1984)
Meat	10–270 $\mu\text{g}/\text{kg}$	0.03–0.83 (200 g/day)	Cantoni et al. (1969); Noleau & Toulemonde (1986)
Beer	0.8–20 $\mu\text{g}/\text{l}$	0.01–0.31 (1 litre/day)	Hashimoto & Eshima (1977); Greenhoff & Wheeler (1981)
Wine	300–700 $\mu\text{g}/\text{l}$	2.3–5.4 (0.5 litre/day)	Sponholz (1982)

^a Adapted from Eder et al. (1999).

^b Further data may be found in section 6.1.1.3.

with an estimated daily intake of this compound through each route for a 65-kg adult.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

7.1 Absorption and distribution

2-Butenal is formed endogenously during lipid peroxidation and forms protein and DNA adducts (Chung et al., 1996; Ichihashi et al., 2001; Luczaj & Skrzdewska, 2003).

There were no studies specifically studying the absorption and distribution of 2-butenal after its exogenous administration by any route.

However, protein and DNA adducts of 2-butenal have been found and studied in a large number of tissues in the body. DNA adducts have been found in almost all investigated tissues (skin, liver, lung, kidney, brain, intestinal epithelial cells, and leukocytes) from rats and mice, showing the wide distribution of 2-butenal in the body with and without external administration of the compound (Nath & Chung, 1994; Eder et al., 1996, 1999; Nath et al., 1996). 2-Butenal–DNA adducts have been detected in human liver (Nath & Chung, 1994), leukocytes and mammary glands (Nath et al., 1996), and oral tissues (Chung et al., 1999).

2-Butenal strongly reacts with protein amino groups to form the stable protein-bound 2-butenal — for example, *N*^ε-(2,5-dimethyl-3-formyl-3,4-dehydro-piperidino)lysine adducts. These adducts have been found in glial cells (Kawaguchi-Niida et al., 2006). Protein-bound 2-butenal has also been identified in human skin (Hirao & Takahashi, 2005).

7.2 Metabolism

In general, aldehydes are readily metabolized by three principal routes: 1) oxidation to acids; 2) reduction to alcohols; and 3) conjugation with sulfhydryls, such as glutathione (Brabec, 1993). The reaction of alkenals with glutathione to form glutathione conjugates by Michael addition is a major detoxification pathway.

2-Butenal is not easily oxidized by aldehyde dehydrogenase (Cederbaum & Dicker, 1982; Dicker & Cederbaum, 1984; Mitchell & Petersen, 1993).

In vivo, the subcutaneous injection of 2-butenal leads to reduction of the glutathione level in the liver (Oguro et al., 1990). In vitro, 2-butenal reacts rapidly

with cellular sulfhydryl groups and glutathione directly and to a small degree by enzyme catalysis (Boyland & Chasseaud, 1967; Gray & Barnsley, 1971; Witz et al., 1987, 1988). In vitro studies show glutathione *S*-transferase-catalysed conjugation of glutathione with 2-butenal (Pal et al., 2000). This is confirmed by the presence of 3-hydroxy-1-methylpropylmercapturic acid (6–15% of the applied quantity) (Figure 2) and small amounts of 2-carboxy-1-methylethylmercapturic acid in rat urine 24 h after subcutaneous injection of 2-butenal (0.7 nmol/kg body weight, corresponding to about 53 mg/kg body weight) (Gray & Barnsley, 1971), indicating the addition of the thio group onto the double bond of 2-butenal, probably via a Michael addition (Tillian et al., 1985).

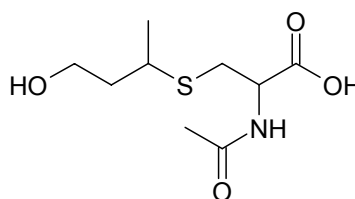


Figure 2: Structure of 3-hydroxy-1-methylpropylmercapturic acid

3-Hydroxy-1-methylpropylmercapturic acid was also detected in human urine in 39 regular cigarette smokers using a method developed by Scherer et al. (2006) (see section 9.2).

7.3 Mode of action

2-Butenal is a highly reactive compound owing to its aldehyde functional group and its olefinic double bond. It reacts with cellular macromolecules and can form protein adducts and histone–DNA crosslinks (Kurtz & Lloyd, 2003). Like other α,β -unsaturated compounds, 2-butenal can form DNA adducts and therefore can be a source of DNA damage (see section 8.5).

There is increasing evidence for the cytotoxicity of 2-butenal and other alkenals, which induce cell death by acute exposure of cells to oxidative stress through consumption of the antioxidant glutathione. Metabolically proficient cells rich in glutathione and glutathione *S*-transferase may be efficiently protected against the genotoxic effects of alkenals. However, reductions in glutathione cause a marked carbonylation of a wide range of cellular proteins and trigger carcinogenesis by chronic injury of DNA (Cooper et al., 1987; Eisenbrand et al., 1995). In isolated mouse hepatocytes, crotyl alcohol undergoes alcohol dehydrogenase-catalysed conversion to 2-butenal, the formation of which was

accompanied by marked glutathione depletion, protein carbonylation, and cell death (Fontaine et al., 2002).

8. EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS

8.1 Single exposure

2-Butenal is acutely toxic (rat: oral LD₅₀ 200–300 mg/kg body weight; inhalation LC₅₀ 200–290 mg/m³; rabbit: dermal LD₅₀ 128–324 mg/kg body weight) (see Table 12).

After acute inhalation exposure, rats and mice exhibited respiratory and neurotoxic symptoms, as well as decreased body weight gain (Rinehart, 1967). Pathological findings were haemorrhaging rhinitis, hyperaemias, and haemorrhages in the lung, heart, liver, and kidney (Skog, 1950; Kennedy & Graepel, 1991).

The subcutaneous application of 2-butenal in rats and mice resulted in excitation and pronounced reddening of the nose, ears, and feet, as well as tremor and convulsions (Skog, 1950). Intravenous administration caused respiratory symptoms in cats (Skog, 1952).

Dalhamn & Rosengren (1971) found that the effects and dosimetry of 2-butenal were comparable to those of acrolein and formaldehyde in terms of the inhibition of tracheal ciliary activity. Acetaldehyde was much less potent. 2-Butenal at a concentration of 5 mmol/l caused ciliostasis in chicken tracheal organ cultures after 5 min (cf. 1 min with acrolein) (Pettersson et al., 1982). In vitro inhibition of ciliary movement in sheep tracheal epithelium occurred at 25–35 ml/m³ (73–102 mg/m³) (cf. acrolein; Guillerm et al., 1967) (see also section 10.1).

8.2 Irritation and sensitization

The lowest concentration of 2-butenal producing irritation of the mucous membranes was specified as being 50 mg/m³ for the rabbit and 9 mg/m³ for the cat (Trofimov, 1962).

Among the α,β -unsaturated aldehydes, 2-butenal was among the more potent irritants to the murine respiratory tract, being only slightly less irritating than acrolein and formaldehyde. The concentration that reduces the respiratory rate to 50% was reported to be 10.0 mg/m³ in mice (cf. acrolein 2.3 mg/m³ and formaldehyde 3.6 mg/m³) (Steinhagen & Barrow, 1984) and 66.6 mg/m³ in rats (Babiuk et al., 1985). Unsaturated aldehydes are much more potent irritants

than saturated aldehydes (Schaper, 1993; Alarie et al., 1998).

The in vivo contraction of guinea-pig bronchial musculature was noted at 116–146 mg/m³ (Guillerm et al., 1967).

2-Butenal causes severe injury to the rabbit eye (Smyth & Carpenter, 1944); no further details were given.

8.3 Short-term and medium-term exposure

8.3.1 Oral exposure

Ten male and 10 female F344 rats each received oral doses of 2.5, 5, 10, 20, or 40 mg 2-butenal/kg body weight per day administered by gavage in corn oil over 13 weeks (Wolfe et al., 1987). Compound-related mortality was observed in rats of both sexes at doses of 5 mg/kg body weight per day and above. Mean body weights were significantly decreased for male rats in the 40 mg/kg body weight per day group at termination. Compound-related gross necropsy lesions (thickened forestomach or nodules) were observed in male and female rats at 20 and 40 mg/kg body weight per day. Microscopic lesions (hyperplasia of the forestomach epithelia) were observed in the stomach of the rats at 10 mg/kg body weight per day, and forestomach hyperkeratosis, ulcers, moderate necrosis, and acute inflammation were observed at 40 mg/kg body weight per day. Acute inflammation of the nasal cavity was noted in male rats at 20 and 40 mg/kg body weight per day and in female rats from 5 mg/kg body weight per day.

Ten male and 10 female B6C3F1 mice each received oral doses of 2.5, 5, 10, 20, or 40 mg 2-butenal/kg body weight per day administered by gavage in corn oil over 13 weeks (Wolfe et al., 1987). In contrast to the rats in the same study, all mice survived to termination, and no compound-related gross necropsy lesions were noted. Microscopic lesions (hyperplasia of the epithelial lining of the stomach) were observed only in the 40 mg/kg body weight per day group.

8.3.2 Inhalation exposure

After continuous inhalation exposure of rats and mice to 2-butenal for a period of 3 months, concentrations from 1.2 mg/m³ led to alterations of motor activity as well as of the haemoglobin content of blood (Voronin et al., 1982).

8.3.3 Other routes of exposure

A daily intraperitoneal treatment of NMRI mice with 75 mg 2-butenal/kg body weight for 5 days and a

Table 12: Data on LD₅₀ and LC₅₀ values of 2-butenal in various species.^a

Species	Application	Dose (mg/kg body weight)	Effect	Reference
Rat	Oral	300	LD ₅₀	Smyth & Carpenter (1944)
Rat	Oral	206	LD ₅₀	Voronin et al. (1982)
Mouse	Oral	98	LD ₅₀	Zhen et al. (1985)
Mouse	Oral	104	LD ₅₀	Voronin et al. (1982)
Rat	Intraperitoneal	70	LD ₅₀	Brabec (1993)
Rat	Subcutaneous	140	LD ₅₀	Skog (1950)
Mouse	Subcutaneous	160	LD ₅₀	Skog (1950)
Cat	Intravenous	30–40	Lethal	Skog (1952)
Rabbit	Dermal	128–170	LD ₅₀	Brabec (1993)
Rabbit	Dermal	324	LD ₅₀	Brabec (1993)
Guinea-pig	Dermal	~25	LD ₅₀	Smyth & Carpenter (1944)
Guinea-pig	Dermal	426–852	LD ₅₀	Brabec (1993)

Species	Application	Concentration (mg/m ³)	Effect	Reference
Rat	4-h inhalation	200	LC ₅₀	Voronin et al. (1982)
Rat	4-h inhalation	247	LC ₅₀	Rinehart (1967)
Rat	4-h inhalation	290	LC ₅₀	Kennedy & Graepel (1991)
Rat	0.5-h inhalation	4000	LC ₅₀	Skog (1950)
Mouse	2-h inhalation	1510	LC ₅₀	Trofimov (1962)
Mouse	2-h inhalation	580	LC ₅₀	Voronin et al. (1982)

LC₅₀, median lethal concentration; LD₅₀, median lethal dose.

^a From BUA (1993).

booster injection of 100 mg 2-butenal/kg body weight on the 8th day led to reduced body weights and thymus and spleen weights, accompanied by thymic necrosis and one splenic atrophy. The adrenal glands showed a weight increase. After the booster injection, the plasma total lactate dehydrogenase activity was measured and was found to increase, reaching a peak after about 10 h. Repeated injections caused a progressively less pronounced effect, indicating an acquired tolerance to the aldehyde. Similar results were found with acrolein and formaldehyde (Warholm et al., 1984).

8.4 Long-term exposure and carcinogenicity

In a drinking-water study performed for 113 weeks, groups of 23–27 male F344 rats were administered 0, 42, or 420 mg 2-butenal/l (corresponding to about 0, 2.1, or 15.75 mg/kg body weight per day) (Chung et al., 1986a). In the lower dose group, neoplastic lesions in the liver appeared in 9 of the 27 rats, and hepatocellular carcinomas were observed in 2 of 27 rats. Twenty-three of these 27 rats showed altered liver cell foci. In the higher dose group, reduction of body weight gain and moderate to extensive liver damage were reported in 10 of the 23 rats (fatty metamorphoses, focal liver necroses, fibroses, cholestases, and mononuclear cell infiltration); however, none of these animals showed any pre-neoplastic or neoplastic lesions. In the remaining 13

animals of this group, liver cell foci were noted; in one animal, a neoplastic liver lesion was observed. In the controls (23 rats), there were neither neoplastic lesions nor hepatocellular carcinomas, although 1 of 23 animals showed liver cell foci. The incidence of tumours of other organs was not statistically different between the treated and control groups.

2-Butenal was tested for carcinogenicity in the B6C3F1 neonatal mouse assay by administering a total dose of 0, 1500, or 3000 nmol (about 0, 21, and 42 mg/kg body weight, assuming a body weight of 5 g) by intraperitoneal injection at 8 and 15 days of age to 24 mice per dose group. After 12 months, the incidence of liver tumours was not above that of the solvent controls (von Tungeln et al., 2002). However, the authors suggested that this assay is not sensitive enough to detect carcinogens that induce an increase in endogenous DNA adduct formation through lipid peroxidation or oxidative stress.

In a cell transformation test on BALB/3T3 mice cells conducted with concentrations of 0.000 01–0.01 nl 2-butenal/ml test medium, no significant increase in transformed foci could be determined (Hoechst AG, 1981a).

8.5 Genotoxicity and related end-points

2-Butenal has been extensively studied for its genotoxic potential. Tables 13 and 14 summarize the data on genotoxicity.

8.5.1 *In vitro*

2-Butenal is non-mutagenic both with and without metabolic activation (rat liver S9 mix) in the plate incorporation procedure with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and BA9, as well as with *Escherichia coli* strain WP2. In a modified liquid suspension test, the preincubation test, 2-butenal was mutagenic in the *S. typhimurium* strains TA100, TA104, and BA9 with and without exogenous metabolic activation (BUA, 1993; IARC, 1995).

2-Butenal was not mutagenic in the SOS chromotest in *E. coli* PQ37 and PQ243 without metabolic activation (Eder et al., 1992). However, when ethanol was used as solvent instead of DMSO, 2-butenal was clearly positive (Eder & Deininger, 2002). A weak SOS response was seen in *S. typhimurium* TA1535/pSK1002 without metabolic activation (Benamira & Marnett, 1992). At concentrations up to 5 mg/plate, 2-butenal did not induce any mitotic recombinations in *Saccharomyces cerevisiae* D3 (Simmon et al., 1977). No mutagenic effect in HGPRT in CHO cells was detected at concentrations of up to 1 mmol/l (Foiles et al., 1990).

Treatment of the shuttle vector plasmid pZ189 with 2-butenal resulted in DNA damage, including point mutations (mainly G:C), deletions, insertions, and inversions; the vector was transfected into human lymphoblastoid cell line GM0621 (Czerny et al., 1998). In another study, using plasmid pMY189 in human fibroblasts, 2-butenal produced mainly GC:TA transversions at G:C hot spots (Kawanishi et al., 1998).

2-Butenal was positive in the comet assay in primary rat hepatocytes (Kuchenmeister et al., 1998) and primary rat epithelium cells of the stomach and colon (Gölzer et al., 1996).

2-Butenal can induce chromosomal aberrations and sister chromatid exchanges in CHO cells (Galloway et al., 1987). Unscheduled DNA synthesis was not induced by incubation of rat hepatocytes with 2-butenal (Williams et al., 1989).

To summarize, the results show that, *in vitro*, 2-butenal is a direct mutagen and that the plate incorporation assay is not suited to show this effect. The chromosomal aberrations in CHO cells (Galloway et al., 1987), micronuclei, and analysis of micronuclei using centromere-specific sampling (Dittberner et al., 1995) showed clearly the genotoxic effects of 2-butenal.

8.5.2 *In vivo*

2-Butenal gave positive results in a host-mediated assay on CD-1 mice after oral application and simultaneous intravenous injection of *S. typhimurium* TA100 (Hoechst AG, 1981b).

In the sex-linked recessive lethal test with *Drosophila melanogaster*, injection of 2-butenal induced recessive lethal mutations and reciprocal translocations, whereas no genotoxic effects were seen after oral application of 4000 µg/l in the feed for 3 days (Woodruff et al., 1985).

The bone marrow micronuclei test with male and female NMRI mice with 2-butenal orally administered at doses of 0.8, 8, and 80 mg/kg body weight was clearly negative (Hoechst AG, 1980b). No cytotoxicity was observed at these doses. Body weight changes of the animals were not influenced by 2-butenal.

In mice, after intraperitoneal and oral ingestion in drinking-water, it was shown that 2-butenal can induce chromosome damage in all stages of spermatogenesis as well as special meiotic anomalies, such as degenerated cell nuclei, multispindle cells and polyploids, and sperm anomalies (Moutschen-Dahmen et al., 1975, 1976) (see also section 8.6 and Table 14).

8.5.3 DNA adducts

Cyclic adducts to dG have been detected following reaction of 2-butenal or acrolein (both α,β -unsaturated aldehydes) with DNA (Chung & Hecht, 1983; Chung et al., 1984). Cyclization of the aldehyde group of the initial adduct to a suitably disposed amine group of dG is favoured by entropy (Marnett, 1988; Sako et al., 2002).

2-Butenal reacts with DNA bases *in vitro* to form the diastereomeric 8-hydroxy-6-methyl-1,*N*²-PdG adducts (Figure 3). The orientation of the hydroxyl and methyl groups is mainly (94%) *trans*, and in only a small amount of a diastereomeric pair is the orientation *cis*. 2-Butenal also forms adducts to dG residues by reaction with N7 and C8. These cyclic adducts, in which the methyl and hydroxyl groups can be either *cis* or *trans*, are unstable in DNA and undergo spontaneous depurination (Eder & Hoffman, 1992; Marnett, 1994).

Other DNA adducts are formed via a second major pathway, in which 3-hydroxybutanal, formed by addition of water to 2-butenal, reacts with DNA to produce the Schiff base *N*²-(3-hydroxybut-1-ylidene)dG and then to 1,*N*²-PdG, as well as forming several diastereomers of *N*²-paradol-dG (Hecht et al., 2001, 2002; Sako et al., 2002).

Table 13: In vitro genotoxicity of 2-butenal.^a

End-point	Test organism	Examined concentrations	Result		Remarks	References
			Without MA	With MA		
<i>Salmonella typhimurium</i> mutagenicity assay	TA98	0.03, 0.3, 3, 30 µmol/plate	-	-	Plate incorporation test	Florin et al. (1980)
	TA100		-	-		
	TA1535		-	-		
	TA1538		-	-		
<i>S. typhimurium</i> mutagenicity assay	TA98	0.004–0.75 µl/plate	-	-	Plate incorporation test; S9	Hoechst AG (1979a, 1979b, 1980a)
	TA100		-	-		
	TA1535		-	-		
	TA1537		-	-		
	TA1538		-	-		
<i>S. typhimurium</i> mutagenicity assay	TA100	0.2–0.8 µl/plate	+	nt	Preincubation test	Hoechst AG (1980a)
<i>S. typhimurium</i> mutagenicity assay	TA100	0.075–0.5 µl	+	nt	30 min	Eder et al. (1992)
		0.015–0.35 µl	+	+	90 min preincubation test; S9	
<i>S. typhimurium</i> mutagenicity assay	TA100	0.05–0.4 µl/ml	-	-	Plate incorporation test; S9	Neudecker et al. (1981)
			+	+	Preincubation test; pH 7.4; S9	
			+	+	Preincubation test; pH 6.6; S9	
			-	-		
	TA98	-	-			
	TA1535	-	-			
	TA1537	-	-			
	TA1538	-	-			
<i>S. typhimurium</i> mutagenicity assay	TA98	Up to 1 µg	-	-	Preincubation test; >45 min in water; S9	Lijinsky & Andrews (1980)
	TA100		+	+		
	TA1535		-	-		
	TA1537		-	-		
	TA1538		-	-		
<i>S. typhimurium</i> mutagenicity assay	TA100	612–1224 nmol/plate	-	nt	Plate incorporation test	Ruiz-Rubio et al. (1984)
		306–1224 nmol/plate	+	nt	Preincubation test	
<i>S. typhimurium</i> mutagenicity assay	TA100	33.0–450 mg/plate	+	nt	Preincubation test	Haworth et al. (1983)
<i>S. typhimurium</i> mutagenicity assay	TA100	0.25–1.06 mmol/l	-	nt	Preincubation test; 30 min; at 0.9 mmol/l microcolonies; purity 85%	Cooper et al. (1987)

Table 13 (contd)

End-point	Test organism	Examined concentrations	Result		Remarks	References
			Without MA	With MA		
<i>S. typhimurium</i> mutagenicity assay	TA100	0.04–0.3 µl/plate	+	nt	Preincubation test; 30 min	Neudecker et al. (1989)
			+	nt	Preincubation test; 90 min	
<i>S. typhimurium</i> mutagenicity assay	TA104	0.075–1.4 µmol/plate	+	nt	Preincubation test; S9	Marnett et al. (1985)
	TA102		–	–		
SOS test (<i>umu</i> gene)	<i>S. typhimurium</i> TA1535/pSK1002	25–950 µmol	+/-	nt	At 300 µmol, 1.5-fold increase; cytotoxic as of 950 µmol	Benamira & Marnett (1992)
SOS chromotest	<i>Escherichia coli</i> PQ37	130–540 nmol	–	nt	DMSO as solvent	Eder et al. (1992)
	<i>E. coli</i> PQ243		–	nt		
SOS chromotest	<i>E. coli</i> PQ37	5–600 nmol	–	nt	DMSO as solvent	Eder & Deininger (2002)
		130–470 nmol	+	nt	Ethanol as solvent	
Plasmid gene mutation test	Plasmid pMY189; treatment of plasmid for 5 days, transfection in WI38-VA13 cells for 72 h	Mutations of plasmids in KS40/pKY241 <i>E. coli</i> cells examined	+	nt	Dose-dependent increase of mutations in plasmid, dose-dependent decrease of survival mutations in <i>supF</i> gene: 85% base substitution; mainly GC:TA transversions at G:C hot spots	Kawanishi et al. (1998)
			+	nt		
Plasmid gene mutation test	Plasmid pZ189; transfection in GM0621 cells	Analysis of mutations of plasmid in MBM7070 <i>E. coli</i> cells	+	nt	Dose-dependent increase of mutations in plasmid; dose-dependent decrease of the number of bacterial colonies; 39% point mutations (mainly G:C), 46% deletions, and 12% insertions, 3% inversions in <i>supF</i> gene	Czerny et al. (1998)
Plasmid gene mutation test	Incorporation of 6- <i>R</i> -methyl-8-hydroxy- and 6- <i>S</i> -methyl-8-hydroxy-1, <i>N</i> ² -PdG adducts in pMS2; transfection in COS-7 cells	Analysis of mutations in DH10B <i>E. coli</i> cells	+	nt	5–6% mutations; mainly G:T transversions	Fernandes et al. (2005)
Covalent DNA binding (³² P-postlabelling)	Calf thymus DNA	0.6 mmol	+	nt	16 h	Chung et al. (1984, 1989)
Covalent DNA binding (³² P-postlabelling)	CHO cell line AS52	0, 1, 4, 7, 10 mmol/l	+	nt	Dose-dependent increase of stable adducts after 1 h	Foiles et al. (1990)
Covalent DNA binding (³² P-postlabelling)	Human primary fibroblasts	0, 1, 10, 100 µmol/l	+	nt	Dose-dependent increase	Wilson et al. (1991)
DNA adducts (UV, LC-APCI-MS; MS/MS)	Calf thymus DNA	No details	+	nt	In form of Schiff's base	Hecht et al. (2001, 2002); Wang et al. (2001)

Table 13 (contd)

End-point	Test organism	Examined concentrations	Result		Remarks	References
			Without MA	With MA		
DNA adducts	Calf thymus DNA (100 µg/250 µl)	0, 0.2, 2 mmol/l	+	nt	At 0.2 mmol/l: 10-fold increase in the adducts; limit of detection 1×10^6 nucleotides; 5 h	Gölzer et al. (1996)
DNA adducts	Calf thymus DNA (20 mg/5 ml)	0, 18 mmol/l	+	nt	8 or 48 h; 37 or 60 °C At 60 °C: 6.8 adducts/ 10^7 nucleotides 8 h later and $8.8/10^5$ nucleotides 48 h later At 37 °C: 2 adducts/ 10^7 nucleotides 8 h later and 4.8 adducts/ 10^5 nucleotides 48 h later; limit of detection 3×10^9 nucleotides	Budiawan & Eder (2000)
DNA strand breaks (alkali elution)	L1210-Zellen	0, 500, 800 µmol	+	nt	At 800 µmol with accompanying cytotoxicity	Eder et al. (1993)
DNA strand breaks (alkali elution)	Namalva-Zellen	0.1–0.4 mmol/l	+	nt	Cytotoxicity at 0.8 mmol/l	Eisenbrand et al. (1995)
DNA strand breaks (alkali elution)	Primary rat hepatocytes	0.5–1.5 mmol/l	+	nt	No cytotoxicity	Eisenbrand et al. (1995)
DNA strand breaks (sequencing)	488 bp <i>supF</i> gene of the plasmid pZ189	0, 200 mmol/l	+	nt	DNA single strand breaks; 2 h	Czerny et al. (1998)
DNA–histone crosslinks	Calf thymus DNA with pUC13 plasmid	0–10.0 mmol/l	+	nt	At 0.1153 mmol/l, DNA–protein crosslinks	Kuykendall & Bogdanffy (1992)
Comet assay	Rat hepatocytes	0, 2.5 mg/ml	+	nt	Small condensed areas within DNA spots	Kuchenmeister et al. (1998)
			–	nt	For tail moment	
Comet assay; DNA damage	Primary epithelial cells of the stomach and colon of rats	0, 0.4, 0.8 mmol/l	+	nt	Increase of DNA damage as dose-dependent result of tail moment (0.8 mmol/l): 15% heavily damaged; 55% damaged and 20% normal cells; 80% of the cells were vital; 30 min	Gölzer et al. (1996)
Sister chromatid exchange	CHO cells	0.16–1.6 µg/ml	+	nt	From 0.5 µg/ml, significant	Galloway et al. (1987)
		1.6–160 µg/ml	nt	+	S9; from 1.6 µg/ml, significant	
Sister chromatid exchange	Namalva-cells (cell line of Burkitt lymphoma)	5–250 µmol/l	+	nt	From 40 µmol/l, significant	Dittberner et al. (1995)
	Human lymphocytes	5–250 µmol/l	+	nt	From 10 µmol/l, significant	
Unscheduled DNA synthesis test	Rat, hepatocytes	1×10^{-4} mol/l	–	nt	No more details provided	Williams et al. (1989)
Aneuploidy test	Human lymphocytes	5–250 µmol/l	–	nt		Dittberner et al. (1995)
Chromosomal aberrations	CHO cells	0.5–5 µg/ml	+		From 1.6 µg/ml, significant	Galloway et al. (1987)
		1.6–16 µg/ml	nt	+	S9; at 16 µg/ml, significant	

Table 13 (contd)

End-point	Test organism	Examined concentrations	Result		Remarks	References
			Without MA	With MA		
Chromosomal aberrations	Namalva cells	5–250 µmol/l	+	nt	From 100 µmol/l, significant	Dittberner et al. (1995)
	Primary human lymphocytes	5–250 µmol/l	+	nt	From 10 µmol/l, significant	
Micronucleus test with centromere analysis	Namalva cells	5–250 µmol/l	+	nt	From 40 µmol/l, significant; at 50 µmol/l and 150 µmol/l, respectively, 52% and 56% centromere-positive micronuclei	Dittberner et al. (1995)
	Human lymphocytes	5–250 µmol/l	+	nt	From 40 µmol/l, significant; at 50 µmol/l and 150 µmol/l, respectively, 51% and 56% centromere-positive micronuclei	
Test for 6-thioguanine resistance	CHO cells	Up to 1 mmol/l	–	nt	Higher concentrations toxic	Foiles et al. (1990)

APCI, atmospheric pressure chemical ionization; bp, base pairs; CHO, Chinese hamster ovary; DMSO, dimethyl sulfoxide; DNA, deoxyribonucleic acid; LC, liquid chromatography; MA, metabolic activation; MS/MS, tandem mass spectrometry; nt, not tested; PdG, propano-2'-deoxyguanosine; UV, ultraviolet.

^a Adapted from MAK (2007).

Table 14: In vivo genotoxicity of 2-butenal.

End-point	Test organism; animals/dose group; organ	Examined concentrations	Result	Remarks	References
X-chromosomal recessive lethal mutations (sex-linked recessive lethal test)	<i>Drosophila melanogaster</i>	3.5 µg/ml; injection	+	Recessive lethal mutations and reciprocal translocations	Woodruff et al. (1985)
X-chromosomal recessive lethal mutations (sex-linked recessive lethal test)	<i>D. melanogaster</i>	4.0 µg/ml; feed	-		Woodruff et al. (1985)
Host-mediated assay	Mouse, CD-1; 6 males/group; liver	0, 0.009, 0.032, 0.094 ml/kg body weight (~0, 7.6, 27.2, 80 mg/kg body weight) once per gavage; TA100 intravenously; 1 h	+	From 7.6 mg/kg body weight, dose-dependent increase of the mutants up to 27.2 mg/kg body weight; at 80 mg/kg body weight, mutant frequency as in control; 2 of 6 animals of the high-dose group died	Hoechst AG (1981b)
DNA adducts (³² P-postlabelling method)	Mouse, Sencar; 5 females/group; epidermis	0, 6.7 mg in acetone (total 100 mg); dermal; 5 times/week; 3 weeks	+	Detection of cyclic 1,N ² -PdG adducts; ~0.24 µmol/mol guanine	Chung et al. (1989)
DNA adducts (³² P-postlabelling method)	Rats, Fischer 344; 4 females/group; liver, lungs, kidneys, colon, epithelial cells	0, 200, 300 mg/kg body weight; oesophageal feeding tube; once; 12, 20 h	+	200 mg/kg body weight after 20 h: 2.9 adducts/10 ⁸ nucleotides 300 mg/kg body weight after 20 h: 3.4 adducts/10 ⁸ nucleotides liver > lungs > kidneys > 0.5/10 ⁸ colon epithelial cells; detection of cyclic 1,N ² -PdG adducts; limit of detection: 3 × 10 ⁹ nucleotides; no 2-butenal adducts in the control	Eder et al. (1999); Budiawan & Eder (2000)
DNA adducts (³² P-postlabelling method)	Rats, Fischer 344; 4 females/group; liver	0, 1, 10 mg/kg body weight; gavage; 5 times/week; 6 weeks; 12, 20 h	+	10 mg/kg body weight: 6.2 adducts/10 ⁸ nucleotides 1 mg/kg body weight: 2 adducts/10 ⁸ nucleotides 1 and 2 weeks after the treatment, 69% and 18% of the adducts, respectively, were detectable; detection of cyclic 1,N ² -PdG adducts; limit of detection: 3 adducts/10 ⁹ nucleotides; no 2-butenal adducts in the control and not-treated calf thymus DNA	Eder et al. (1999); Budiawan & Eder (2000)
DNA adducts (³² P-postlabelling method)	Humans, 11 smokers and 12 non-smokers (control); gingival tissue	0, 5–15 cigarettes per day; inhalation	+	1,N ² -PdG adduct 1: 8.8-fold increase (0.53 [smokers] compared with 0.07 µmol/mol guanine [non-smokers]); 1,N ² -PdG adduct 2: 5.5-fold increase (1.72 [smokers] compared with 0.31 µmol/mol guanine [non-smokers])	Nath et al. (1998); Chung et al. (1999)

Table 14 (Contd)

End-point	Test organism; animals/dose group; organ	Examined concentrations	Result	Remarks	References
Micronucleus test	Mouse, NMR1; 5 males and 5 females/group; bone marrow	0, 0.8, 8.0, 80.0 mg/kg body weight twice within 24 h; gavage	-	No cytotoxicity	Hoechst AG (1980b)
Micronucleus test	Mouse, B6C3F1; 10 males and 10 females/group; peripheral erythrocytes	0, 2.5, 5, 10, 20, 40 mg/kg body weight; 13 weeks; gavage, 24 h after treatment	-	No cytotoxicity	NTP (2006)
Investigations with germ cells	Mouse, Q-stem; 20 males/group	0, 30 mg/kg body weight, intraperitoneally; investigation time 50 days	+	Mortality ~20%; degenerative changes in all stages of spermatogenesis: swelling of nucleus, pycnotic cells, and loss of acrosomes, multipolar anaphases, C-mitoses, fragments in metaphases and anaphases of the spermatogonia and spermatocytes; special meiotic anomalies; altered sperm morphology; no negative control	Moutschen-Dahmen et al. (1975, 1976)
Investigations with germ cells	Mouse, Q-stem; 20 males/group	0, 2000 mg/l (300 mg/kg body weight); oral, in drinking-water; for 50 days; post-trial observation time	+	Results were similar to those of intraperitoneal treatment; no mortality; no control	Moutschen-Dahmen et al. (1975, 1976)

DNA, deoxyribonucleic acid; PdG, propano-2'-deoxyguanosine.

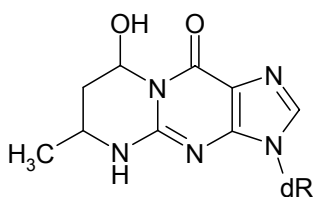


Figure 3: Structure of 8-hydroxy-6-methyl-1,*N*²-propano-2'-deoxyguanosine

Cyclic 1,*N*²-PdG adducts were detected in vitro under physiological conditions in calf thymus (Chung et al., 1984, 1989; Gölzer et al., 1996; Budiawan & Eder, 2000; Hecht et al., 2001, 2002; Wang et al., 2001), CHO cell line AS52 (Foiles et al., 1990), and human primary fibroblasts (Wilson et al., 1991).

Using a ³²P-postlabelling method specific for the detection of cyclic PdG adducts, these adducts were detected in vivo in the epidermis of mice, the skin of which had been treated topically with 2-butenal (Chung et al., 1989). 1,*N*²-PdG adducts were also detected in rat liver, kidneys, and lungs (Eder et al., 1999; Budiawan & Eder, 2000).

In human oral (gingival) tissues, 5.5-fold and 8.8-fold significant increases in these adducts (1,*N*²-PdG; two diastereomers) derived from 2-butenal were found in smokers compared with non-smokers (Nath et al., 1998; Chung et al., 1999). Similar results were found for the acrolein-derived 1,*N*²-PdG.

Synthetic 2-butenal adducts (6-*R*- and 6-*S*-methylated 8-hydroxy-1,*N*²-PdG) were investigated by inserting them into a shuttle vector and replicating them in COS-7 mammalian cells. Stein et al. (2006) carried out a similar study using human xeroderma pigmentosum A cells. The resulting spectrum of mutations agreed with those found by Kawanishi et al. (1998) in which the mutations with the highest frequency were G:T transversions.

Histones appear to accelerate the formation of these adducts (Sako et al., 2003). 2-Butenal is a DNA-protein crosslinking agent, but not as potent as formaldehyde or acrolein (Kuykendall & Bogdanffy, 1992; Kurtz & Lloyd, 2003).

8.6 Reproductive and developmental toxicity

In a sperm morphology test, 2-butenal at 0, 8, 16, or 32 µl/kg body weight (0, 6.8, 13.7, and 27.2 µg/kg body weight) was administered intraperitoneally as a single treatment to male Swiss albino mice (five animals per dose and time tested). The animals were sacrificed 1, 3,

and 5 weeks after treatment. A statistically significant increase in the percentage of abnormal sperm heads was recorded at the two highest doses (16 and 32 µl/kg body weight) after 1 and 3 weeks of treatment and only at the highest dose after 5 weeks of treatment (Jha & Kumar, 2006). This suggests that 2-butenal reached the germ cells. However, there were methodological deficiencies, in that no sperm cell counts were given with which to evaluate the cytotoxicity (MAK, 2007).

Chromosomal damage in all stages of spermatogenesis as well as meiotic anomalies and altered sperm morphology were observed after intraperitoneal injection of 2-butenal (30 mg/kg body weight) to Q strain mice or exposure of the same mouse strain to 2-butenal at 2000 mg/l (300 mg/kg body weight) in drinking-water for 50 days (Moutschen-Dahmen et al., 1975, 1976). The study is limited, as it had neither positive nor negative controls. However, it does suggest that 2-butenal reaches the germ cells (MAK, 2007).

8.7 Immunotoxicity

Thirteen chemicals present in tobacco smoke were assessed for their effect on viability and proliferation of mouse lymphocytes in vitro (Poirier et al., 2002). Of these, the α,β-unsaturated aldehydes acrolein and 2-butenal not only inhibited T cell and B cell proliferation, but also acted on viability, with IC₅₀ values of 2.70 × 10⁻⁵ mol/l and 4.26 × 10⁻⁵ mol/l, respectively. Acetaldehyde and butyraldehyde, for example, showed no cytotoxic or antiproliferative effects; whereas formaldehyde and propionaldehyde inhibited T cell and B cell proliferation, they did not induce a cytotoxic effect in the cell viability assay.

Lambert et al. (2005) confirmed that acrolein and 2-butenal are the predominant inhibitors of cytokine production, inhibiting IL-2 with an IC₅₀ of 3 and 6 µmol/l in contrast to the saturated aldehydes (e.g. acetaldehyde, which did not inhibit IL-2 production).

8.8 Neurotoxicity

Using a specific antibody against protein-bound 2-butenal adducts, it was shown that the number of protein-bound 2-butenal-immunoreactive cells in the grey matter was larger in patients with Alzheimer disease (cases) than in controls. In the patients with Alzheimer disease, protein-bound 2-butenal immunoreactivity was localized in reactive astrocytes and microglia around senile plaques and present in the neurophil, whereas it was weakly detectable in neurons and neurofibrillary tangles. In contrast to protein-bound 2-butenal, immunoreactivities for protein-bound acrolein were mainly localized to neurons and rarely seen in glial cells (Kawaguchi-Niida et al., 2006).

9. EFFECTS ON HUMANS

9.1 Irritating effects

2-Butenal at a concentration of 0.5 mg/m³ (1-min exposure) was reported as irritating to mucous membranes (eyes and respiratory system in humans) (Trofimov, 1962). Fifteen-minute exposures to 2-butenal at 12 mg/m³ were highly irritating to the nose and upper respiratory tract and produced lacrimation in human volunteers in 30 s (Sim & Pattle, 1957). However, Rinehart (1967) reported that 2-butenal at 44 mg/m³ for the same duration of exposure was detected as a strong but not intolerable odour, and no irritation was reported. Concentrations of 131 mg/m³ for 30 min or less were found to be extremely unpleasant and caused irritation of the conjunctiva. Amoores & Hautala (1983), quoting Katz & Talbert (1930), gave the odour threshold as 0.35 mg/m³ and the irritation thresholds for nose and eyes as 41 mg/m³ and 55 mg/m³, respectively.

Eight cases of corneal injury from industrial exposure to 2-butenal have been reported; however, the intensity of exposure was not specified. Healing was complete in 48 h (McLaughlin, 1946).

Six hundred patients of different ages, all of whom had mild eczema, mostly localized on the hands, and were attending an outpatient department, were patch tested with a mixture of 2-butenal (7.5%) and sodium lauryl sulfate (4%) in water. This treatment caused a primary irritancy in the aluminium patch test. The reaction was independent of the age of the subject (Coenraads et al., 1975).

Bainova & Madzhunov (1984) found the concentration of 2-butenal in plant oil that caused skin irritation in healthy subjects to be 0.12% following 24-h dermal contact.

9.2 Effects of smoking

Smoking is known to increase endogenous lipid peroxidation (Morrow et al., 1995). Products of endogenous lipid peroxidation include both 2-butenal and acrolein (Nath et al., 1996).

In a brand-switching study with 39 regular smokers, the effects of smoking cellulose acetate filter-tipped cigarettes and charcoal filter-tipped cigarettes were compared. The mean reduction in excretion rates in urine per day or per cigarette reached significance for the 2-butenal metabolite, 3-hydroxy-1-methylpropyl-mercapturic acid, in smokers smoking charcoal filter-tipped cigarettes, reflecting a lower exposure to 2-butenal (Scherer et al., 2006; see also sections 4.2.3.4 and 7.2).

9.3 Studies of cancer risk

Cancer incidence was investigated between 1967 and 1972 among 220 employees in an aldehyde production factory in the former German Democratic Republic, including 150 workers who had been exposed for more than 20 years to a mixture of various aldehydes and alcohols, including 2-butenal (Bittersohl, 1975). Owing to the exposure to several aldehydes and to the fact that all patients were smokers, no conclusions concerning the carcinogenicity of 2-butenal itself can be drawn from this study. Further, the data were too sparse for an evaluation of the carcinogenicity from the aldehyde exposure as a whole (IARC, 1995).

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Aquatic environment

Table 15 summarizes the data available on the effects of 2-butenal on aquatic biota, including some microorganisms.

2-Butenal caused the inhibition of cell reproduction (biomass yield) in *Pseudomonas putida*, with a 16-h EC₁₀ value of 16 mg/l (nominal) and 10.4 mg/l (measured) (Trénel & Kühn, 1982).

For the ciliates (*Paramecium caudatum*), the 48-h LC₅₀ value for 2-butenal was 20 mg/l; for the genus *Actinosphaerium*, the 30-h LC₅₀ value was ≥15 mg/l (Gottschaldt, 1970). The 48-h EC₁₀ (for inhibition of cell multiplication) was 2.3 mg/l in *Chilomonas paramecium* Ehrenberg (Bringmann et al., 1982).

The toxicity threshold (EC₃) for the inhibition of cell multiplication of the green alga (*Scenedesmus quadricauda*) with 2-butenal was 1.4 mg/l (nominal) and 0.8 mg/l (measured) (Trénel & Kühn, 1982). In a freshwater alga (species not given), the 96-h EC₅₀ value was <0.88 mg/l (Eastman Kodak Company, 1990). In a 7-day study on a marine alga species (*Dunaliella bioculata*), cell multiplication did not occur at 10 mg/l, whereas 1 mg/l did not inhibit growth (Izard & Testa, 1968).

For water fleas (*Daphnia magna*), the measured 24-h EC₅₀ value (immobilization) with 2-butenal is 3.4 mg/l (Trénel & Kühn, 1982); the 48-h EC₅₀ value was given as 2.0 mg/l (Eastman Kodak Company, 1990). In an acute invertebrate toxicity test with *Gammarus fasciatus* (96-h mortality), the LC₅₀ was 2.6 mg/l; the NOEC was given as 1.1 mg/l.

Table 15: Toxicity of 2-butenal to aquatic biota.

Organism	End-point	Concentration (mg/l)	Conditions/remarks	Reference
Algae				
<i>Pseudomonas putida</i>	16-h EC ₁₀ (population growth)	16 (nominal) 10.4 (measured)		Trénel & Kühn (1982)
Green alga (<i>Scenedesmus quadricauda</i>)	8-day EC ₃ (cell reproduction)	1.4 (nominal) 0.8 (measured)		Trénel & Kühn (1982)
Freshwater alga (no further details)	96-h EC ₅₀ (population growth)	<0.88		Eastman Kodak Company (1990)
Marine alga (<i>Dunaliella bioculata</i>)	EC ₉₀ (immobilization)	75 (nominal)	26–28 °C; 90 min	Izard & Testa (1968)
Marine alga (<i>D. bioculata</i>)	Effective threshold concentration (population growth)	10 (nominal)	26–28 °C; 7 days	Izard & Testa (1968)
Saprophytic flagellate protozoa (<i>Chilomonas paramecium</i>)	48-h EC ₁₀ (population growth)	2.3	Increases in toxicity shown in combination with other aldehydes	Bringmann et al. (1982)
Invertebrates				
Water flea (<i>Daphnia magna</i>)	24-h EC ₅₀ (immobilization)	3.9 (nominal) 3.4 (measured)		Trénel & Kühn (1982)
Water flea (<i>D. magna</i>)	48-h EC ₅₀ NOEC (immobilization)	2.0 0.61		Eastman Kodak Company (1990)
Water flea (<i>D. magna</i>)	28-day EC ₅₀ (lethality, immobilization, reproduction)	>1.5 (nominal)	Flow-through TSCA Test Standard No. 797-1330	Eastman Kodak Company (1993)
Amphipod (<i>Gammarus fasciatus</i>)	96-h LC ₅₀ NOEC	2.6 1.1	Flow-through	Eastman Kodak Company (1990)
Vertebrates				
Fathead minnow (<i>Pimephales promelas</i>)	96-h LC ₅₀	0.84 (nominal)	Flow-through	Eastman Kodak Company (1990)
Fathead minnow (<i>P. promelas</i>)	Early life stage experiment (length of young fish); 33 days LOEC NOEC MATC	0.22 0.11 >0.1 and <0.22 (measured)	Flow-through, TSCA Test Standard No. 797-1600	Eastman Kodak Company (1993)
Rainbow trout (<i>Oncorhynchus mykiss</i>)	96-h LC ₅₀ NOEC (for both lethal and sublethal effects)	0.71 0.25 (nominal)	Flow-through	Eastman Kodak Company (1990)
Bluegill sunfish (<i>Lepomis macrochirus</i>)	96-h LC ₅₀	3.5 (nominal)	Static test; no aeration in the first 24 h; after that, low aeration; 23 °C	Dawson et al. (1977)
Tidewater silversides (<i>Menidia beryllina</i>)	96-h LC ₅₀	1.3 (nominal)	Static test with continuous aeration at 20 °C	Dawson et al. (1977)
Guppy (<i>Poecilia reticulata</i>)	14-day LC ₅₀	0.56 (nominal)	Semi-static	Deneer et al. (1988)

EC, effective concentration; LC, lethal concentration; LOEC, lowest-observed-effect concentration; MATC, maximum acceptable toxicant concentration; NOEC, no-observed-effect concentration; TSCA, Toxic Substances Control Act.

In an early life stage experiment (length of young fish) with *Pimephales promelas*, the NOEC (growth) was 0.11 mg/l (Eastman Kodak Company, 1993). For several species of fish, the nominal 96-h acute toxicity LC₅₀ values ranged from 0.65 to 3.5 mg/l; the 96-h NOEC values of 0.25 and 0.27 mg/l were reported (see Table 15). In the prolonged fish toxicity test under semi-static conditions, a 14-day LC₅₀ value of 0.56 mg/l (nominal) for the guppy (*Poecilia reticulata*) has been determined (Deneer et al., 1988).

When several aldehydes were tested using the gills of clams as a test organ, the greatest ciliostatic effect was displayed by formaldehyde, acrolein, and 2-butenal (Wynder et al., 1965).

10.2 Terrestrial environment

Table 16 summarizes the toxicity of 2-butenal to terrestrial organisms.

A fungicidal effect (EC₅₀) has been observed for phytopathogenic fungi at concentrations ≥ 80 mg/m³¹ following exposure of wheat and barley to 2-butenal over the gaseous phase. The parasitic fungi were about 5 times more sensitive than the respective host plants (Lyr et al., 1983).

2-Butenal is phytotoxic to higher plants (e.g. wheat and barley). The 24-h EC₅₀ was 385 mg/m³ (see footnote) following exposure over the gaseous phase. Other types of plants (bean, tomato, cucumber, begonia) were reported to be more sensitive, but no details were reported (Lyr et al., 1983). The 5-h exposure of 10-day-old oat seedlings and 30-day-old alfalfa, endive, sugar beet, and spinach plants to 2-butenal at a concentration of 2.9 mg/m³ did not cause any damage (e.g. wilting, appearance of large necrotic areas, tip burning, chlorosis, bleaching, or minute pitting of the leaves) to the leaves of these plants (Haagen-Smit et al., 1952). The 3-day EC₅₀ for the inhibition of lettuce seed germination amounted to about 24 mg/l (agar medium) (Reynolds, 1977).

Following 5-h exposure of wireworm larvae [*Limonius (Pheletes) californicus* Mann] over the gaseous phase, LC₀ and LC₁₀₀ values of 450 mg/m³ and 1100 mg/m³, respectively, have been found (Lehman, 1933). The LC₉₅ value for eggs and larvae of fruit flies fumigated for 2 h was $\geq 10\,000$ mg/m³ (Woodruff et al., 1985).

¹ Taken or recalculated from the original (slightly different figures are given in BUA, 1993). In the originals, the units used are contradictory between the three publications: Lyr & Banasiak (1983), Lyr et al. (1983), and Banasiak et al. (1984).

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose-response assessment

2-Butenal is an important industrial chemical. Together with other aldehydes, further anthropogenic sources include automobile exhaust and cigarette smoke. Therefore, 2-butenal is a ubiquitous environmental pollutant in ambient air.

2-Butenal is endogenously formed during lipid peroxidation. Protein and DNA adducts have been found endogenously and after exogenous administration of 2-butenal in almost all investigated tissues (skin, liver, lung, kidney, intestinal epithelial cells) from rats and mice. DNA adducts have also been detected in human oral tissue.

There are few human data with which to perform a risk assessment for the toxicological effects of 2-butenal. 2-Butenal causes irritation and inflammation of the skin, respiratory tract, and eyes. In humans, the lowest concentration irritating the mucosa of the eyes and respiratory tract is given as 0.5 mg/m³ (Trofimov, 1962). There are no reports of acute intoxication, perhaps because of the pungent odour of this chemical. Its strong odour and irritancy may limit exposure to this substance.

There are no adequate epidemiological studies on 2-butenal.

Data from experimental animals are also scarce. 2-Butenal is acutely toxic. It causes irritation and inflammation of the skin, respiratory tract, and eyes.

There are no detailed studies available on the short-, medium-, or long-term inhalation exposure to 2-butenal.

In a 13-week oral gavage study, compound-related mortality was observed in rats of both sexes at a dose of 5 mg/kg body weight per day. Mean body weights were significantly decreased for male rats in the 40 mg/kg body weight per day group at termination. Compound-related gross necropsy lesions (thickened forestomach or nodules) were observed in male and female rats at 20 and 40 mg/kg body weight per day, respectively. Microscopic lesions (hyperplasia of the forestomach epithelium) were observed in the stomach of the rats from 10 mg/kg body weight, and forestomach hyperkeratosis, ulcers, moderate necrosis, and acute inflammation were noted at 40 mg/kg body weight. Acute inflammation of the nasal cavity was noted in the male rats at 20 mg/kg body weight and in female rats from 5 mg/kg body weight. However, male and female

Table 16: Toxicity of 2-butenal to terrestrial organisms.

Organism	Exposure conditions	End-point	Concentration ^a	Reference
Fungi				
Tree-inhabiting, wood-destroying fungus (<i>Trametes versicolor</i>)	72 h in closed glass containers at 25 °C	Reduction of radial growth		Lyr et al. (1983)
		EC ₅₀	6.4 mg/m ^{3*}	
Soil fungus (<i>Pythium</i> sp.)	24 h in closed glass containers at 25 °C	EC ₅₀	174 mg/m ^{3*}	Lyr et al. (1983)
		EC ₉₅	14.0 mg/m ^{3*}	
Soil fungus (<i>Rhizoctonia solani</i>)	24 h in closed glass containers at 25 °C	EC ₅₀	73 mg/m ^{3*}	Lyr et al. (1983)
		EC ₉₅	3.8 mg/m ^{3*}	
Wheat rust (<i>Puccinia triticina</i>)	Wheat seedlings infected with spores and then exposed 24 h at 25 °C; spores counted after 10–12 days	Inhibitory effects		Lyr & Banasiak (1983); Lyr et al. (1983); Banasiak et al. (1984)
		EC ₅₀	90 mg/m ^{3*}	
Barley rust (<i>Erysiphe graminis</i>)		EC ₅₀	80 mg/m ^{3*}	Lyr & Banasiak (1983); Lyr et al. (1983); Banasiak et al. (1984)
<i>Fusarium graminearum</i>	On 2% malt agar; 6 days	Growth inhibition, LOEC	≥400 mg/l	McGowan et al. (1948)
<i>Penicillium digitatum</i>	On 2% malt agar; 6 days	Growth inhibition, LOEC	≥400 mg/l	McGowan et al. (1948)
<i>Botrytis allii</i>	In synthetic nutrient	Inhibition of spore germination, LOEC	≥500 mg/l	McGowan et al. (1948)
<i>Monilinia fructicola</i>	Agar culture medium, 4–5 days at 25 °C	Hyphen growth and reproduction	No effect at 100 and 400 mg/l	Horsfall & Rich (1955)
Plants				
Oat seedlings; alfalfa, endive, sugar beet, spinach plants	5 h in fumigation chamber	Leaf damage, NOEC	No effect at 2.9 mg/m ³	Haagen-Smit et al. (1952)
Wheat seedlings	Seedlings were sprayed with 1 ml solution	Number of dead or severely damaged leaves or plants		Lyr & Banasiak (1983); Lyr et al. (1983); Banasiak et al. (1984)
		LC ₅₀	405 mg/m ^{3*}	
Barley seedlings	Seedlings were sprayed with 1 ml solution	Number of dead or severely damaged leaves or plants		Lyr & Banasiak (1983); Lyr et al. (1983); Banasiak et al. (1984)
		LC ₅₀	385 mg/m ^{3*}	
<i>Lactuca sativa</i> (dicotyledon)	3-day exposure; 30 °C; 0.5% agar	Inhibition of germination		Reynolds (1977)
		EC ₅₀	24.1 mg/l	
Invertebrates				
Fruit fly (<i>Dacus dorsalis</i>)	48 h after 2-h exposure to eggs and larvae	2-h LC ₅₀		Hinman (1954)
		Eggs (23–26 h old)	6500 mg/m ³	
		Third-instar larvae	5500 mg/m ³	
Fruit fly (male) (<i>Drosophila melanogaster</i>)	24 h after injection	Impairment of fertility		Woodruff et al. (1985)
		Sterility rate 4%	3500 mg/l	
Wireworm larvae [<i>Limonius (Pheletes) californicus</i> Mann]	72 h after feeding	Sterility rate 0%	4000 mg/l	Lehman (1933)
		Lethality		
		5-h LC ₀	450 mg/m ³	
	After 10-day observation period	5-h LC ₅₀	740 mg/m ³	
		5-h LC ₁₀₀	1100 mg/m ³	

Table 16 (Contd)

Organism	Exposure conditions	End-point	Concentration ^a	Reference
Vertebrates				
Developing chicken embryo (cross between White Leghorn and Red Rhode Island)	One injection of 2-butenal in olive oil on 3rd day of embryonal development; reincubation until 12th day	Teratogenic effects; <i>n</i> = 383	≥1.75 µg/embryo (lowest dose tested)	Abramovici & Rachmuth-Roizman (1983)

EC, effective concentration; LC, lethal concentration; LOEC, lowest-observed-effect concentration; NOEC, no-observed-effect concentration.

^a Concentrations marked with an asterisk (*) have been taken or recalculated from the original (differ slightly from figures given in BUA, 1993). In the originals, the units used are contradictory between the three publications.

mice tested at the same dose and duration showed no compound-related morbidity or gross necroscopic lesions. Microscopic lesions (hyperplasia of the fore-stomach epithelium) were found only in the highest dose group (40 mg/kg body weight per day) (Wolfe et al., 1987).

After long-term oral administration of 2-butenal to rats, liver damage and induction of liver tumours were reported. 2-Butenal induced altered liver foci and neoplastic lesions in 9 of 27 rats and hepatocellular carcinomas in 2 of 27 rats after chronic oral administration (113 weeks) at concentrations of 42 mg 2-butenal/l in drinking-water. At 10 times this dose, there was moderate to extensive liver damage in 10 of 23 rats; these animals did not show any preneoplastic or neoplastic lesions. The remaining 13 animals of this group developed liver cell foci, and a neoplastic liver lesion occurred in one of these animals (Chung et al., 1986a).

2-Butenal is a highly reactive compound. It reacts with cellular macromolecules and can form protein adducts and histone–DNA crosslinks. Like other α,β -unsaturated compounds, 2-butenal can form DNA adducts and therefore can be a source of DNA damage.

11.1.2 Criteria for setting a tolerable concentration for 2-butenal

Unlike other aldehyde compounds such as formaldehyde and acrolein, the database for 2-butenal is scarce.

The only carcinogenicity study in experimental animals had limitations (see section 11.1.4). 2-Butenal is genotoxic, mutagenic, and clastogenic in vitro and in vivo.

Acrolein, like 2-butenal, is an α,β -unsaturated aldehyde and a highly reactive compound. In the evaluation of acrolein, non-neoplastic effects in the respiratory tract of experimental animals were considered critical for the derivation of a tolerable concentration (IPCS, 2002). In the murine respiratory tract, 2-butenal was only slightly less irritating than acrolein and formaldehyde (Steinhagen & Barrow, 1984)

and comparable to these aldehydes in an in vitro test on the inhibition of tracheal ciliary activity (Dalhamn & Rosengren, 1971). The lowest concentration producing irritation of the mucous membranes was specified as being 0.5 mg/m³ for humans (Trofimov, 1962), although other studies give higher values. These are all older studies, and the discrepancies may be due to analytical problems. However, no histopathological studies on the respiratory tract were reported for 2-butenal. There were no further short-term inhalation studies, nor were there any medium- or long-term inhalation studies.

Therefore, owing to a lack of data, it is not possible to adequately evaluate 2-butenal or to derive a tolerable concentration.

11.1.3 Sample risk characterization

Owing to its pungent odour and irritancy, and owing to it being mainly an intermediate chemical, exposure to this aldehyde in industrial scenarios is probably limited under closed conditions.

2-Butenal is produced endogenously and is present in foodstuffs. Other sources of 2-butenal include vehicle exhaust and cigarette smoke, and this compound is detected in ambient air, in particular near vehicle traffic and in a smoking atmosphere. Reported concentrations of 2-butenal are at maxima of 1 µg/m³ in tunnel studies and 10 µg/m³ in polluted cities. From cigarette smoke, exposure is probably 1000 times higher. There are some data concerning workplace concentrations of 2-butenal in various scenarios; the maximum value reported was 3.2 mg/m³ (see section 6.1.1.3).

In environmental scenarios, one cannot consider the effects of 2-butenal alone, as this compound is always together with other saturated aldehydes (e.g. formaldehyde and acetaldehyde) and unsaturated aldehydes (e.g. acrolein) with similar effects. Therefore, the effects due to 2-butenal are only a part of the combined effect.

In the murine respiratory tract, 2-butenal was only slightly less irritating than acrolein and formaldehyde and was comparable to these aldehydes in an in vitro test

on the inhibition of tracheal ciliary activity. 2-Butenal is genotoxic, mutagenic, and clastogenic in vitro and in vivo. The only carcinogenicity study in experimental animals had limitations, so it was not possible to evaluate this end-point.

Owing to the lack of toxicological data, a sample risk characterization cannot be made. However, in the environment, 2-butenal is usually present at much lower concentrations than aldehydes such as formaldehyde and acrolein.

11.1.4 Uncertainties in the evaluation of health risks

There are few human data with which to perform a risk assessment for the toxicological effects of 2-butenal. The marked discrepancies in the results of controlled inhalation trials with volunteers exposed to 2-butenal make the interpretation of human irritation in response to this compound difficult. Analytical differences in these studies may be a factor in these discrepancies.

Data from experimental animals are also scarce. There are no detailed studies available on the short-, medium-, or long-term inhalation exposure to 2-butenal. In particular, because of its similarity to acrolein, histopathological studies studying degenerative changes in the nasal olfactory epithelium and other parts of the respiratory system would give information as to the toxicity of this compound. Although there was some evidence for the carcinogenicity of 2-butenal after exposure of male rats via drinking-water, the increases of hepatic neoplastic nodules and altered liver cell foci were not dose related, only two doses were tested, and only a relatively small number of animals was used.

2-Butenal can form DNA adducts and therefore can be a source of DNA damage. However, DNA lesions are likely to be repaired at low concentrations of the chemical. Further, in vivo, at low concentrations, 2-butenal is detoxified by glutathione.

There is some suggestive evidence that 2-butenal reaches the germ cells.

11.2 Evaluation of environmental effects

11.2.1 Assessment end-points

2-Butenal is unlikely to partition out of the air when released into that medium, based on its physicochemical properties. Data on the presence of 2-butenal in water or soil are scarce. 2-Butenal is intrinsically biodegradable under aerobic and anaerobic conditions. There are no available studies on its bioaccumulation. However, from its log K_{ow} of 0.63, no bioaccumulation is expected.

In the atmosphere, rapid photodegradation takes place by reaction with hydroxyl radicals and more slowly by nitrate radicals or ozone. Decomposition by direct photolysis does not occur. Since 2-butenal is not persistent in air, environmental effects are expected to be greatest in urban areas where traffic volume is high and continuous.

In the aquatic compartment, 2-butenal is reported to be toxic to bacteria, freshwater and marine algae, water fleas (*Daphnia magna*), and several species of fish. The key studies for the hazard assessment are summarized in Table 17.

Table 17: Key studies for hazard assessment in the aquatic environment.

Species	End-point	Value (mg/l)	Reference
Vertebrates			
<i>Oncorhynchus mykiss</i>	96-h LC ₅₀ (mortality)	0.65	Eastman Kodak Company (1990)
<i>Pimephales promelas</i>	33-day NOEC (embryo-larval test: growth)	0.11	Eastman Kodak Company (1993)
Invertebrates			
<i>Daphnia magna</i>	48-h EC ₅₀ (immobilization)	2	Eastman Kodak Company (1990)
	28-day NOEC (chronic toxicity: lethality, immobilization, reproduction)	>1.5	Eastman Kodak Company (1993)
Algae			
<i>Scenedesmus quadricauda</i>	7-day EC ₃ (inhibition of cell population growth)	0.8 (measured)	Trénel & Kühn (1982)
Freshwater algae (species not given)	96-h EC ₅₀ (inhibition of cell population growth)	<0.88 (nominal)	Eastman Kodak Company (1990)
Micro-organisms			
<i>Pseudomonas putida</i>	16-h EC ₁₀ (inhibition of cell population growth)	10.4	Trénel & Kühn (1982)

EC, effective concentration; LC, lethal concentration; NOEC, no-observed-effect concentration.

For the aquatic environment, taking 0.11 mg/l as the lowest NOEC from the embryo-larval test and applying a safety factor of 10 because there are three long-term NOECs for species from three trophic levels, the PNEC_{aqua} = 11 µg/l.

For soil, the 3-day EC_{50} of 24.1 mg/l for *Lactuca sativa* (Reynolds, 1977) can be used to derive the PNEC. As only one study is available, the safety factor is 1000, and $PNEC_{soil} = 24 \mu\text{g/l}$.

2-Butenal is fungicidal, with EC_{50} s given in one experiment of about 80 mg/m^3 . The parasitic fungi were about 5 times more sensitive than the respective host plants, wheat and barley (about 400 mg/m^3). Other types of plants (bean, tomato, cucumber, and begonia) were reported to be more sensitive, but no details were provided. Exposure of 10-day-old oat seedlings and 30-day-old alfalfa, endive, sugar beet, and spinach plants to 2-butenal at a concentration of 2.9 mg/m^3 did not cause any damage to the leaves of these plants (Haagen-Smit et al., 1952). Owing to the uncertainty of the other values (Lyr et al., 1983), the value of 2.9 mg/m^3 is taken as the NOEC.

11.2.2 Sample risk characterization

Toxicological assessment of 2-butenal is focused on terrestrial organisms exposed via air, as this is the most relevant exposure scenario. Reported concentrations of 2-butenal are at maxima of $1 \mu\text{g/m}^3$ in tunnel studies and $10 \mu\text{g/m}^3$ in polluted cities (see section 6). Given that the NOEC is 2.9 mg/m^3 , these concentrations of 2-butenal alone would not be expected to cause damage to plants. However, in environmental scenarios, this compound is always present together with other saturated aldehydes (e.g. formaldehyde and acetaldehyde) at higher (e.g. 30-fold) concentrations as well as unsaturated aldehydes (e.g. acrolein), so the effects due to 2-butenal are only a part of the combined effect. For example, in the same study by Haagen-Smit et al. (1952) quoted above, alfalfa plants showed effects (speckled surface necrosis) due to acrolein at $233 \mu\text{g/m}^3$.

There were no data on 2-butenal in the hydrosphere to enable a sample risk characterization for aquatic species to be performed.

11.2.3 Uncertainties in the evaluation of environmental effects

There are scarce data on which to base an assessment of toxicity of 2-butenal in the air. Haagen-Smit et al. (1952) tested only one dose of 2-butenal (2.9 mg/m^3), so the NOEC could be higher. The data of Lyr & Banasiak (1983), Lyr et al. (1983), and Banasiak et al. (1984) on wheat, barley, and other plants are not reliable due to the mix-up of units in the three papers and due to a lack of further details. Only acute lethality data from fruit flies (*Drosophila*) and wireworm larvae were available.

12. PREVIOUS EVALUATIONS BY IOMC BODIES

There is inadequate evidence in humans for the carcinogenicity of 2-butenal. There is inadequate evidence in experimental animals for the carcinogenicity of 2-butenal. Overall, 2-butenal is not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1995).

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APPENDIX 1 — ACRONYMS AND ABBREVIATIONS

APCI	atmospheric pressure chemical ionization
BUA	GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance
CAS	Chemical Abstracts Service
CHO	Chinese hamster ovary
CICAD	Concise International Chemical Assessment Document
dG	deoxyguanosine
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DNPH	2,4-dinitrophenylhydrazine
EC ₁₀	effective concentration for a 10% response
EC ₅₀	median effective concentration
GC	gas chromatography
HPLC	high-performance liquid chromatography
IC ₅₀	median inhibitory concentration
ICSC	International Chemical Safety Card
IL-2	interleukin-2
IOMC	Inter-Organization Programme for the Sound Management of Chemicals
IPCS	International Programme on Chemical Safety
K _{ow}	<i>n</i> -octanol/water partition coefficient
LC	liquid chromatography
LC ₅₀	median lethal concentration
LD ₅₀	median lethal dose
LOEC	lowest-observed-effect concentration
MA	metabolic activation
MAK	(Commission for the) Investigation of Health Hazards of Chemical Compounds in the Work Area
MATC	maximum acceptable toxicant concentration
MS	mass spectrometry
MS/MS	tandem mass spectrometry
NOEC	no-observed-effect concentration
nt	not tested
PdG	propano-2'-deoxyguanosine
PM _{2.5}	particulate matter 2.5 µm in size or less
PNEC	predicted no-effect concentration
ppb	parts per billion
S9	9000 × <i>g</i> rat liver supernatant
SI	International System of Units
TSCA	Toxic Substances Control Act
USA	United States of America
UV	ultraviolet
WHO	World Health Organization

APPENDIX 2 — SOURCE DOCUMENTS

BUA (1993) Crotonaldehyde. GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance (BUA), ed. Weinheim, VCH, pp. 1–1132 (BUA Report 98) [English translation published in 1994].

MAK (1981) 2-Butenal. In: Deutsche Forschungsgemeinschaft (DFG), ed. *Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung vom MAK-Werten.* Weinheim, Wiley-VCH Verlag, 4 pp.

MAK (2007) 2-Butenal (crotonaldehyd). In: Deutsche Forschungsgemeinschaft (DFG), ed. *Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung vom MAK-Werten.* Weinheim, Wiley-VCH Verlag, 17 pp.

For the BUA review process, the company that is in charge of writing the report (usually the largest producer in Germany) prepares a draft report using literature from an extensive literature search as well as internal company studies. This draft is subject to a peer review in several readings of a working group consisting of representatives from government agencies, the scientific community, and industry.

The scientific documents of the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) are based on critical evaluations of the available toxicological and occupational medical data from extensive literature searches and of well documented industrial data. The evaluation documents involve a critical examination of the quality of the database, indicating inadequacy or doubtful validity of data and identifying data gaps. This critical evaluation and the classification of substances are the result of an extensive discussion process by the members of the Commission, proceeding from a draft documentation prepared by members of the Commission, by ad hoc experts, or by the Scientific Secretariat of the Commission. Scientific expertise is guaranteed by the members of the Commission, which consists of experts from the scientific community, industry, and employer associations.

APPENDIX 3 — CICAD PEER REVIEW

The draft CICAD on 2-butenal was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. An open invitation to participate in the peer review process was also published on the IPCS web site. Comments were received from:

Dr R. Benson, Environmental Protection Agency, Denver, CO, USA

Dr S. Bull, Chemical Hazards and Poisons Division, Health Protection Agency, Chilton, United Kingdom

Dr V. Chan, National Industrial Chemicals Notification and Assessment Scheme, Sydney, Australia

Dr R. Chhabra, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

Dr E. Elovaara, Finnish Institute of Occupational Health, Helsinki, Finland

Dr H. Gibb, Sciences International Inc., Alexandria, VA, USA

Dr R. Hertel, Federal Institute for Risk Assessment (BfR), Berlin, Germany

Mr P. Howe, Centre for Ecology and Hydrology, Monks Wood, United Kingdom

Dr J. Stauber, CSIRO Centre for Environmental Contaminants Research, Sydney, Australia

Dr F. Sullivan, United Kingdom

APPENDIX 4 — CICAD FINAL REVIEW BOARD

Helsinki, Finland
26–29 March 2007

Members

Dr A. Aitio, Finnish Institute of Occupational Health, Helsinki, Finland

Professor H. Bouwman, School of Environmental Sciences and Development, North-West University, Potchefstroom, South Africa

Dr C. De Rosa, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

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Ms M.E. Meek, Health Canada, Ottawa, Ontario, Canada

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Dr B. Sonawane, National Center for Environmental Assessment, Office of Research and Development, Environmental Protection Agency, Washington, DC, USA

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Dr M. Sweeney, Division of Surveillance, Hazard Evaluations & Field Studies, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Dr P. Watts, BIBRA Information Services Ltd, Sutton, United Kingdom

Ms D. Willcocks, Australian Department of Health and Ageing, Sydney, Australia

Dr K. Zieger-Skylakakis, Secretariat of the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission), Munich, Germany

Secretariat

Dr J. Bartram, Assessing and Managing Environmental Risks to Health, World Health Organization, Geneva, Switzerland

Mrs S. Marples, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Ms L. Onyon, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Mr M. Shibatsuji, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

CAS #	4170-30-3	Propylene aldehyde	
RTECS #	GP9499000	2-Butenal	
UN #	1143	beta-Methylacrolein	
EC ANNEX 1	605-009-00-9	Methyl propenal	
INDEX #	224-030-0	C ₄ H ₆ O / CH ₃ CH=CHCHO	
EC/EINECS #		Molecular mass: 70.1	
TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Highly flammable. Many reactions may cause fire or explosion.	NO open flames, NO sparks, and NO smoking. NO contact with oxidants and incompatible substances (see Chemical Dangers).	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Vapour/air mixtures are explosive.	Closed system, ventilation, explosion-proof electrical equipment and lighting. Do NOT use compressed air for filling, discharging, or handling.	In case of fire: keep drums, etc., cool by spraying with water. Combat fire from a sheltered position.
EXPOSURE		PREVENT GENERATION OF MISTS! STRICT HYGIENE!	IN ALL CASES CONSULT A DOCTOR!
Inhalation	Burning sensation. Cough. Laboured breathing. Shortness of breath. Sore throat. Symptoms may be delayed (see Notes).	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention. Half-upright position. Artificial respiration may be needed.
Skin	Redness. Burning sensation. Pain.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower. Refer for medical attention.
Eyes	Corrosive. Redness. Pain. Severe deep burns.	Face shield, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Burning sensation. Cough. Laboured breathing. Shortness of breath. Sore throat. Symptoms may be delayed (see Notes).	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Give one or two glasses of water to drink. Refer for medical attention.
SPILLAGE DISPOSAL	PACKAGING & LABELLING		
Evacuate danger area! Consult an expert! Chemical protection suit including self-contained breathing apparatus. Ventilation. Remove all ignition sources. Collect leaking and spilled liquid in sealable containers as far as possible. Absorb remaining liquid in sand or inert absorbent and remove to safe place. Do NOT absorb in saw-dust or other combustible absorbents. Do NOT let this chemical enter the environment.	EU Classification Symbol: F, T+, N R: 11-24/25-26-37/38-41-48/22-50-68 S: 1/2-26-28-36/37/39-45-61 UN Classification UN Hazard Class: 6.1 UN Subsidiary Risks: 3 UN Pack Group: I		
EMERGENCY RESPONSE	STORAGE		
Transport Emergency Card: TEC (R)-61GTF1-I NFPA Code: H4; F3; R2;	Fireproof. Separated from food and feedstuffs. See Chemical Dangers. Cool. Keep in the dark. Well closed. Store only if stabilized.		

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE

COLOURLESS LIQUID , WITH PUNGENT ODOUR. TURNS PALE YELLOW ON EXPOSURE TO LIGHT AND AIR.

PHYSICAL DANGERS

The vapour is heavier than air and may travel along the ground; distant ignition possible.

CHEMICAL DANGERS

The substance can presumably form explosive peroxides. The substance may polymerize with fire or explosion hazard. The substance is a strong reducing agent and reacts violently with oxidants and many other substances causing fire and explosion hazard. Attacks plastic and many other substances.

OCCUPATIONAL EXPOSURE LIMITS

TLV: 0.3 ppm; (Ceiling value); (skin); A3; (ACGIH 2003).
MAK: skin absorption (H); Carcinogen category: 3B; Germ cell mutagen group: 3B (DFG 2006).

ROUTES OF EXPOSURE

The substance can be absorbed into the body by inhalation of its vapour, through the skin and by ingestion.

INHALATION RISK

A harmful contamination of the air can be reached very quickly on evaporation of this substance at 20°C.

EFFECTS OF SHORT-TERM EXPOSURE

Lachrymation. The vapour is severely irritating to the skin, the respiratory tract, and is corrosive to the eyes. Inhalation of high concentrations may cause lung oedema (see Notes). Inhalation of high concentrations may cause death. Medical observation is indicated.

PHYSICAL PROPERTIES

Boiling point: 104°C
Melting point: (trans) -76.5; (cis) -69°C
Relative density (water = 1): 0.85
Solubility in water, g/100 ml: 15-18
Vapour pressure, kPa at 20°C: 4.0
Relative vapour density (air = 1): 2.41

Relative density of the vapour/air-mixture at 20°C (air = 1): 1.06
Flash point: 13°C o.c.
Auto-ignition temperature: 232.2°C
Explosive limits, vol% in air: 2.1-15.5
Octanol/water partition coefficient as log Pow: 0.63

ENVIRONMENTAL DATA

The substance is toxic to aquatic organisms.

NOTES

The occupational exposure limit value should not be exceeded during any part of the working exposure. Rinse contaminated clothes (fire hazard) with plenty of water. Check for peroxides prior to distillation; eliminate if found. Crotonaldehyde is stabilized with water. The symptoms of lung oedema often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation is therefore essential. Card has been partly updated in October 2006: see sections Occupational Exposure Limits, Ingestion first aid.

ADDITIONAL INFORMATION

LEGAL NOTICE

Neither the CEC nor the IPCS nor any person acting on behalf of the CEC or the IPCS is responsible for the use which might be made of this information

RÉSUMÉ D'ORIENTATION

Le présent CICAD¹ relatif au 2-buténal a été préparé par l'Institut Fraunhofer de toxicologie et de médecine expérimentale de Hanovre (Allemagne) et par la Commission allemande MAK. Il s'appuie principalement sur les rapports respectifs de la BUA (1993) et de la Commission allemande MAK (MAK, 1981, 2007) portant sur ce composé. Une recherche bibliographique exhaustive a également été effectuée jusqu'en août 2006 dans les bases de données pertinentes afin de retrouver toute référence intéressante postérieure à celles qui sont prises en compte dans ces trois rapports. L'appendice 2 donne des renseignements sur l'examen par des pairs des sources bibliographiques utilisées. Des informations sur l'examen par des pairs du présent CICAD figurent à l'appendice 3. Ce CICAD a été examiné et approuvé en tant qu'évaluation internationale lors de la 14^{ème} réunion du Comité d'évaluation finale qui s'est tenue à Helsinki (Finlande) du 26 au 29 mars 2007. La liste des participants à cette réunion figure à l'appendice 4. La Fiche internationale sur la sécurité chimique du 2-buténal (ICSC 0241) établie par le Programme international sur la sécurité chimique (IPCS, 2003) est également reproduite dans le présent document.

Le présent document porte sur le 2-buténal. Toutefois, pour permettre d'évaluer cet aldéhyde et de le situer dans le contexte de l'hygiène de l'environnement, d'autres aldéhydes tels que le formaldéhyde, l'acétaldéhyde et l'acroléine sont également mentionnés à titre de comparaison, le cas échéant, dans les sections correspondantes.

Le 2-buténal est un aldéhyde α,β -insaturé et par conséquent, il est très réactif. Il est utilisé comme intermédiaire principalement dans la fabrication de sorbates et de divers solvants et, dans une moindre mesure, pour la préparation de produits pharmaceutiques et d'arômes chimiques.

Le 2-buténal est également produit par voie endogène et se retrouve dans de nombreuses denrées alimentaires dans des proportions pouvant aller jusqu'à quelques milligrammes par kilogramme par suite de certains processus enzymatiques ou abiotiques (auto-oxydatifs ou thermiques). Il est émis dans l'atmosphère par la combustion de certains produits - en particulier la combustion des carburants pour véhicules automobiles, la combustion du bois ou celle qui résulte de la consommation de tabac.

Il n'y a pas d'études spécifiquement consacrées à l'absorption et à la distribution du 2-buténal chez des animaux de laboratoire après administration par une voie exogène quelconque. Il y a formation endogène de ce composé lors de la peroxydation des lipides. Des adduits avec l'ADN ou avec des protéines ont été mis en évidence chez le rat et la souris soit après formation endogène, soit après administration exogène de 2-buténal dans presque tous les tissus étudiés (peau, foie, poumon, rein, cellules de l'épithélium intestinal). On a également décelé la présence d'adduits avec l'ADN dans des tissus buccaux humains.

La voie métabolique générale des 2-alcénals comporte une oxydation en acides correspondants sous l'action des enzymes du cytosol et des microsomes hépatiques. Toutefois, l'aldéhyde-déshydrogénase ne catalyse pas facilement l'oxydation du 2-buténal. La principale voie de détoxification du 2-buténal fait intervenir le glutathion et conduit à la formation de conjugués avec cette molécule. Après injection sous-cutanée de 2-buténal à des rats, on a retrouvé au bout de 24 heures de l'acide 1-méthylpropylmercapturique et une petite quantité d'acide 2-carboxy-1-méthyléthylmercapturique dans leur urine.

Le 2-buténal est susceptible de provoquer des intoxications aiguës (chez le rat, la DL₅₀ par voie orale est de 200 à 300 mg/kg de poids corporel; la CL₅₀ par inhalation est de 200 à 290 mg/m³. Chez le lapin, la DL₅₀ par voie cutanée est de 128 à 324 mg/kg de poids corporel). Après exposition aiguë par la voie respiratoire, on a observé des symptômes respiratoires et neurotoxiques chez le rat et la souris. A l'autopsie, on a constaté la présence d'effets pulmonaires, cardiaques, hépatiques et rénaux.

Le 2-buténal provoque une irritation et une inflammation de la peau, des voies respiratoires et de l'œil chez l'Homme et les animaux de laboratoire. Son odeur puissante et son caractère irritant sont de nature à limiter l'exposition.

La plupart des études font état du potentiel génotoxique de ce composé. Le 2-buténal a donné des résultats positifs dans toute une série de tests de génotoxicité in vitro (mutation de gènes bactériens, aberrations chromosomiques dans des cellules CHO, test des comètes sur cellules de mammifères). Les données concernant le pouvoir mutagène in vivo de ce composé restent limitées. Le test des micronoyaux sur moelle osseuse de souris a donné des résultats négatifs.

Le 2-buténal est un composé très réactif. Il attaque les macromolécules cellulaires et peut former des adduits avec les protéines et des pontages histone-ADN. Comme les autres composés α,β -insaturés, le 2-buténal

¹ La liste complète des acronymes et abréviations utilisés dans le présent rapport se trouve à l'appendice 1.

peut former des adduits avec l'ADN in vitro et in vivo et il risque par conséquent d'endommager l'ADN.

Après administration prolongée par voie orale à des rats, on a constaté que le composé provoquait des lésions au niveau du foie et induisait la formation de tumeurs hépatiques. Toutefois, il n'y avait pas de relation entre la dose administrée et l'augmentation observée des nodules néoplasiques hépatiques et des foyers lésionnels hépatocellulaires; par ailleurs l'expérimentation n'a porté que sur deux doses.

On ne dispose que d'informations limitées concernant les effets du 2-buténal sur la fécondité. Certaines données incitent à penser que ce composé peut atteindre les cellules germinales. On ne dispose d'aucune étude sur la toxicité pour le développement.

La seule étude épidémiologique disponible est une étude de l'incidence du cancer dans une cohorte d'ouvriers travaillant à la production d'aldéhyde. Toutefois, les données se sont révélées trop limitées pour que l'on puisse en tirer la moindre conclusion concernant l'action du 2-buténal à ce niveau.

Pour l'évaluation de l'acroléine, qui est également un aldéhyde α,β -insaturé très réactif, on a estimé que les effets non-néoplasiques observés au niveau des voies respiratoires chez les animaux de laboratoire sont d'une importance capitale pour la détermination d'une concentration tolérable. Le 2-buténal s'est révélé juste un peu moins irritant pour les voies respiratoires des muridés que l'acroléine et le formaldéhyde et comparable à ces deux aldéhydes lors d'un test in vitro portant sur l'inhibition de l'activité ciliaire trachéale. La concentration la plus faible capable de produire une irritation des muqueuses respiratoires et oculaires a été établie à 0,5 mg/m³ pour l'Homme, encore que d'autres études fassent état de valeurs plus élevées. On ne dispose d'aucune étude histopathologique relative aux effets du 2-buténal sur les voies respiratoires. Il n'y a aucune autre étude comportant une exposition inhalatoire de courte durée et aucune étude de durée moyenne ou longue n'a été consacrée à l'exposition par cette voie.

Dans ces conditions et en raison de l'absence de données fiables, il n'est pas possible d'évaluer la toxicité du 2-buténal pour l'Homme ni de définir une concentration tolérable.

En ce qui concerne l'évaluation écotoxicologique de ce composé, on indique que dans le milieu aquatique, le 2-buténal se révèle toxique pour les bactéries ainsi que pour les algues, les daphnies (*Daphnia magna*) et les poissons d'eau douce et de mer.

Compte tenu de ses propriétés physico-chimiques, il est peu probable que le 2-buténal, une fois libéré dans

l'air, ne se répartisse hors de ce milieu. On a rarement signalé la présence de 2-buténal dans l'eau ou le sol. Ce composé est intrinsèquement biodégradable en aérobiose ou en anaérobiose. On ne dispose d'aucune étude sur son accumulation biologique. Toutefois, comme son log K_{ow} est égal à 0,63, il n'y a vraisemblablement aucune bioaccumulation de ce composé. Le 2-buténal est relativement stable dans l'eau pure mais il subit une hydrolyse si le pH de l'eau est faible ou élevé.

Par conséquent, l'évaluation écotoxicologique du 2-buténal doit être centrée sur les organismes terrestres exposés à l'air. Dans l'atmosphère, il est rapidement photodécomposé par l'action des radicaux hydroxyles et plus lentement en présence de radicaux nitrates ou d'ozone. Il n'y a pas de décomposition par photolyse directe. Comme le 2-buténal ne séjourne pas dans l'air, c'est vraisemblablement en milieu urbain - où la circulation automobile est dense et continue - que ses effets environnementaux sont les plus marqués.

Le 2-buténal a une action fongicide et sa CE_{50} a été estimée lors d'une étude expérimentale à environ 80 mg/m³. Les parasites fongiques se sont révélés environ 5 fois plus sensibles que leurs plantes hôtes respectives le blé et l'orge (CE_{50} d'environ 400 mg/m³). D'autres espèces végétales sont plus sensibles (haricots, tomates, concombres et bégonias), mais aucun détail n'a été fourni à ce sujet. L'exposition de jeunes pousses d'avoine âgées de 10 jours ou de pousses de luzerne, d'endives, de betteraves sucrières ou d'épinards âgées de 30 jours de du 2-buténal à la concentration de 2,9 mg/m³, n'a causé aucun dommage foliaire à ces végétaux. En raison de l'incertitude dont sont entachées les autres valeurs, on a considéré que cette valeur de 2,9 mg/m³ peut être prise comme la NOEC (concentration sans effet observé).

Les concentrations de 2-buténal observées dans l'air atteignent au maximum 1 $\mu\text{g}/\text{m}^3$ selon les études effectuées dans des tunnels et 10 $\mu\text{g}/\text{m}^3$ selon celles qui ont été réalisées dans des agglomérations polluées. Compte tenu des données ci-dessus, le 2-buténal ne peut à lui tout seul et à ces concentrations, provoquer des dégâts aux espèces végétales. Toutefois, dans l'environnement, il est toujours accompagné d'autres aldéhydes saturés (comme le formaldéhyde ou l'acétaldéhyde par ex.) présents à des concentrations plus élevées (par ex. 30 fois plus) ou d'aldéhydes insaturés (comme l'acroléine, par ex.), de sorte que le 2-buténal n'intervient que pour une part dans les effets combinés de ces substances.

RESUMEN DE ORIENTACIÓN

El presente CICAD¹ sobre el 2-butenal, preparado por el Instituto Fraunhofer de Toxicología y de Investigación sobre los Aerosoles de Hannover (Alemania) y la Comisión Alemana de Investigación de los Peligros para la Salud de las Sustancias Químicas en el Entorno de Trabajo (Comisión MAK), se basa fundamentalmente en el informe preparado por el Comité Consultivo Alemán sobre las Sustancias Químicas Importantes para el Medio Ambiente (BUA) (1993) y los informes de la Comisión MAK (MAK, 1981, 2007) sobre este compuesto. Se realizó una búsqueda bibliográfica amplia de bases de datos pertinentes hasta agosto de 2006 a fin de localizar cualquier referencia de interés publicada después de las incorporadas a estos tres informes. La información relativa a los documentos originales y su examen colegiado figura en el Apéndice 2. La información sobre el examen colegiado de este CICAD se presenta en el Apéndice 3. La Junta de Evaluación Final lo examinó y aprobó como evaluación internacional en su 14ª reunión, celebrada en Helsinki (Finlandia) del 26 al 29 de marzo de 2007. La lista de participantes en la Junta de Evaluación Final figura en el Apéndice 4. También se reproduce en este documento la Ficha internacional de seguridad química (ICSC 0241) para el 2-butenal, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 2003).

Este documento se concentra en el 2-butenal. Sin embargo, para facilitar la comprensión y evaluación de este aldehído en el marco de la higiene del medio, cuando es necesario se mencionan en las secciones pertinentes otros aldehídos, como el formaldehído, el acetaldehído y la acroleína, con fines de comparación.

El 2-butenal es un aldehído α , β -insaturado, y por consiguiente un compuesto muy reactivo. Es un intermediario químico que se utiliza fundamentalmente en la fabricación de sorbatos y disolventes y, en menor medida, de productos farmacéuticos y sustancias químicas aromáticas.

La producción de 2-butenal es endógena y también se encuentra en numerosos alimentos en cantidades incluso inferiores al mg por kg, debido a los procesos enzimáticos y abióticos (autooxidativo, térmico). Las emisiones a la atmósfera se deben a la combustión, sobre todo de los combustibles de los vehículos y de la madera, así como al humo del tabaco.

No hay estudios en los que se investigue de manera específica la absorción y distribución del 2-butenal en

¹ En el Apéndice 1 figura una lista completa de las siglas y abreviaturas utilizadas en el presente informe.

los animales de experimentación tras la administración exógena por cualquier vía. El 2-butenal de producción endógena se forma durante la peroxidación de los lípidos. Se han encontrado aductos de ADN y proteínas de formación endógena y tras la administración exógena de 2-butenal en casi todos los tejidos investigados (piel, hígado, pulmón, riñón y células epiteliales intestinales) de ratas y ratones. También se han detectado aductos de ADN en el tejido bucal humano.

Una ruta general del metabolismo de los 2-alquenas es la oxidación a los ácidos correspondientes mediante las enzimas citosólicas y microsomales del hígado. Sin embargo, la aldehído deshidrogenasa no oxida el 2-butenal con facilidad. La principal vía de desintoxicación del 2-butenal es mediante el glutatión, para formar conjugados. A las 24 horas de la administración subcutánea de 2-butenal a ratas se encontraron en la orina ácido 3-hidroxi-1-metilpropilmercaptúrico y pequeñas cantidades de ácido 2-carboxi-1-metiletilmercaptúrico.

El 2-butenal es muy tóxico (en la rata, la DL_{50} por vía oral es de 200–300 mg/kg de peso corporal; la CL_{50} por inhalación es de 200–290 mg/m³; en el conejo, la DL_{50} por vía cutánea es de 128–324 mg/kg de peso corporal). Tras la exposición aguda por inhalación, las ratas y los ratones manifestaron síntomas respiratorios y neurotóxicos. En la autopsia se observaron efectos en los pulmones, el corazón, el hígado y el riñón.

El 2-butenal provoca irritación e inflamación de la piel, el aparato respiratorio y los ojos en el ser humano y los animales de experimentación. Su olor intenso e irritante puede limitar la exposición a esta sustancia.

En la mayor parte de los estudios se identificó un posible efecto genotóxico del 2-butenal. Este compuesto ha dado resultados positivos en una serie de pruebas *in vitro* de genotoxicidad (mutaciones de genes en bacterias, aberraciones cromosómicas en células de ovario de hámster chino y valoración “comet” en células de mamíferos). Los datos sobre la mutagenicidad *in vivo* son limitados. Se obtuvieron resultados negativos en una prueba de micronúcleos de la médula ósea en ratones.

El 2-butenal es un compuesto muy reactivo. Reacciona con macromoléculas celulares y puede dar lugar a aductos de proteínas y enlaces de histonas - ADN. Análogamente a otros compuestos α , β -insaturados, el 2-butenal puede producir aductos de ADN tanto *in vitro* como *in vivo* y, por consiguiente, ser una fuente de lesiones del ADN.

Tras una administración prolongada a ratas por vía oral, se notificaron lesiones hepáticas y la inducción de tumores de hígado. Sin embargo, el aumento de nódulos neoplásicos en el hígado y de focos de células hepáticas

alteradas no estaban relacionados con la dosis, y además sólo fueron dos las dosis que se sometieron a prueba.

La información sobre los efectos del 2-butenal en la fecundidad es limitada. Algunas pruebas parecen indicar que afecta a las células germinales. No se dispone de ningún estudio sobre la toxicidad en el desarrollo.

El único estudio epidemiológico disponible se refiere a la incidencia de cáncer en una cohorte de trabajadores de la producción de aldehídos. Sin embargo, los datos eran demasiado limitados para poder sacar conclusiones con respecto a este compuesto.

En la evaluación de la acroleína, que también es un aldehído α , β -insaturado y un compuesto altamente reactivo, los efectos no neoplásicos en el aparato respiratorio de los animales de experimentación se consideraron decisivos para la obtención de una concentración tolerable. El 2-butenal fue sólo ligeramente menos irritante que la acroleína y el formaldehído en el aparato respiratorio de los murinos y comparable a estos aldehídos en una prueba *in vitro* de inhibición de la actividad ciliar de la tráquea. Se determinó que la concentración más baja que producía irritación de las membranas mucosas del aparato respiratorio y los ojos en el ser humano era de 0,5 mg/m³, aunque en otros estudios se obtuvieron valores más elevados. No se notificó ningún estudio histopatológico del 2-butenal en el aparato respiratorio. No se dispone de otros estudios de exposición por inhalación de corta duración, ni tampoco de duración media o prolongada.

Por consiguiente, debido a la falta de datos fidedignos, no es posible evaluar de manera adecuada la toxicidad del 2-butenal en el ser humano u obtener una concentración tolerable.

Con respecto a la evaluación ecotoxicológica, se informa de que en el compartimento acuático el 2-butenal es tóxico para las bacterias, las algas de agua dulce y marinas, las pulgas de agua dulce (*Daphnia magna*) y los peces.

Basándose en sus propiedades físicoquímicas, es poco probable que las emisiones de 2-butenal a la atmósfera se distribuyan fuera de ese medio. Raramente se ha notificado su presencia en el agua o el suelo. Este compuesto es intrínsecamente biodegradable en condiciones aerobias y anaerobias. No hay ningún estudio sobre su bioacumulación. Sin embargo, dado que su log K_{ow} es de 0,63, no cabe prever que se produzca. El 2-butenal es relativamente estable en el agua pura, pero se hidroliza en presencia de agua con pH bajo o alto.

Por lo tanto, la evaluación ecotoxicológica del 2-butenal se debería concentrar en los organismos

terrestres expuestos al aire. En la atmósfera tiene lugar una fotodegradación rápida por reacción con radicales hidroxilo, y más lenta por reacción con radicales nitrato o el ozono. No se produce descomposición por fotólisis directa. Habida cuenta de que el 2-butenal no es persistente en el aire, cabe suponer que los efectos en el medio ambiente serán mayores en las zonas urbanas con un volumen de tráfico elevado y continuo.

El 2-butenal es fungicida, habiéndose obtenido en un experimento valores de la CE_{50} de unos 80 mg/m³. Los hongos parásitos eran unas cinco veces más sensibles que las plantas huéspedes respectivas, trigo y cebada (valores de la CE_{50} de unos 400 mg/m³). Se notificaron otros tipos de plantas (judía, tomate, pepino y begonia) más sensibles, pero no se proporcionaron detalles. La exposición de plántulas de avena de 10 días y de plantas de alfalfa, endivia, remolacha azucarera y espinaca de 30 días a 2-butenal en una concentración de 2,9 mg/m³ no provocó ninguna lesión en las hojas de estas plantas. Debido a la incertidumbre de los otros valores, se toma como NOEC el valor de 2,9 mg/m³.

Las concentraciones notificadas de 2-butenal en el aire son como máximo de 1 $\mu\text{g}/\text{m}^3$ en estudios de túneles y de 10 $\mu\text{g}/\text{m}^3$ en ciudades contaminadas. Considerando los datos anteriores, no cabe esperar que estas concentraciones de 2-butenal por sí solas puedan causar lesiones en las plantas. Sin embargo, en los modelos de medio ambiente este compuesto siempre está presente con otros aldehídos saturados (por ejemplo, formaldehído y acetaldehído) en concentraciones más altas (por ejemplo, 30 veces más), así como con aldehídos insaturados (por ejemplo, acroleína), de manera que los efectos debidos al 2-butenal son sólo una parte del efecto combinado.

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