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REVIEW ARTICLE

IRRITANT COMPOUNDS: ALDEHYDES

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Summary

Many aldehydes are respiratory irritants which can cause inflammation or other adverse reactions in the respiratory system after being inhaled. Depending on the type and amount of irritant compound inhaled, victims can exhibit symptoms ranging from minor respiratory discomfort to acute airway and lung injury and even death. The lungs are susceptible to many airborne irritants. There are hundreds of substances that can pollute air and harm lungs. Aldehydes are just one type of airborne pollutants that can adversely affect lungs. Some of these agents may be directly toxic. They are also strong irritants for the skin, eyes, and nasal passages. The vapor is irritating to the eyes and respiratory tract. Aldehydes as acrolein or glutaraldehyde are also corrosive substances.

Key words: respiratory irritants; volatile aldehydes; inflammation; formaldehyde; acetaldehyde; acrolein; crotonaldehyde; benzaldehyde; malonaldehyde; glutarladehyde

INTRODUCTION

Aldehyde is an organic compound containing a formyl group. This functional group, with the structure R-CHO, consists of a carbonyl center bonded to hydrogen and an R group, which is any generic alkyl or side chain. The group without R is called aldehyde group or formyl group. Aldehydes are common in organic chemistry. Many fragrances are aldehydes. Aldehydes are highly reactive and participate in many reactions. From the industrial perspective, important reactions of aldehydes are condensations and reductions. From the biological perspective, the key reactions involve addition of nucleophiles to the formyl carbon and further formation of imines and hemiacetals. Some aldehydes are toxic and have strong irritant effects (Sato et al., 1996). Irritants are substances which can cause inflammation or other adverse reactions in the respiratory system after being inhaled or come into direct contact with skin or eyes (Patocka and Kuca, 2014). The major harmful effect on human health of airborne aldehydes is irritation of eyes, nose and throat (Babiuk et al., 1985). Aldehydes are one of the major pollutants of indoor air and cause sick building syndrome (SBS) and sick house syndrome, the major symptoms of which are irritation and indefinite complaints (Endo et al., 2001). Toxicologically significant aldehydes are particularly

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formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, acrolein, crotonaldehyde, propargyl aldehyde, benzaldehyde, and glutaraldehyde. Inhalation of saturated aldehydes show decreasing toxicity with increasing chain length in the sequence formaldehyde, acetaldehyde, propionaldehyde, isobutyraldehyde, n-butyraldehyde, n-valeraldehyde and isovaleraldehyde (Gosselin et al, 1984). Some important physical properties of some aldehydes are summarized in Table I.

Table I. Physical Properties of Aldehydes

Aldehyde	m.p. °C	b.p. °C	pK_a	logP (octanol-water)	Water solubility (g/100 ml)	Vapor pressure (mm Hg)	Density (g/cm^3)
Formaldehyde	- 92.0	- 19.0	13.27	0.35	40	3886	0.8153
Acetaldehyde	- 123.5	20.1	13.57	-0.34	Soluble in all proportions	902	0.7849
Propionaldehyde	- 81	48		0.59	80	317	0.81
Butyrylaldehyde	- 99	74.8		0.88	7.6	111	0.80
Acrolein	- 88	53		-0.01	Very soluble	274	0.839
Crotonaldehyde	- 76.5	104		0.600	19	30	0.846
Propyrgyl aldehyde		60 118[1]		-0.450			1.064
Benzaldehyde	- 26	176.1		1.48	0.657	0.127	1.045
Malonaldehyde	72	108		-1.16			0.991
Succinaldehyde		58[2]					1.06
Glutaraldehyde	- 14	187		-0.18	16.7	0.6	1.06

[1] At 13 mm Hg
[2] At 9 mm Hg

Formaldehyde

Formaldehyde (methanal, H-CHO, CAS Number 50-00-0) is an important compound used widely by industry to produce building materials and numerous household products. It is also a by-product of combustion and certain other natural processes (Böhm et al., 2012). Formaldehyde is a widely used chemical and may be present in substantial concentrations both in indoors and outdoors air. The rapid growth of formaldehyde-related industries in the past two decades reflects the result of its increased use in building materials and other commercial sectors. Consequently, formaldehyde is encountered almost every day from large segments of society due to its various sources (Kim et al., 2011). Sources of formaldehyde in the home include building materials, smoking, household products, etc. Formaldehyde, by itself or in combination with other chemicals, serves a number of purposes in manufactured products. It is used to add permanent-press qualities to clothing and draperies, as a component of glues and adhesives, as a preservative in some paints and coating materials, etc.

In homes, the most significant sources of formaldehyde are likely to be pressed wood products made by using adhesives containing urea-formaldehyde resins (Varga, 1998). Pressed wood products made for indoor use include: particleboard which is used as sub-flooring and shelving and in cabinetry and furniture, hardwood plywood paneling which is used for decorative wall covering and is used in cabinets and furniture, and medium density fiberboard which is used for drawer fronts, cabinets, and furniture tops. Average concentrations in older homes are generally well - below 0.1 (ppm). In homes with significant amounts of new pressed wood products, levels can be higher than 0.3 ppm (Golden, 2011).

Formaldehyde, a colorless, pungent-smelling gas, can cause watery eyes, burning sensations in the eyes and throat, nausea, and difficulty in breathing in some humans exposed at elevated levels (above 0.1 ppm) (Lang et al., 2008; Vimercati et al., 2010; Golden, 2011). High concentrations may trigger attacks in people with astma (McGwin et al., 2011). There is evidence that some people can develop a sensitivity to formaldehyde (Sorg et al., 2004). It has also been

shown to cause cancer in animals, so it may cause cancer in humans (Dreyfuss, 2010; Kumari et al., 2012). Formaldehyde is together with formic acid, a major toxic metabolite of methanol in humans (Skrzydlewska, 2003).

Published toxicological data of formaldehyde for different organisms and different routes of application are summarized in Table II.

Acetaldehyde

Acetaldehyde (ethanal, CH_3CHO, CAS Number 75-07-0) is one of the most important aldehydes, widely occuring in nature and being produced on a large scale industrially. It is a colorless volatile liquid with a pungent suffocating odor. Acetaldehyde is a highly flammable and reactive chemical that is miscible with water as well as with the majority of common solvents. Acetaldehyde occurs naturally in many biological sources, and is produced by plants as a part of their normal metabolism. Acetaldehyde occurs naturally in alcoholic beverages (Lachenmeier et al., 2009) and may occur naturally or as an added flavour in foods (Uebelacker and Lachenmeier, 2011). It is also industrially produced by oxidation of ethylene and is popularly believed to be a cause of hangovers after alcohol consumption. Pathways of exposure include air, water, land or groundwater as well as drink and smoke.

Table II. Toxic Parameters of Formaldehyde Acute Toxicity

Organism	Test Type *	Route	Reported Dose	Source
cat	LCLo	inhalation	400 mg/m^3 (2 hr)	Izmerov et al., 1982
cat	LDLo	intravenous	30 mg/kg	Skog, 1952
mouse	LDLo	intraperitoneal	16 mg/kg	Epstein et al., 1972
rabbit	LD_{50}	skin	0.27 mL/kg	Union Carbide, 1967
rabbit	LDLo	intravenous	48 mg/kg	Logemann, Miori, 1955
rat	LD_{50}	intravenous	87 mg/kg	Langecker, 1954
rat	LD_{50}	oral	100 mg/kg	Til et al., 1988
human	TCLo	inhalation	17 mg/m^3 (30 min)	Sim, Pattle, 1957
woman	LDLo	oral	108 mg/kg	Lefaux, Cleveland, 1968

* LD_{50} - Median Lethal Dose, TCLo - Lowest Published Toxic Concentration, LDLo - Lowest Published Toxic Dose

Acetaldehyde is toxic when applied externally for prolonged periods, an irritant, and a probable carcinogen. Acetaldehyde is a well-known upper respiratory tract irritant and occurs simultaneously as pollutant in many indoor and outdoor environments. The upper respiratory tract, and especially the nose, is the prime target for inhaled acetaldehyde (Cassee et al., 1996a; Morris, 1997). Acetaldehyde is metabolized by aldehyde dehydrogenase to acetic acid. The formation of acetic acid is important in the sensory nerve-mediated vasodilatory response to increase, but perhaps not to decrease, concentration of acetaldehyde (Stanek et al., 2001). Acetaldehyde also proved to be a strong sensory and skin irritator (Cassee et al., 1996b). The threshold skin irritating concentration is 1.2% acetaldehyde in plant oil (Baĭnova and Madzhunov, 1984).

Published toxicological data of acetaldehyde for different organisms and different routes of application are summarized in Table III.

Acetaldehyde is a genotoxic carcinogen (Salaspuro, 2011). In 2009 the International Agency for Research on Cancer classified acetaldehyde, included in and generated endogenously from alcoholic beverages, in a Group I human carcinogen. In addition, acetaldehyde is damaging to DNA and causes abnormal muscle development as it binds to proteins (Aberle et al., 2004). A study of 818 heavy drinkers found out that those who are exposed to more acetaldehyde than normal through a defect in the gene for acetaldehyde dehydrogease are at greater risk of developing cancers of the upper gastrointestinal tract and liver (Homann et al., 2006).

Table III. Toxic Parameters of Acetaldehyde Acute Toxicity

Organism	Test Type *	Route	Reported Dose	Source
hamster	LC_{50}	inhalation	17000 ppm (4 hr)	Feron, 1979
hamster	LD_{50}	intratracheal	96 mg/kg	Feron, 1979
mouse	LD_{50}	intraperitoneal	500 mg/kg	Anonymous, 1985
rat	LD_{50}	oral	661 mg/kg	Sprince et al., 1974
human	TCLo	inhalation	134 ppm (30 min)	Sim, Pattle, 1957

* LC_{50} - Median Lethal Concentration, LD_{50} - Median Lethal Dose, TCLo - Lowest Published Toxic Concentration

Propionaldehyde

Propionaldehyde (propanal, CH_3CH_2CHO, CAS Number 123-38-6) is a colourless liquid with a slightly irritating, fruity odour. Propionaldehyde is mainly produced industrially where several hundred thousand tons are produced annually. It is principally used as a precursor of trimethylolethane, important inter-mediate in the production of alkyd resins (Papa, 2011).

The vapor of propionaldehyde may cause respiratory irritation but is not sufficiently strong irritant of eyes or respiratory tract to be considered a significant factor in smog (Grant, 1986). In an experimental study with humans, irritation of the eyes and upper respiratory tract commenced at 14 to 16 mg/m^3 (Anonymous, 2007). Inhalation can irritate the respiratory tract and may cause nosebleeds, sore throat, cough and phlegm. Higher exposures can cause pulmonary edema, a medical emergency that can be delayed for several hours. This can cause death. Long term exposure can irritate the lungs and bronchitis may develop. Propionaldehyde may also irritate the skin causing a burning sensation and rash after the contact (Sitting, 2002).

Published toxicological data of propionaldehyde for different organisms and different routes of application are summarized in Table IV.

NIOSH has statistically estimated that 2,086 workers (187 of them were female) were potentially exposed to propionaldehyde in the USA. Occupational exposure to propionaldehyde may occur through inhalation and dermal contact with this compound at workplaces where this chemical is produced or used (Jurvelin et al., 2003).

Butyraldehyde

n-Butyraldehyde (n-butanal, $CH_3CH_2CH_2CHO$, CAS Number 123-72-8) is a colourless flammable liquid with an acrid smell. It is miscible with most organic solvents. Butyraldehyde is produced by the hydroformylation of propylene or by the catalytic dehydrogenation of *n*-butanol (Cornils et al., 2000).

Table IV. Toxic Parameters of Propionaldehyde Acute Toxicity

Organism	Test Type *	Route	Reported Dose	Source
guinea pig	LD_{50}	skin	10 mL/kg	NTIS, 1991a
mouse	LC_{50}	inhalation	21800 mg/m^3 (2 hr)	Izmerov et al., 1982
mouse	LD_{50}	intraperitoneal	200 mg/kg	NTIS, 1991a
mouse	LDLo	oral	800 mg/kg	Kodak, 1971
rabbit	LD_{50}	skin	2460 mg/kg	NTIS, 1991b
rat	LD_{50}	intraperitoneal	200 mg/kg	NTIS, 1991a

* LC_{50} - Median Lethal Concentration, LD_{50} - Median Lethal Dose, LDLo - Lowest Published Toxic Dose

Published toxicological data of n-butyraldehyde for different organisms and different routes of application are summarized in Table V.

Butyraldehyde may act as irritant and may produce skin and eye burns after contact (Budavari, 1989) and possible permanent damage. High exposure can cause dizziness and light headedness. Higher exposures can cause pulmonary edema, a medical emergency that can be delayed for several hours (Sitting, 2002). Butyraldehyde is extremely destructive for tissues of the mucosal membranes and upper respiratory tract, as well as for tissues of the eyes and skin. Inhalation may be fatal as a result of spasm, inflammation, and edema of the larynx and bronchi, chemical pneumonia, and pulmonary edema. Signs and symptoms of overexposure are a burning sensation, coughing, wheezing, laryngitis, shortness of breath, headache, nausea, and vomiting (Bingham et al., 2001). Butyraldehyde had no effect on the rate of sister chromatid exchange in human lymphocytes *in vitro* (Obe and Beek, 1979). Exposure to butyraldehyde may be implicated in observed associations between the occurrence of respiratory epithelium cancer in workers and lung cancer associated with high-temperature cooking. However, coexposures with the other more reactive aldehydes do not support a role for butyraldehyde acting alone (Bingham et al., 2001).

Butyraldehyde was found in 10 of 15 personal air samples at a mean concentration of 0.68 ppb from samples taken in Helsinki, tested from May to September 1997 (Jurvelin et al., 2003). Butyraldehyde was detected, not quantified, in 6 from 12 samples of human milk collected from volunteers in Bayonne, NJ, Jersey City, NJ, Bridgeville, PA, and Baton Rouge, LA (Pellizzari et al., 1982).

Table V. Toxic Parameters of Butyraldehyde Acute Toxicity

Organism	Test Type *	Route	Reported Dose	Source
mouse	LC_{50}	inhalation	44610 mg/m^3 (2 hr)	Izmerov et al., 1982
rabbit	LD_{50}	skin	3.56 mL/kg	Union Carbide, 1965
rat	LCLo	inhalation	8000 ppm (4 hr)	NTIS, 1991c
rat	LD_{50}	oral	2490 mg/kg	NTIS, 1991c

* LC_{50} - Median Lethal Concentration, LD_{50} - Median Lethal Dose, LCLo – Lowest Published Toxic Concentration

Acrolein

Acrolein (propenal, CH_2=CH-CHO, CAS Number 107-02-8) is the simplest unsaturated aldehyde. It is a colourless liquid with a piercing, disagreeable, acrid smell. It is produced industrially from propylene and mainly used as a biocide and as a building block to other chemical compounds synthesis, such as the amino acid methionine. Approximately 500,000 tons of acrolein are produced annually in North America, Europe, and Japan. When glycerol is heated to 280 °C, it decomposes into acrolein. The smell of burnt fat (as when cooking oil is heated to its smoke point) is caused by glycerol present in the burning fat breaking down into acrolein (Mestdagh et al., 2008).

Acrolein is a relatively electrophilic compound and a reactive one, hence its high toxicity. Acrolein is mainly used as a contact herbicide to control submersed and floating weeds, as well as algae, in irrigation canals. It is used at a level of 10 ppm in irrigation and recirculating waters. In the oil and gas industry, it is used as a biocide in drilling waters, as well as a scavenger for hydrogen sulfide and mercaptans (Faroon et al, 2008).

Acrolein is toxic and is a strong irritant for the skin, eyes, and nasal passages. The vapor is irritating to the eyes and respiratory tract. Liquid acolein is a corrosive substance. It is a cytotoxic agent. *In vitro* cytotoxicity has been observed as low as 0.1 mg/liter. The substance is highly toxic to experimental animals and humans following a single exposure via different routes. Published toxicological data of acrolein for different organisms and different routes of application are summarized in Table VI.

The WHO suggests a "tolerable oral acrolein intake" of 7.5 mg/day per kilogram of body weight.

Table VI. Toxic Parameters of Acrolein Acute Toxicity

Organism	Test Type *	Route	Reported Dose	Source
cat	LCLo	inhalation	1750 mg/m^3 (2 hr)	Skog, 1952
cat	LDLo	intravenous	15 mg/kg	Skog, 1952
mouse	LC_{50}	inhalation	66 ppm (6 hr)	Philippin et al, 1970
mouse	LD_{50}	intraperitoneal	9.0 mg/kg	Anonymous, 1986
rabbit	LD_{50}	skin	200 mg/kg	Union Carbide, 1971
rat	LD_{50}	intraperitoneal	4 mg/kg	Murphy et al., 1983
rat	LD_{50}	oral	26 mg/kg	Murphy et al., 1983
child	TCLo	inhalation	5.5 ppm (2 min)	Gosselin et al., 1979
human	TCLo	oral	108 mg/kg	Deichman, 1969

* LC_{50} - Median Lethal Concentration, LD_{50} - Median Lethal Dose, TCLo - Lowest Published Toxic Concentration, LDLo - Lowest Published Toxic Dose, LCLo - Lowest Published Toxic Concentration

Although acrolein occurs in French fries, the levels are only a few micrograms per kilogram (Abraham et al., 2011; Osório and de Lourdes Cardeal, 2011). Nevertheless, regular consumption of select deep-fried foods, such as fast food consumption, is associated with increased prostate cancer risk (Stott-Miller et al., 2013). In animals and humans the reactivity of acrolein effectively confines the substance to the site of exposure, and pathological findings are also limited to these sites. Acrolein reacts directly with protein and non-protein sulfhydryl groups and with primary and secondary amines (Włodek , 1988). The main metabolic pathway of acrolein is the alkylation of glutathione (Yoshida et al., 2008).

Acrolein is a cytotoxic agent. *In vitro* cytotoxicity has been observed as low as 0.1 mg/liter. The substance is highly toxic to experimental animals and humans following a single exposure via different routes. At higher single exposure levels, degeneration of the respiratory epithelium, inflammatory sequelae, and perturbation of respiratory function develop (Bein and Leikauf, 2011). In general, body weight gain reduction, decrement of pulmonary function, and pathological changes in nose, upper airways, and lungs have been documented in most species exposed to concentrations of 1.6 mg/cu m or more for 8 hr/day. Pathological changes include inflammation, metaplasia, and hyperplasia of the respiratory tract (Moretto et al., 2012).

Significant mortality has been observed following repeated exposures to acrolein vapor at concentrations above 9.7 mg/m^3. In experimental animals acrolein has been shown to deplete tissue glutathione and in *in vitro* studies, to inhibit enzymes by reacting with sulfhydryl groups at active sites (Struve et al., 2008).

Acrolein is very toxic to aquatic organisms. Acute EC_{50} and LC_{50} values for bacteria, algae, crustacea, and fish are between 0.02 and 2.5 mg/liter, bacteria being the most sensitive species (Ghilarducci and Tjeerdema, 1995).

Crotonaldehyde

Crotonaldehyde (2-butenal, CH_3-CH=CH-CHO, CAS Number 4170-30-3) is a highly reactive unsaturated aldehyde, usually sold as a mixture of E- (CAS Number 123-73-9) and Z-isomers (CAS Number 15798-64-8), which differ with respect to the relative position of the methyl and formyl groups. The E-isomer is more common. In the pure crotonaldehyde, the ratio of E- and Z-isomers is approximately 20:1.

Crotonaldehyde is produced by the aldol condensation of acetaldehyde and its main application is to be a precursor to fine chemicals. Crotonaldehyde is a strong irritant. Exposure to crotonaldehyde can occur through inhalation, ingestion, eye or skin contact, and absorption through the skin (Sittig, 1991). Contact with crotonaldehyde vapors may cause lacrimation and corneal injury (Parmeggiani, 1983).

Crotonaldehyde is a respiratory, eye, and skin irritant in experimental animals. Published toxi-

Table VII. Toxic Parameters of Crotonaldehyde Acute Toxicity

Organism	Test Type *	Route	Reported Dose	Source
cat	LDLo	intravenous	30 mg/kg	Skog, 1952
mouse	LD_{50}	oral	104 mg/kg	Parmeggiani, 1983
rabbit	LD_{50}	skin	0.38 ml/kg	Union Carbide, 1971
rabbit	LD_{50}	skin	380 mg/kg	NIOSH 1995
rat	LC_{50}	inhalation	380 mg/m^3 (2 hr)	ACGIH, 1991
human	TCLo	inhalation	12 mg/m^3 (10 min)	Sim and Pattle, 1957

* LC_{50} - Median Lethal Concentration, LD_{50} - Median Lethal Dose, TCLo - Lowest Published Toxic Concentration, LDLo - Lowest Published Toxic Dose

toxicological data of crotonaldehyde for different organisms and different routes of application are summarized in Table VII.

The LC_{50} in rats is 1,500 ppm for 30 minutes, and the dermal LD_{50} in rabbits is 380 mg/kg (NIOSH, 1995). A single 200-minute exposure to 10 ppm of crotonaldehyde caused adverse changes in pulmonary performance in rats (ACGIH, 1991), and a 10-minute exposure to 1,650 ppm induced respiratory distress, excitation, and terminal convulsions; at autopsy pulmonary edema and bronchiolar damage were seen (Hathaway et al., 1991).

Crotonaldehyde is a strong irritant of the eyes, mucous membranes, and skin also in humans. Contact of crotonaldehyde with the eye may cause corneal burns. Exposure to 4 ppm for 10 minutes induced lacrimation, and even brief exposure to 45 ppm caused conjunctival irritation (Parmeggiani 1983; Hathaway et al. 1991). In a series of eight cases of corneal injury by exposure to crotonaldehyde, healing was complete in 48 hours; the severity of exposure was not specified. Crotonaldehyde exposure has not been linked to chronic effects, although cases of sensitization to crotonaldehyde have been reported in workers (Hathaway et al. 1991; ACGIH 1991).

The current OSHA permissible exposure limit (PEL) for crotonaldehyde is 2 ppm (6 milligrams per cubic meter (mg/m^3) as an 8-hour time-weighted average (TWA) concentration. The NIOSH has established a recommended exposure limit (REL) for crotonaldehyde of 2 ppm (6 mg/m^3) as a TWA for up to a 10-hour workday and a 40-hour workweek (NIOSH, 1992).

Crotonaldehyde is a genotoxic substance. Its genotoxicity was detected by employing bone marrow and spermatocyte chromosomal aberration and dominant lethal mutation assays in Swiss albino mice. (Jha et al., 2007). Crotonaldehyde induced a dose related increase in the percentage of abnormal sperm heads. A statistically significant increase in percentage of abnormal sperm heads was recorded at 16 and 32 microl/kg b.w. after 1 and 3 weeks of treatment and only at 32 microl/kg b.w. after 5 weeks of treatment (Jha and Kumar, 2006).

Crotonaldehyde is also a major component of cigarette smoke and an ubiquitous environmental widespread pollutant. It is a risk factor for many diseases (e.g., chronic pulmonary inflammation). However, its toxicity and its mechanism of action is not sufficiently explored. According to Liu et al (2010) crotonaldehyde induces cell death by apoptosis, and is gradually transitioned to necrosis at high doses. The results of Yang and his co-workers (Yang et al., 2013) show that crotonaldehyde induces apoptosis and immunosuppresion in alveolar macrophages and can cause adverse effects in alveolar macrophages via multiple mechanisms, and may contribute to compromised lung immunological response in smokers.

Propargyl aldehyde

Propargyl aldehyde (propioaldehyde, H-C≡C-CHO, CAS Number 624-67-9) is a strong lacrymator and cytotoxic compound. As shown by Moridani et al. (2001), propargyl alcohol-induced cytotoxicity involves metabolic activation by CYP 2E1 to form propiolaldehyde that causes hepatocyte lysis as a result of GSH depletion and lipid peroxidation. Propargyl

aldehyde is a potent inhibitor of rat liver (DeMaster et al., 1986) and human liver aldehyde dehydrogenase (Ferencz-Biro and Pietruszko, 1984). Propargyl aldehyde is also the main metabolite of pargyline (N-Methyl-N-propargylbenzylamine hydrochloride), an irreversible inhibitor of monoamine oxidase (MAO) that is used clinically to treat moderate hypertension, and is responsible for this drug hepatotoxicity (DeMaster et al., 1982).

Benzaldehyde

Benzaldehyde (C_6H_5-CHO, CAS Number 100-52-7) is the simplest aromatic aldehyde and one of the most industrially useful. This colorless liquid has a characteristic pleasant almond-like odor. In fact, benzaldehyde is the primary component of bitter almond oil and can be extracted from a number of other natural sources. It is only slightly soluble in water and is completely soluble in ethanol and diethyl ether.

Benzaldehyde is a respiratory, eye, and skin irritant and is one of the most common substances causing contact dermatitis in workers at a parfume factory (Schubert, 2006) and in a confectioner (Seite-Bellezza et al., 1994).

The acute toxicity of benzaldehyde has been tested in mice by intraperitoneal (LD_{50} = 9 mg/kg) and oral application (LD_{50} = 28 mg/kg) (Caprino et al., 1976). Subacute toxicity inhalation studies in rats at 500, 750 and 1000 ppm indicated hypothermia and other CNS effects at all doses, with abnormal gait, severe tremors, and convulsions occurring at the highest concentration. Female rats were more susceptible to the lethal effects of 750 and 1000 ppm of benzaldehyde, whereas males showed a higher incidence of goblet cell metaplasia of the respiratory epithelium in the nasal septum, which did not differ in severity between the 500 and 1000 ppm groups after 14 days of 6-hr/day exposures (Laham et al., 1991).

Kluwe et al. (1983) orally treated groups of 10 mice of each sex with 0, 75, 150, 300, 600 or 1200 mg/kg/day of benzaldehyde, and groups of 10 rats of each sex with 0, 50, 100, 200, 400 or 800 mg/kg/day of ben-zaldehyde, 5 days/week for 13 weeks by corn oil gavage. Administration of 600 mg/kg/day in mice was associated with renal tubular necrosis, and administration of 400 mg/kg/day to rats resulted in forestomach hyperplasia and hyperkeratosis. Using the rat NOEL of 200 mg/kg/day, multiplying by 5 days/7 days, and dividing by an uncertainty factor of 1000, results in a reference dose of 0.1 mg/kg/day.

Mice, but not rats, showed increased incidences of squamous cell papillomas and hyperplasia of the forestomach in 2-year carcinogenicity studies of benzaldehyde administered by oral gavage. Benzaldehyde is generally regarded as a safe (GRAS) food additive in the United States and is accepted as a flavoring substance in the European Union. A Cosmetic Ingredient Review Expert Panel considered benzaldehyde not to be a carcinogenic risk to humans (Pohanish, 2002; Andersen, 2006).

Malonaldehyde

Malonaldehyde (malondialdehyde, OHC-CH_2-CHO, CAS Number 542-78-9) is a highly reactive compound that is not typically observed in pure form. In the laboratory it can be generated *in situ* by hydrolysis of 1,1,3,3-tetramethoxypropane, which is commercially available. It is easily deprotonated to give the sodium salt of the enolate (Nair et al., 2008).

Malonaldehyde is a strong irritant (Beauchamp et al., 1992). It is reactive and potentially mutagenic (Hartman, 1983) but no epidemiological data relevant to the carcinogenicity of malonaldehyde are available. There is limited evidence in experimental animals for the carcinogenicity of this compound (Basu et al., 1984; Marnett et al., 1985; Von Tungeln et al., 2002). Malonaldehyde is not classifiable as to its carcinogenicity to humans (IARC, 1999). It has been found in heated edible oils such as sunflower and palm oils (Dourerdjou and Koner, 2008).

Oral acute toxicity of malonaldehyde was estimatedy by Crawford et al. (1965) and is characterized by LD_{50} value of 632 mg/kg.

Succinaldehyde

Succinaldehyde (succindialdehyde, OHC-CH_2-CH_2-CHO, CAS Number 638-37-9) is a highly reactive compound. Usually, it is handled as hydrate or methanol-derived acetal. It is used as a crosslinking agent but is less widely used than its related dialdehyde glutaraldehyde. Succinaldehyde is similar in toxicity and contact allergy (Krecisz and Kieć-Swierczyńska, 1998) as formaldehyde, but in comparison with the latter it is not a strong sensitizer or carcinogen (Fraud et al., 2001). No further toxicological data are available.

Glutaraldehyde

Glutaraldehyde (OHC-CH_2-CH_2-CH_2-CHO, CAS Number 111-30-8) is a pungent colorless oily liquid. It has a wide spectrum of medical, scientific and industrial applications. It is used to desinfect medical and dental equipment (Deng et al., 2008; Chang et al., 2012). It is also used for industrial water treatment and as a preservative (Leung, 2001). Glutaraldehyde is used in biological electron microscopy as a fixative (Jerome, 1981). It kills cells quickly by crosslinking their proteins and is usually employed alone or mixed with formaldehyde as the first of two fixative processes to stabilize specimens such as bacteria, plant material, and human cells. Another example of application for treatment of proteins with glutaraldehyde is the inactivation of bacterial toxins to create toxoid vaccines (Relyveld et al., 1973). Glutaraldehyde is produced industrially and is widely used as a desinfectant and sterilizing agent against bacteria and virus in hospital and veterinary facilities. Glutaraldehyde or its metabolites may reach aquatic ecosystems due to incomplete or inadequate treatment of wastewaters. In a battery of toxicity tests with several aquatic organisms, Pereira et al. (2013) have shown that glutaraldehyde is moderately toxic (doses > 1mg/l) to aquatic organisms, independently of the trophic level. However, considering the varied range of effects depending on the life stage and organism tested.

Glutaraldehyde is irritating and corrosive to the skin, eyes and respiratory tract (IPCS, 2000) and is recognized as a cause of health problems in those handling it. The acute toxicity of glutaraldehyde has been investigated in many studies with various animal species. Published toxicological data are summarized in Table VIII.

Table VIII. Toxic Parameters of Glutaraldehyde Acute Toxicity

Organism	Test Type *	Route	Reported Dose	Source
mouse	LD_{50}	oral	100 mg/kg	Uemitsu et al., 1976
mouse	LD_{50}	intravenous	15.4 mg/kg	Uemitsu et al., 1976
mouse	LD_{50}	skin	5840 mg /kg	Uemitsu et al., 1976
rabbit	LD_{50}	skin	0.56 ml/kg	Union Carbide, 1971
rat	LD_{50}	skin	2500 mg/kg	Ohno et al., 1991
rat	LD_{50}	oral	134 mg/kg	Ohno et al., 1991

* LD_{50} - Median Lethal Dose

Acute peroral LD_{50} in rats treated with glutarladehyde concentrations from 1 to 50% ranged from 12.3 to 1.19 ml /kg, or from 99 to 733 mg glutaraldehyde/kg, respectively. LD_{50} values expressed in ml/kg increased with dilution rates, while those expressed in mg glutaraldehyde/kg decreased with increasing dilution rates. Therefore, if water is taken following accidental ingestion of glutaraldehyde in high concentration, the toxicity of GA may be enhanced (Ballantyne and Myers, 2001). Signs of acute oral toxicity in rats and mice given 2% glutaraldehyde solution included suppression of spontaneous behavior, piloerection and abdominal swelling (Uemitsu et al., 1976). Whether aging affects sensitivity to glutarladehyde was examined by Ohno et al. (1991). Young (5–6 wk) and old (57–60 wk) rats were administered glutaraldehyde by gavage (young: 200–1,600 mg/kg, old: 50–400 mg/kg). The LD_{50} values were 283 mg/kg for young and 141 mg/kg for old rats.

CONCLUSION

Aldehydes (R-CHO) are carbonyl compounds and attractive building blocks due to their chemical reactivity. The major effect on human health of airborne aldehydes is irritation of the eyes, nose and throat. Some aldehydes are toxic and have strong irritant effects. Irritant volatile aldehydes, when inhaled, are dissolved in the water of the respiratory tract mucosa and cause an inflammatory response, usually by the release of acidic or alkaline radicals.

Irritant aldehyde exposures predominantly affect the airways, causing tracheitis, bronchitis, and bronchiolitis. In the contact with the skin, many aldehydes cause contact allergy.

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