CURRENT INTELLIGENCE BULLETIN 55

Carcinogenicity of Acetaldehyde and Malonaldehyde, and Mutagenicity of Related Low-Molecular-Weight Aldehydes

U.S. Department of Health and Human Services
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National Institute for Occupational Safety and Health
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FOREWORD

Current Intelligence Bulletins (CIBs) are issued by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control, Atlanta, Georgia, to disseminate new scientific information about occupational hazards. A CIB may draw attention to a formerly unrecognized hazard, report new data on a known hazard, or disseminate information about hazard control.

CIBs are distributed to representatives of academia, industry, organized labor, public health agencies, and public interest groups as well as to Federal agencies responsible for ensuring the safety and health of workers. Copies are available to individuals upon request from the Division of Standards Development and Technology Transfer, NIOSH (Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, OH 45226). We welcome suggestions concerning the content, style, and distribution of these documents.

The purpose of this bulletin is to disseminate recent information about the potential carcinogenicity of acetaldehyde and malonaldehyde. Also discussed is the mutagenicity of nine related low-molecular-weight aldehydes (acrolein, butyraldehyde, crotonaldehyde, glutaraldehyde, glyoxal, paraformaldehyde, propiolaldehyde, propionaldehyde, and valeraldehyde).

Results of recent studies in animals indicate an increased incidence of laryngeal cancer in hamsters and nasal cancer in rats following exposure to acetaldehyde. Malonaldehyde administered to rats produced an increased incidence of adenomas and carcinomas of the thyroid gland and pancreatic islet cell adenomas. Acetaldehyde is a probable metabolite in the metabolism of malonaldehyde by rat liver mitochondria. Acetaldehyde and malonaldehyde both meet the criteria of the Occupational Safety and Health Administration (OSHA) for classifying substances as potential occupational carcinogens [Title 29 of the *Code of Federal Regulations*, Part 1990]. NIOSH therefore considers acetaldehyde and malonaldehyde to be potential occupational carcinogens and recommends that exposures to each be reduced to the lowest feasible concentration. The potential for acetaldehyde or malonaldehyde to produce cancer in humans has not been determined, but reducing occupational exposures to these chemicals should lower the risk.

The carcinogenic potential of the nine related low-molecular-weight aldehydes has not been adequately evaluated by appropriate experimentation. However, some studies indicate that their chemical reactivity and mutagenicity are similar to those of acetaldehyde and malonaldehyde. Thus NIOSH is also concerned about occupational exposure to these nine aldehydes because they (in addition to acetaldehyde and malonaldehyde) may be used as

ABSTRACT

The National Institute for Occupational Safety and Health (NIOSH) has determined that acetaldehyde and malonaldehyde are potentially carcinogenic to occupationally exposed workers. NIOSH is also concerned about exposure to nine related low-molecular-weight aldehydes: acrolein, butyraldehyde, crotonaldehyde, glutaraldehyde, glyoxal, paraformaldehyde, propiolaldehyde, propionaldehyde, and valeraldehyde.

Long-term inhalation studies of acetaldehyde produced laryngeal cancers in hamsters and nasal cancers in rats. A long-term gavage study of malonaldehyde produced adenomas and carcinomas of the thyroid gland and adenomas of the pancreatic islet cells in rats. Acetaldehyde and malonaldehyde have also been shown to be mutagenic in a variety of assays.

Adequate epidemiologic data are not available from workers exposed to acetaldehyde or malonaldehyde. However, both chemicals meet the criteria of the Occupational Safety and Health Administration (OSHA) for potential carcinogens [Title 29 of the *Code of Federal Regulations*, Part 1990]. NIOSH therefore considers acetaldehyde and malonaldehyde to be potential occupational carcinogens and recommends that worker exposure to acetaldehyde and malonaldehyde be reduced to the lowest feasible concentration.

NIOSH is concerned about the nine related aldehydes because their chemical reactivity and mutagenicity are similar to those of acetaldehyde and malonaldehyde, and they may be used as substitutes for formaldehyde, a regulated carcinogen. Although their carcinogenic potential has not been adequately evaluated by in vitro research or studies in experimental animals, careful consideration should be given to reducing occupational exposures to these low-molecular-weight aldehydes.

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ABBREVIATIONS

BP	benzo[a]pyrene
Ca	potential occupational carcinogen
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary cell culture
CIB	Current Intelligence Bulletin
CL	ceiling limit
CPC	chemical protective clothing
°C	degree Celsius
DENA	diethylnitrosamine
DHHS	Department of Health and Human Services
DMBA	dimethylbenz[a]anthracene
DNA	deoxyribonucleic acid
DSDTT	Division of Standards Development and Technology Transfer
°F	degree Fahrenheit
g	gram
Hg	mercury
HGPRT	hypoxanthine guanine phosphoribosyl transferase
hr	hour
IARC	International Agency for Research on Cancer
kg	kilogram
LC_{50}	lethal concentration for 50% of the exposed animals
LD_{50}	lethal dose for 50% of the exposed animals
m	meter
MCA	Manufacturing Chemists Association
mg	milligram
min	minute
ml	milliliter
mm	millimeter
MSHA	Mine Safety and Health Administration
Na	sodium
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program
ODC	ornithine decarboxylation activity
OSHA	Occupational Safety and Health Administration
P	probability
PEL	permissible exposure limit
ppm	parts per million

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CURRENT INTELLIGENCE BULLETIN 55

Carcinogenicity of Acetaldehyde and Malonaldehyde, and Mutagenicity of Related Low-Molecular-Weight Aldehydes

INTRODUCTION

This Current Intelligence Bulletin (CIB) presents recent information about the potential carcinogenicity and mutagenicity of acetaldehyde and malonaldehyde (synonym, propanedial); the document also discusses the chemical reactivity and mutagenicity of nine related low-molecular-weight aldehydes: acrolein, butyraldehyde, crotonaldehyde, glutaraldehyde, glyoxal, paraformaldehyde, propiolaldehyde, propionaldehyde, and valeraldehyde. Guidelines are included for minimizing occupational exposures.

Published inhalation studies of acetaldehyde have shown the production of laryngeal carcinomas in male and female hamsters and carcinomas and adenocarcinomas of the nasal cavity in male and female rats. Malonaldehyde administered to rats by gavage produced an increase in adenomas and carcinomas of the thyroid gland in males and females and an increase in adenomas of the pancreatic islet cells in male rats. Research on the carcinogenic potential of the nine related aldehydes is not complete, but data suggest that their chemical reactivity and mutagenicity are similar to those of acetaldehyde, malonaldehyde, and formaldehyde. NIOSH is therefore concerned about possible increases in the occupational use of all nine compounds as substitutes for formaldehyde, a carcinogen recently regulated by the Occupational Safety and Health Administration (OSHA) [29 CFR* 1910.1048]. For example, acetaldehyde and glyoxal have been used to replace formaldehyde in embalming fluids [CRCS 1984]. Aldehydes such as glyoxal and malonaldehyde [Ura et al. 1983] may be used to replace formaldehyde as an intermediate for resins employed to treat paper [IARC 1982]. In addition, acetaldehyde, malonaldehyde, acrolein, butyraldehyde, crotonaldehyde, glutaraldehyde, and propionaldehyde have been used as reagents in laboratories [Auerbach et al. 1977]. Therefore, careful consideration should be given to reducing exposure to these aldehydes.

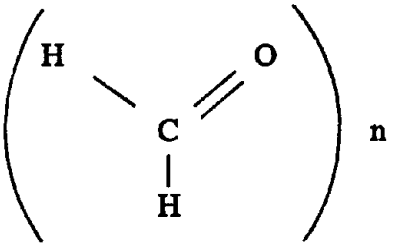
*Code of Federal Regulations. See CFR in references.

PHYSICAL AND CHEMICAL PROPERTIES

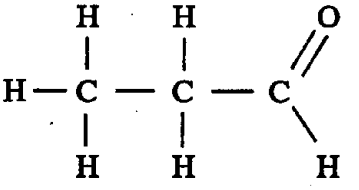
Acetaldehyde is a two-carbon compound with a carbonyl group (HC=O) (see Figure 1) and a molecular weight of 44.05. This clear liquid boils at 20.8°C (69.5°F). Its pleasant, fruity odor at dilute concentrations becomes pungent and suffocating at high concentrations. Acetaldehyde is readily oxidized within the body to acetate and acetic acid by liver mitochondrial acetaldehyde dehydrogenase [Lubin and Westerfeld 1945; Parrilla et al. 1974].

Malonaldehyde is a three-carbon compound with two carbonyl groups (see Figure 1) and a molecular weight of 72.06 (propanedial, sodium salt with a molecular weight of 94.04). The chemical and physical properties of malonaldehyde are similar to acetaldehyde and other low-molecular-weight monoaldehydes and dialdehydes [Brabec 1981]. Pure malonaldehyde is unstable and is precipitated as a sodium salt immediately before its use in

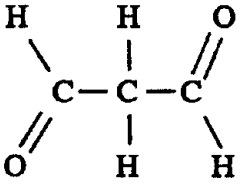
Paraformaldehyde



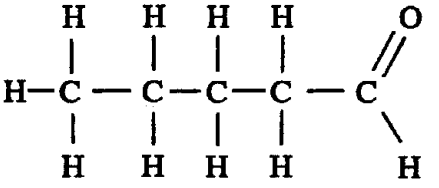
Propionaldehyde



Propanedial



Valeraldehyde



Propiolaldehyde

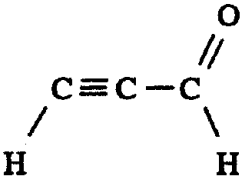


Figure 1 (Continued). Structures for acetaldehyde, malonaldehyde, and nine related low-molecular-weight aldehydes.

Table 1.—Physical and chemical properties of acetaldehyde and malonaldehyde*

Item	Acetaldehyde	Malonaldehyde	Propanedial (sodium salt)
CAS† registry no.	75-07-0	542-78-9	24382-04-5
RTECS‡ no.	AB1925000	TX6475000	ON8930000
Odor threshold	0.21 ppm	NA§	NA
Molecular formula	C_2H_4O	$C_3H_4O_2$	$C_3H_3O_2Na$
Molecular weight	44.05	72.06	94.04
Boiling point (760 mm Hg)	20.8°C (69.5°F)	NA	NA
Melting point	-121°C (-185.8°F)	72°C (161°F)	NA
Specific gravity (g/ml)	0.788 at 20°C	NA	NA
Refractive index	1.3316	NA	NA
Vapor pressure (mm Hg @ 20°C)	740	NA	NA
Flash point:			
Open cup	-40°C (-40°F)	NA	NA
Closed cup	-38.89°C (-38°F)	NA	NA
Temperature of autoignition	175°C (347°F)	NA	NA
Explosive limit in air, vol.%	4-57	NA	NA
Solvents	Water, alcohol, ether, acetone, benzene, toluene, solvent naphtha, turpentine, gasoline	Water	Water

*Data from Baxter [1979], Hagemeyer [1978], Hawley [1977], Hess et al. [1978], IARC [1985a], NIOSH [1986a], Patty [1981], Sax [1979], Weiss [1980], and Windholz et al. [1983].
†Chemical Abstracts Service.
‡Registry of Toxic Effects of Chemical Substances [NIOSH 1986a].
§Not available.

EVIDENCE OF CARCINOGENICITY IN ANIMALS

Acetaldehyde

Woutersen et al. [1986]

Woutersen et al. [1986] reported evidence for the carcinogenicity of acetaldehyde in their chronic inhalation study. Three groups (each composed of 55 male and 55 female Wistar rats) were exposed to acetaldehyde vapor 6 hr/day, 5 days/wk for 28 months at mean concentrations of 0, 735, or 1,412 ppm. A fourth group of the same size was initially exposed to 3,033 ppm. By day 360, exposure of the latter group was gradually reduced to a final concentration of 977 ppm because of severe growth retardation, loss of body weight, and early mortality. The study was terminated after 120 to 122 wk. A concentration-related incidence of squamous cell carcinoma of the nasal cavity occurred in both male and female rats. This increased incidence was statistically significant ($P<0.001$) in males and females exposed to 977 to 3,033 ppm and in males exposed to 1,412 ppm ($P<0.05$). These carcinomas infiltrated the submucosa of the nasal epithelium, filled one or both sides of the nasal cavity, destroyed turbinates, invaded the nasal bones, and extended into the subcutis and brain. Adenocarcinomas occurred in statistically significant numbers in the nasal cavities of rats of both sexes exposed to all three concentrations of acetaldehyde ($P<0.001$, except $P<0.05$ in female rats exposed to 735 ppm). The adenocarcinomas ranged in size from small groups of atypical cells in the olfactory epithelium that invaded only nerve bundles, to large osteolytic tumors that grew into the subcutis outside the nose and invaded the cerebrum through the olfactory lobe. The authors concluded that the nasal tumors arose from the respiratory and olfactory epithelia that were damaged by acetaldehyde.

Feron et al. [1982]

Feron et al. [1982] conducted inhalation studies in which male and female Syrian golden hamsters were exposed (7 hr/day, 5 days/wk) to a gradual reduction of acetaldehyde vapor as follows:

Average vapor concentration in ppm (mg/m^3)	Exposure period (study weeks)
2,500 (4,500)	1-9
2,250 (4,050)	10-20
2,000 (3,600)	21-29
1,800 (3,240)	30-44
1,650 (2,970)	45-52

An equal number of control animals received filtered and conditioned air. Hamsters of the acetaldehyde-exposed and the air-control groups were further subdivided into five treatment groups (Table 2). Inhalation exposure to acetaldehyde and benzo[a]pyrene (BP) or diethylnitrosamine (DENA) treatments were conducted simultaneously for 52 wk, and the study ended at wk 81 after a 29-wk recovery period. A statistically significant increase ($P<0.05$) occurred in the incidence of combined laryngeal tumors (carcinoma in situ, squamous cell carcinoma, and adeno-squamous carcinoma) in hamsters of both sexes exposed to acetaldehyde vapor when compared with unexposed, pooled controls (Groups 1 and 2).

A statistically significant increase ($P<0.05$) occurred in the incidence of squamous cell carcinoma in the trachea, larynx, and bronchi of males instilled with a total BP dose of 36.4 mg/hamster and exposed to acetaldehyde compared with males instilled with the same dose of BP and exposed to air (Group 4). An increased incidence of squamous cell carcinoma of the trachea (statistical significance was not given) occurred in females instilled with 0.35% BP and exposed to acetaldehyde compared with females instilled with the same dose of BP and exposed to air (Group 4). Males and females exposed to acetaldehyde and instilled with a total BP dose of 18.2 mg/hamster had a statistically increased incidence ($P<0.05$) of squamous cell carcinoma of the larynx compared with controls instilled with the same dose of BP (Group 3).

In hamsters exposed to acetaldehyde and subcutaneously injected with a total of 0.0021 mg DENA/hamster, the incidence of carcinoma in situ of the larynx was increased in males and the incidences of carcinoma in situ and squamous cell carcinoma of the larynx in females were statistically increased ($P<0.05$) compared with the controls exposed to air and injected with an equivalent dose of DENA (Group 5). The incidence of tumors in the control animals treated with BP or DENA and exposed to air were not different from the controls treated with saline and exposed to air.

Malonaldehyde

NTP [1988]

The National Toxicology Program (NTP) [1988] conducted a 2-yr study of malonaldehyde exposure in F344/N rats and B6C3F1 mice. Highly purified anhydrous malonaldehyde (propanedial, sodium salt) was administered by gavage 5 days/wk for 103 wk at doses of 0, 50, and 100 mg/kg (in distilled water) to groups of 50 male and 50 female rats. Doses of 0, 60, and 120 mg/kg (in distilled water) were administered by gavage to groups of 50 male and 50 female mice on the same schedule. There was no evidence of carcinogenic activity in the mice. The incidence of thyroid gland follicular cell hyperplasia was statistically increased ($P<0.001$) in the female rats given 100 mg malonaldehyde/kg compared with the vehicle controls. In male and female rats that received 100 mg malonaldehyde/kg, the incidence of follicular cell adenomas and carcinomas (combined) was statistically increased ($P<0.05$) when compared with that of the corresponding vehicle controls. The incidence of pancreatic islet cell adenomas was statistically increased ($P=0.001$) in male rats receiving 50 mg malonaldehyde/kg compared with the vehicle controls. Incidences of pancreatic islet cell tumors in female rats were not significantly different from those observed in the female vehicle controls.

The NTP study concluded that the increased incidences of follicular cell adenomas and carcinomas (combined) of the thyroid gland provided clear evidence of carcinogenic activity for male and female F344/N rats administered malonaldehyde (propanedial, sodium salt). Pancreatic islet cell adenomas were also observed at a significantly increased incidence in low-dosed male rats.

Shamberger et al. [1974, 1975]

In a two-stage mouse-skin initiation assay [Shamberger et al. 1974, 1975], groups of 30 female Swiss mice, 55 days old, were treated with one application of 6 or 12 mg malonaldehyde in acetone or with 0.125 mg of 7,12-dimethylbenz[a]anthracene (DMBA) in acetone to their shaved backs. After 3 wk, the backs of the mice were treated for 27 wk (5 days/wk) with 0.1% croton oil in acetone. Control groups received either no treatment or one application of the following: malonaldehyde, DMBA, or acetone. By the end of the 30-wk experiment, 52% of the mice receiving malonaldehyde and croton oil had tumors, and 95% of the mice treated with DMBA and croton oil had tumors. No tumors appeared in the control groups. Statistical significance was not given.

In a second experiment, 30 female Swiss mice were treated with 12 mg malonaldehyde daily for 9 wk [Shamberger et al. 1974]. Because this concentration was toxic, daily skin application was reduced to 0.36 mg malonaldehyde for an additional 39 wk. No tumors occurred in the 12 mice that died during the first 4 to 6 wk of the experiment. Five of the six mice that died during wk 7 through 9 had tumors, including four liver carcinomas (three of which were metastatic to the kidney, rectum, or lung) and one rectal carcinoma. No other tumors were seen through wk 48, and no tumors were seen in the control animals. Statistical significance was not given.

Table 3.—Summary of positive mutagenic responses to acetaldehyde

Type of mutation	Organism	References
SCE*	Human lymphocytes	He and Lambert [1985] Jansson [1982] Knadle [1985] Norppa et al. [1985] Ristow and Obe [1978] Véghelyi and Osztovics [1977]
	CHO†	Brambilla et al. [1986] Obe and Beek [1979]
	Chinese hamster bone marrow	Korte and Obe [1981]
	CBA mouse chromosomes	Obe et al. [1979]
Chromosomal aberrations	Rat skin fibroblasts	Bird et al. [1982]
	Human lymphocytes	Obe et al. [1979]
	Rat fetuses	Barilyak and Kozachuk [1983]
DNA cross-links	Human lymphocytes	Lambert et al. [1985]
	Rat nasal mucosa	Lam et al. [1986]
	CHO	Marinari et al. [1984]
	Calf thymus	Ristow and Obe [1978]
Zone inhibition	*Escherichia coli* pol A_1-	Rosenkranz [1977]
Sex-linked recessive lethal mutation	*Drosophila melanogaster*	Woodruff et al. [1985]
Inhibited RNA and DNA synthesis	Human bronchial epithelial cells	Saladino et al. [1985]
Inhibited DNA synthesis	Reuber rat hepatoma (H35) and (Hep 10C)	Dreosti et al. [1981]
Inhibited protein and RNA synthesis	Rat pancreatic acini	Majumdar et al. [1986]
Initiation	C3H/10T1/2 mouse cells	Abernethy et al. [1982]

*SCE: Sister chromatid exchange.
†CHO: Chinese hamster ovary cell culture.

and a prechronic inhalation study of butyraldehyde in mice and rats. Isobutyraldehyde, an isomer of butyraldehyde, has been tested in a prechronic inhalation study, and a 2-yr inhalation study in rats and mice is now in progress.

Crotonaldehyde administered in the drinking water of rats induced a statistically significant incidence ($P<0.001$) of well circumscribed, noninvasive, and nonmetastatic hepatocellular neoplasms [Chung et al. 1986]. Crotonaldehyde was mutagenic in *S. typhimurium* assays [Marnett et al. 1985; Neudecker et al. 1981; Haworth et al. 1983; Lutz et al. 1982]. This aldehyde induced chromosomal damage and meiotic anomalies in male mice during spermatogenesis [Moutschen-Dahmen et al. 1976] and sex-linked recessive lethal mutations in *D. melanogaster* [Woodruff et al. 1985]. NTP [1990] has completed the prechronic testing of crotonaldehyde by corn oil gavage in rats and mice.

Glutaraldehyde was mutagenic in *S. typhimurium* assays [Marnett et al. 1985; Haworth et al. 1983; Levin et al. 1982]. NTP [1990] canceled the original skin painting study of rats and mice with glutaraldehyde. Chronic testing of glutaraldehyde is planned by NTP following a prechronic inhalation study.

Glyoxal induced unscheduled DNA synthesis and increased ornithine decarboxylase activity in the pyloric mucosa of rats, indicating a potential initiating activity in carcinogenesis of the stomach [Furihata et al. 1985]. Glyoxal was mutagenic in *S. typhimurium* assays [Sasaki and Endo 1978; Yamaguchi and Nakagawa 1983; Levin et al. 1982; Marnett et al. 1985] and in an *E. coli* mutagenesis assay [Chopra 1966]. Glyoxal also induced sex-linked recessive lethal mutations in *D. melanogaster* [Barnett and Munoz 1969]. A prechronic study is in progress with glyoxal by the oral water route in rats and mice [NTP 1991].

Paraformaldehyde induced transformation in rat embryo cells infected with Rauscher leukemia virus [Traul et al. 1981].

Propiolaldehyde was mutagenic in *S. typhimurium* assays [Basu and Marnett 1983].

Propionaldehyde and valeraldehyde induced single-strand breaks in Chinese hamster ovary cells [Marinari et al. 1984]. Valeraldehyde tested negative in the *S. typhimurium* assay, and no other testing is scheduled [NTP 1990].

There is evidence that the nine related aldehydes produce DNA breaks and alterations. Acetaldehyde and malonaldehyde have been shown to induce similar alterations [Lambert et al. 1985; Marinari et al. 1984]. Most chemicals known to cause cancer are also capable of causing a change in the genetic material within a cell (mutation) [Ames et al. 1975]. DNA damage has been related to mutagenicity and is a sensitive indicator of potential chemical carcinogenesis [Goldstein et al. 1975; Lutz 1979]. The interaction of the aldehyde chemical group with DNA, RNA, or enzymes involved in DNA replication, resulting in a change in genetic material, is a possible mechanism for the carcinogenicity of acetaldehyde, malonaldehyde, and formaldehyde [Feron et al. 1982; Chio and Tappel 1969; Auerbach et al. 1977]. The mutagenic effects of the nine related aldehydes are similar to those produced by acetaldehyde and malonaldehyde and thus may indicate carcinogenic potential.

HUMAN HEALTH EFFECTS

Acute exposure of humans to 50 ppm acetaldehyde vapor for 15 min produced mild eye irritation; 200 ppm for 15 min produced bloodshot eyes and reddened eyelids; and 135 ppm for 30 min produced mild irritation of the upper respiratory tract [Silverman et al. 1946; Sim and Pattle 1957]. Acetaldehyde splashed in the eyes is reported to cause painful but superficial injury to the cornea [Grant 1974; McLaughlin 1946]. Systemic effects resulting from chronic acetaldehyde exposure in the workplace have not been reported, but prolonged exposure to acetaldehyde may produce drowsiness [MCA, Inc. 1952].

Classification, and Regulation of Potential Occupational Carcinogens" [29 CFR 1990], also known as the OSHA carcinogen policy) the most appropriate for use in identifying potential occupational carcinogens.*

Exposure to acetaldehyde has produced nasal tumors in rats and laryngeal tumors in hamsters, and exposure to malonaldehyde has produced thyroid gland and pancreatic islet cell tumors in rats. NIOSH therefore recommends that acetaldehyde and malonaldehyde be considered potential occupational carcinogens in conformance with the OSHA carcinogen policy. The excess cancer risk for workers exposed to acetaldehyde or malonaldehyde has not been established, but the probability of developing cancer should be decreased by minimizing exposure. As a matter of prudent public health policy, employers should assess the conditions under which workers may be exposed to acetaldehyde or malonaldehyde and take reasonable precautions (such as appropriate engineering and work practice controls) to reduce exposures to the lowest feasible concentration.

Testing has not been completed to determine the carcinogenicity of the nine related low-molecular-weight aldehydes discussed in this CIB (acrolein, butyraldehyde, crotonaldehyde, glutaraldehyde, glyoxal, paraformaldehyde, propiolaldehyde, propionaldehyde, and valeraldehyde). However, the limited studies that have been conducted indicate that these chemicals have chemical reactivity and mutagenicity similar to acetaldehyde, malonaldehyde, and formaldehyde. Therefore, careful consideration should be given to reducing exposures to these nine related aldehydes.

*"'Potential occupational carcinogen' means any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration. This definition also includes any substance which is metabolized into one or more potential occupational carcinogens by mammals" [29 CFR 1990.103].

GUIDELINES FOR MINIMIZING WORKER EXPOSURE

The following guidelines for minimizing worker exposure to the aldehydes discussed here are general and should be adapted to specific work situations as required.

Exposure Monitoring

NIOSH recommends that each employer who manufactures, transports, packages, stores, or uses aldehydes in any capacity determine whether a potential exists for any worker to be exposed to the chemical. In work areas where exposures may occur, an initial survey should be done to determine the extent of worker exposure.

Samples should be collected over a full shift to determine exposures. When the potential for exposure is periodic, short-term sampling may be needed to replace or supplement full-shift sampling. Personal sampling is preferred to area sampling. If personal sampling is not feasible, area sampling can be substituted only if the results can be used to approximate the workers' exposure. Sampling should be used to (1) identify the sources of emissions so that effective engineering or work practice controls can be instituted, and (2) ensure that controls already in place are operational and effective.

The *NIOSH Manual of Analytical Methods* provides detailed descriptions of sampling and analytical techniques for aldehydes (screening) (Method 2539 [NIOSH 1989]), acetaldehyde (Method 3507 [NIOSH 1986b] and Method 2538 [NIOSH 1989]), acrolein (Method 2501 [NIOSH 1986b]), glutaraldehyde (Method 2532 [NIOSH 1986b] and Method 2531 [NIOSH 1989]), and valeraldehyde (Method 2536 [NIOSH 1989]).

Closed Systems and Ventilation

Engineering controls should be the principal method for minimizing skin and respiratory exposure to aldehydes in the workplace. Achieving and maintaining reduced concentrations of airborne aldehydes depend on adequate engineering controls such as closed-system operations and ventilation systems that are properly constructed and maintained.

Closed-system operations provide the most effective means for minimizing worker exposures to aldehydes. Closed systems should be used for producing, storing, transferring, packaging, and processing aldehydes. For quality control laboratories or laboratories where production samples are prepared for analyses, exhaust ventilation systems should be designed to capture and contain vapors. Guidance for designing local exhaust ventilation systems can be found in *Recommended Industrial Ventilation Guidelines* [Hagopian and Bastress 1976], *Industrial Ventilation—A Manual of Recommended Practice* [ACGIH 1986], and *Fundamentals Governing the Design and Operation of Local Exhaust Systems* [ANSI 1988].

Worker Isolation

The area in which aldehydes are produced or used should be restricted to workers essential to the process or operation. If feasible, these workers should be isolated from direct contact with aldehydes by the use of automated equipment operated from a closed control booth or room. This room should be maintained at greater air pressure than that surrounding the process equipment so that air flows out rather than in. When workers must enter the general work area to perform process checks, adjustments, maintenance, assembly line tasks, and related operations, they should take special precautions such as the use of personal protective equipment.

Personal Protective Equipment

The use of personal protective equipment (CPC, other protective equipment, and respiratory protection devices) is the least desirable method of controlling worker exposures to aldehydes and should not be used as the primary control method during routine operations.

CPC and other protective equipment.—To prevent repeated or prolonged skin contact and absorption, workers who may handle aldehydes should wear appropriate CPC and protective equipment such as gloves and face shields (8-in. length minimum). CPC made from butyl rubber should provide adequate protection for at least 1 hr [Schwope et al. 1985]. Note, however, that the quality of gloves may vary significantly among glove producers [Mickelsen and Hall 1987]. Product-specific chemical permeation data should therefore be obtained from the glove manufacturer. Splashproof goggles or face shields should be worn if there is any possibility that liquid aldehydes will contact the eyes. Safety showers and eye wash stations should be located close to operations that involve aldehydes.

Respiratory protection devices.—NIOSH recognizes that respirators may be required to provide protection in certain situations such as implementation of engineering controls, certain short-duration maintenance procedures, and emergencies. NIOSH maintains that only the most protective respirators should be used for situations involving carcinogens. These respirators include

- any self-contained breathing apparatus equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode, and
- any supplied-air respirator equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode in combination with an auxiliary self-contained breathing apparatus operated in a pressure-demand or other positive-pressure mode.

that will have a better clinical outcome with early detection.

Epidemiologic evidence about the effectiveness of cancer screening programs in improving clinical outcomes can be established only for common cancers such as lung, colon, or breast cancer. Most other cancers do not occur frequently enough for the effectiveness of screening to be evaluated epidemiologically. NIOSH therefore recommends screening when (1) screening tests are widely available, safe, and effective, and (2) limited evidence suggests that screening may be beneficial (at least in high-risk groups) or that state-of-the-art treatment may improve survival.

Several consensus groups have considered the potential usefulness of screening for oral cancer. The Canadian Task Force on the Periodic Health Examination [1979] recommends annual visual inspection of the mouth for males and all smokers. The National Cancer Institute [NCI 1987] and the American Cancer Society [1980] recommend periodic oral examinations for these groups. The Report of the U. S. Preventive Services Task Force [1989] cites evidence that patients whose oral cancer was discovered at an early stage have a better prognosis than those whose cancer was detected later. Because further research is necessary to confirm the value of screening, the task force did not recommend routine screening of asymptomatic persons for oral cancer by primary care clinicians. However, they noted that it "may be prudent for clinicians to perform careful examinations for cancerous lesions of the oral cavity in patients who use tobacco or excessive amounts of alcohol, as well as in those with suspicious symptoms or lesions detected through self-examination." On the basis of these recommendations, NIOSH concludes that workers exposed to acetaldehyde and malonaldehyde are likely to benefit from screening.

Cancer screening recommendations.—NIOSH recommends that workers exposed to acetaldehyde or malonaldehyde be offered medical screening (including cancer screening) along with appropriate counseling. Such counseling should include a discussion of (1) the evidence suggesting that such screening may be beneficial, and (2) the action to be taken if the screening test is positive (e.g., referral for further workup).

The cancer screening program should include the following:

- A medical history with emphasis on the ears, nose, mouth, and throat (e.g., history of dysphagia, sore throat, otalgia, recurrent otitis media, cranial nerve dysfunction, blocked eustachian tubes, nasal obstruction, chronic sinusitis, bleeding, hoarseness, neck lumps, or cough)

- Examination of the nasal passages, buccal cavity, and pharynx (including the nasopharynx) for evidence of cancer or precancerous lesions

- Examination of the cranial nerves (a neurological deficit could result from tumor encroachment in the nasopharyngeal area)

- Examination of the cervical lymph nodes (cervical adenopathy is frequently the first sign of pharyngeal carcinoma) [Fechner 1989]

NIOSH is not aware of studies showing routine cytology of the nasal and oral passages to be beneficial to screened individuals, but any suspicious lesions noted on visual examination should be adequately evaluated (including biopsy and pathological examination if appropriate).

Paraformaldehyde (synonyms: triformol, paraform)	RV0540000 30525-89-4	(30)n	$(CH_2O)n$	dp‡	1.46	Strong alkali	71.1°C (160°F)	<2
Propanedial, ion (1-), sodium (synonym: malonaldehyde, sodium salt)	ON8930000 24382-04-5	94.04	$C_3H_3O_2 \cdot Na$	NA	NA	Water	NA	NA
Propiolaldehyde (synonyms: 2-propynal, proparglyaldehyde)	UD9275500 624-67-9	54.05	$C_3H_2O_2$	59°C (138.2°F)	NA	NA	NA	NA
Propionaldehyde (synonyms: propanal, propionic aldehyde)	UE0350000 123-38-6	58.09	C_3H_6O	48.8°C	0.8058	Water, alcohol	-17.8°C (15°F)	300
Valeraldehyde (synonyms: pentanal, valeric aldehyde)	YV3600000 110-62-3	86.15	$C_5H_{10}O$	103°C (217.4°F)	0.8095	Water, alcohol, ether	12.2°C (54°F) (closed cup)	3.0

*Data from Brabec [1981], CRCS [1984], Fassett [1963], Hawley [1977], IARC [1979, 1985a, 1985b], Weast et al. [1988], and Windholz et al. [1983].
†Not available.
‡Depolymerizes to formaldehyde above 60°C.

Appendix C.—Mutagenicity and toxicity of nine low-molecular-weight aldehydes

Aldehyde	Health effects	Organism	Exposure route	References
Acrolein	Mutagenicity:			
	Hyperplastic and metaplastic changes of the nasal cavity	Hamsters	Inhalation	Feron and Kruysse [1977]
	Adenomas and neoplastic nodules	Rats	Oral administration	Lijinsky and Reuber [1987]
	Mutagenic, cytotoxic response	*Salmonella typhimurium* TA104	In vitro	Marnett et al. [1985]
	Mutagenic response	*Salmonella typhimurium* TA100 ±S9*	In vitro	Haworth et al. [1983]
	Mutagenic response	*Salmonella typhimurium* TA100 −S9	In vitro	Lutz et al. [1982]
	Inhibited activity of DNA polymerase	Regenerating rat liver DNA polymerase	In vitro	Munsch et al. [1973]
	Developmental toxicity:			
	Fetal resorption, malformation	Rats	Intra-amniotic injection	Slott and Hales [1985]
	Malformation	Chick embryos	Injection of air chamber	Korhonen et al. [1983]
	Reduced pregnancy	Mice	Intraperitoneal injection	Epstein et al. [1972]
	Maternal death, malformation, fetal death	Rabbits, yolk sacs	Intravenous injection	Claussen et al. [1980]
	Arrested differentiation	Rats, fetal explants	Exposure in culture	Schmid et al. [1981]
	Acute toxicity:			
	Changes in blood pressure and heart rate	Rats	Cannulation, inhalation	Egle and Hudgins [1974]
	Pulmonary edema, death	Rats	Inhalation	Kutzman et al. [1985]
	LD_{50},† 0.046 g/kg	Rats	Oral administration	Smyth et al. [1951]
	Ciliotoxicity	Tracheal mucosa (species not specified)	In vitro	Dalhamn and Rosengren [1971]
	Lacrimation, irritation, 0.805 ppm/10 min or 1.220 ppm/5 min	Humans	Inhalation	Sim and Pattle [1957]
	RD_{50},‡ 6.0 ppm	Rats	Inhalation	Babiuk et al. [1985]
	RD_{50}, 1.0 ppm	Mice	Inhalation	

(Continued)

See footnotes at end of table.

Butyraldehyde (Continued)	Cardiovascular effects:			
	Bradycardia, arterial hypertension, tachycardia	Dogs	Direct intranodal perfusion	James and Bear [1968]
	Increased blood pressure	Cats	Femoral vein infusion	Eade [1959]
Crotonaldehyde	Mutagenicity:			
	Neoplastic liver lesions	Rats	Oral administration	Chung et al. [1986]
	Sex-linked recessive lethal mutation	*Drosophila melanogaster*	Injection	Woodruff et al. [1985]
	Mutagenic response	*Salmonella typhimurium* TA104	In vitro	Marnett et al. [1985]
	Nonmutagenic response	*Salmonella typhimurium* TA100	In vitro	Cooper et al. [1987]
	Mutagenic response	*Salmonella typhimurium* TA100 ±S9	In vitro	Neudecker et al. [1981]
	Mutagenic response	*Salmonella typhimurium* TA100 ±S9	In vitro	Haworth et al. [1983]
	Mutagenic response	*Salmonella typhimurium* TA100 ±S9	In vitro	Lutz et al. [1982]
	Developmental toxicity:			
	Sperm meiotic anomalies	Mice	Intraperitoneal injection	Moutschen-Dahmen et al. [1976]
		Mice	Oral administration	
	Acute toxicity:			
	Mean fatal dose:			
	1.1×10^5 mg-min/m^3	Mice	Inhalation	Salem and Cullumbine [1960]
	2.0×10^5 mg-min/m^3	Guinea pigs	Inhalation	
	1.9×10^5 mg-min/m^3	Rabbits	Inhalation	
	LD_{50}, 0.14 g/kg	Rats	Subcutaneous injection	Skog [1950]
	LD_{50}, 0.16 g/kg	Mice	Subcutaneous injection	
	LD_{50}, 4.00 mg/l	Rats	Inhalation	
	LD_{50}, 0.30 g/kg	Rats	Oral administration	Smyth and Carpenter [1944]
	LD_{50}, 0.03 ml/kg	Guinea pigs	Skin	
	RD_{50}, 23.2 ppm	Rats	Inhalation	Babiuk et al. [1985]
	RD_{50}, 3.5 ppm	Mice	Inhalation	
	Ciliotoxicity	Tracheal mucosa (species unspecified)	In vitro	Dalhamn and Rosengren [1971]
	Irritation of upper respiratory tract, lacrimation at 4.1 ppm for 10 min	Humans	Inhalation	Sim and Pattle [1957]
	Irritation, lacrimation	Humans	Vapor exposure	Stokinger [1953]

(Continued)

See footnotes at end of table.

Glyoxal (Continued)	Increased DNA synthesis, UDS, ODC***	Rats	Stomach intubation	Furihata et al. [1985]
	Acute toxicity:			
	LD_{50}, 7.07 ml/kg	Rats	Oral administration	Union Carbide Corporation [1965]
	LD_{50}, 10.0 ml/kg	Rabbits	Skin	
	Severe injury	Rabbits	Cornea	Carpenter and Smyth [1946]
	Contact dermatitis	Humans	Skin	Hindson and Lawlor [1982]
Paraformaldehyde	Mutagenicity:			
	Transformation	Rat embryo cells	In vitro	Traul et al. [1981]
	Acute toxicity:			
	Paresthesis	Humans	Root canal	Grossman and Tatoian [1978]
	Necrosis of crestal bone	Humans	Root canal	Stabholz and Blush [1983]
Propiolaldehyde	Mutagenicity:			
	Mutagenic response	*Salmonella typhimurium* hisD3052	In vitro	Basu and Marnett [1984]
	No DNA cross-links	Species not given	In vitro	Basu [1985]
Propionaldehyde	Mutagenicity:			
	DNA breaks	CHO	In vitro	Marinari et al. [1984]
	Acute toxicity:			
	Mean fatal dose:			
	7.9×10^5 mg-min/m^3	Mice	Inhalation	Salem and Cullumbine [1960]
	7.4×10^5 mg-min/m^3	Rabbits	Inhalation	
	RD_{50}, 6,789 ppm	Rats	Inhalation	Babiuk et al. [1985]
	RD_{50}, 2,052 ppm	Mice	Inhalation	
	Mild irritation at 134 ppm for 30 min	Humans	Inhalation	Sim and Pattle [1957]
	LD_{50}, 0.82 g/kg	Rats	Subcutaneous injection	Skog [1950]
	LD_{50}, 0.68 g/kg	Mice	Subcutaneous injection	
	LD_{50}, 62.0 mg/l	Rats	Inhalation	

(Continued)

See footnotes at end of table.

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