

## SUMMARY OF DATA FOR CHEMICAL SELECTION

### ***n*-VALERALDEHYDE**

CAS NO. 110-62-3

#### BASIS OF NOMINATION TO THE CSWG

The nomination of valeraldehyde to the CSWG is based on high production volume, exposure potential, and suspicion of carcinogenicity. Dr. Elizabeth Weisburger, a member of the American Conference of Governmental Industrial Hygienists (ACGIH) TLV Committee as well as the Chemical Selection Working Group (CSWG), provided a list of 281 chemical substances with ACGIH recommended TLVs for which there were no long term studies cited in the supporting data and no designations with respect to carcinogenicity. She presented the list to the Chemical Selection Planning Group (CSPG) for evaluation as chemicals which may warrant chronic testing: it was affirmed at the CSPG meeting held on August 9, 1994, that the 281 "TLV Chemicals" be reviewed as a Class Study. As a result of the class study review, valeraldehyde is presented as a candidate for testing by the National Toxicology Program because of:

- potential for occupational exposures based on high production volume (25-100 million lbs) and estimate of worker exposure
- evidence of occupational exposures based on TLV and other literature documentation
- universal potential for general population exposures based on endogenous and exogenous occurrence in many consumed products and in environmental media
- suspicion of carcinogenicity based on short-term test results and aldehyde structure
- lack of chronic toxicity data.

#### SELECTION STATUS

ACTION BY CSWG: 9/25/96

#### Studies requested:

- Subchronic (90-day)
- Mouse lymphoma (to be performed in the NCI Short-Term Test Program (STTP))

Priority: Moderate

Rationale/Remarks:

- Potential for widespread human exposure
- Suspicion of carcinogenicity

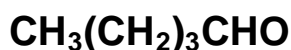
INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee (ITC), Environmental Protection Agency (EPA), provided information on the total annual production level of valeraldehyde and the TSCA ITC status of this chemical (see Regulatory Status section) (Walker, 1995a,b).

## CHEMICAL IDENTIFICATION

<u>CAS Registry Number:</u>	110-62-3
<u>Chemical Abstracts Service Name:</u>	Pentanal (9CI); valeraldehyde (8 CI);
<u>Synonyms:</u>	Amyl aldehyde; <i>n</i> -pentanal; valeral; <i>n</i> -valeraldehyde; valeric acid aldehyde; valeric aldehyde; valerylaldehyde
<u>Structural class:</u>	Aliphatic aldehyde

## Structure, Molecular Formula and Molecular Weight



C<sub>5</sub>H<sub>10</sub>O Mol. Wt.: 86.13

Chemical and Physical Properties  
(from ACGIH, 1992, unless otherwise referenced)

<u>Description:</u>	Colorless, volatile liquid with pungent odor
<u>Boiling Point:</u>	102-103°C
<u>Melting Point</u>	-91.5°C
<u>Specific Gravity:</u>	0.8095 @ 20°C
<u>Vapor Pressure:</u>	26 torr. @ 20°C
<u>Vapor Density:</u>	3.0 (air = 1.0) (Brabec, 1993)
<u>Solubility:</u> ethyl solvents	Slightly soluble in water (1.4% by wt.); soluble in alcohol, ethyl ether, and other common organic (Falbe <i>et al.</i> , 1985)
<u>Volatility:</u>	25,000 ppm @ 25°C (Amoore & Hautala, 1983)
<u>Flash Point:</u>	12.2°C, open cup
<u>Stability:</u> 1991; Lewis, 1993)	Stable; dangerous fire hazard (Eastman Kodak Co.,
<u>Log P:</u>	1.36 (Schultz <i>et al.</i> , 1994)

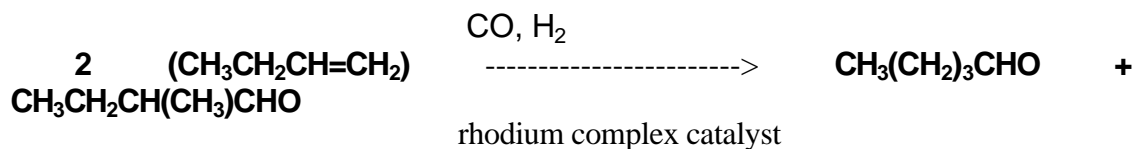
Technical Products and Impurities: Valeraldehyde is available in purities ranging from 95 to greater than 99% from numerous manufacturers or suppliers of research and bulk chemicals (Crescent Chemical Co., Inc., undated; Pfaltz & Bauer, Inc., undated; Mallinckrodt Specialty Chemicals Co., 1989; Janssen Chimica, 1992; Eastman Chemical Co., 1993; Fluka

Chemical Corp., 1995; Lancaster Synthesis, Inc., 1995; Aldrich Chemical Co., Inc., 1996a; TCI America, 1996).

Valeraldehyde is available as a flavor/aroma material which meets Food Chemical Codex (FCC) specifications. This chemical has been assigned Flavor and Extract Manufacturers' Association (FEMA) number 3098 (Aldrich Chemical Co., 1996b).

### EXPOSURE INFORMATION

Production and Producers: Valeraldehyde can be prepared by oxidation of the corresponding alcohol, 1-pentanol or by reduction of n-valeric acid (Opdyke, 1979; Lewis, 1993). Valeraldehyde is one of a number of aliphatic aldehydes industrially prepared by the oxo process, which involves the reaction of olefins with carbon monoxide and hydrogen in the presence of a catalyst. Use of a cobalt carbonyl complex as catalyst required high pressure in an older process, which has been largely replaced by a low-pressure process based on rhodium complex catalysts, such as a tris (alkyldiarylphosphine) rhodium carbonyl hydride. The reaction is depicted by the following scheme, where the ratio of the two products depends on the reaction conditions (Falbe *et al.*, 1985; Oswald *et al.*, 1987; Collins & Richey, 1992).



Valeraldehyde can be produced for marketing as a natural flavoring compound in an enzymatic bioindustrial process from pentanol using the methylotrophic yeast, *Pichia pastoris* (Williams *et al.*, 1988).

Valeraldehyde is listed in the EPA's TSCA Inventory (USEPA, 1991). United States production of valeraldehyde in 1989 was reported to be in the range of 25 - 100 million pounds based on non-confidential data received by the EPA (Walker, 1995a). Falbe *et al.* (1985) reported that the 1980 US consumption of valeraldehyde obtained by the oxo process was 64 million pounds. Valeraldehyde is listed as a chemical in commerce in the U.S. International Trade Commission (USITC) publication, *Synthetic Organic Chemicals, US Production and Sales, 1991/1992/1993* (USITC, 1993, 1994a,b). The reporting company was listed as Union Carbide Corp., Industrial Chemicals Division;

but no production or sales quantities were included. According to the USITC, separate statistics were not published to avoid disclosure of individual company operations. However, the USITC reporting guidelines specify that each company's report of a chemical represents production of  $\geq 4,500$  kg [10,000 lbs] or sales  $\geq$  \$10,000. Based on a search of recent literature sources, including chemical industry catalogs, directories, and databases, the companies presented in Table 1 have been identified as producers/suppliers of valeraldehyde, recent patent assignees for its preparation and/or use, or companies providing toxicity study results to the EPA in response to a TSCA §8(d) rule (Chemical Information Services, Inc., 1994; Hunter, 1994; Van, 1994; CIS, 1995; NLM, 1996; STN International, 1996).

Table 1. Companies producing or supplying valeraldehyde

	Producer/supplier listed in chemical industry catalog and/or directory	Company assigned patent for use and/or preparation	Company providing toxicity study data to EPA
Aceto Corp./Pfaltz & Bauer, Inc.	X		
Acros Organics/Fisher Scientific	X		
Aldrich Chemical Co.	X		
Aldrich Flavors & Fragrances	X		
BASF Corp./BASF A.-G.	X		
Eastman Chemical Co./Eastman Kodak Co.	X	X	X
Exxon Research & Engineering Co.		X	
Fluka Chemical Corp.	X		
Hoechst Celanese/Hoechst A.G.	X	X	
International Flavors & Fragrances, Inc.		X	
Mallinckrodt Spec. Chems. Co.	X		
Phillips Petroleum Co.		X	
Quaker Oats Co.	X		
TCI America	X		
Union Carbide Corp.	X	X	X

Use Pattern: Valeraldehyde is mainly used as a chemical intermediate. As a starting material in industrial organic synthesis, it is hydrogenated to 1-pentanol, oxidized to valeric acid, and aminated to 1-aminopentane (Falbe *et al.*, 1985; NLM, 1996).

Valeraldehyde is also used extensively as a natural and synthetic flavoring agent. It is used as a top note for flavor to give identity (fruity, nutty) on first impression and is a component of rose oil used to flavor foods, beverages and chewing tobacco (Furia, 1972; Rogers, 1981; NLM, 1996).

Valeraldehyde is also used as a polymer modifier and rubber accelerator (Budavari, 1989; ACGIH, 1992; STN International, 1996).

Human Exposure: There is potential for exposures to valeraldehyde in occupational, consumer and environmental settings by inhalation, ingestion, and dermal contact.

### *Occupational Exposure*

The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 1,557 workers, including 276 female employees, were potentially exposed to valeraldehyde in the workplace. The NOES database does not contain information on the frequency, level, or duration of exposure to workers of any chemical listed therein (NIOSH, 1990).

### *Consumer Exposure*

There is potential for consumer oral, inhalation and dermal exposures to low levels of valeraldehyde as a component (at 0.05-0.07%) of rose oil. Rose oil is used as a fragrance ingredient in cosmetics, toilet waters and perfumes and as a flavoring for foods and tobacco products, particularly chewing tobacco (Rogers, 1981). An odor threshold concentration of 0.028 ppm (0.072 mg/m<sup>3</sup>) has been reported for valeraldehyde (Verschueren, 1983; ACGIH, 1992). The *Aldrich Flavors and Fragrances* catalog, a source of natural and synthetic flavor/aroma chemicals, describes the odor characteristics of valeraldehyde as "woody, vanilla, fruity, nutty on dilution" (Aldrich Chemical Co., 1996b).

There is widespread potential for general population, low level, oral exposures to valeraldehyde through its presence as a flavor constituent in many foods and beverages, and as a meat smoking flavorant. Valeraldehyde has been detected in oxidized heated or stored fats and oils, including meat fats, fish and vegetable oils (e.g., olive, corn, cottonseed, sunflower, rapeseed, peanut), in some fruits (e.g., apples, oranges, bananas, black currants) and vegetables (e.g., red and green bell peppers), and in milk and cheese products, black and green teas, coffee beans, and cocoa beans (Opdyke, 1979; NRC, 1981; Urbach, 1987; Shibamoto, 1990; Chun & Kim, 1992; Snyder, 1995). It is reported to be associated with lipid hydroperoxidation and rancidity of edible fats and oils (Chun & Kim, 1992; Frankel *et al.*, 1992; Snyder, 1995). Lin and coworkers (1995) suggested the measurement of carbonyl compounds, including valeraldehyde, from polyunsaturated fatty acids (PUFAs) in human breath as a method of assessing lipid peroxidation and metabolic status *in vivo*.

Ingestion exposures to valeraldehyde are also possible as a result of its occurrence as an ozonation by-product in drinking water (Matsui *et al.*, 1989). Another

potential source of ingestion exposures to valeraldehyde is from food contact with packaging materials. In simulated cooking tests conducted by the FDA, valeraldehyde was identified in 9 of 11 food packaging products for microwave cooking and crisping at a concentration range of 0.35 - 3.1  $\mu\text{g}/\text{in}^2$  (McNeal & Hollifield, 1993). Table 2 lists some food and beverage products in which valeraldehyde has been detected and concentration levels, if reported.

Table 2. Content of valeraldehyde in foods and beverages

Food or Beverage Containing Valeraldehyde	Concentration	Reference
heated pork fat (2 samples)	1033 and 719 $\mu\text{g}/\text{L}$ in headspace	Shibamoto, 1990
heated beef fat	422 $\mu\text{g}/\text{L}$ in headspace	Shibamoto, 1990
non-alcoholic beverages	1.3 ppm	NLM, 1996
ice cream, ices, etc.	5.0 ppm	NLM, 1996
candy	4.2 ppm	NLM, 1996
baked goods	5.4 ppm	NLM, 1996
smoked meat products, including sausage	NR	Gorbatov <i>et al.</i> , 1982
baked potato		de Vincenzi <i>et al.</i> , 1987
drinking water	0.08 mg/kg	NRC, 1981
dairy products	0.5 $\mu\text{g}/\text{L}$	
milk (from several species)		Urbach, 1987
cheeses (several varieties)	NR	STN International, 1996
	NR	

NR = not reported



### *Environmental Exposure*

There is potential for widespread general population inhalation exposures to valeraldehyde as an ubiquitous outdoor and indoor air pollutant.

Pellizzari and coworkers (1982) suggested the measurement of valeraldehyde in mother's milk as a means of monitoring exposures in populations residing in the vicinity of chemical manufacturing plants and other industrial facilities.

Environmental Occurrence: Valeraldehyde is a volatile organic compound (VOC) which is both naturally occurring (e.g., plant volatile) and synthetically produced. It may be released to the environment from industrial facilities during its production, use as a chemical intermediate, storage and transport, or disposal (NRC, 1981; NLM, 1996).

In addition to its identification in occupational settings, valeraldehyde has been detected as an indoor and outdoor air pollutant, waste water and drinking water contaminant, and in soils and sediments. Valeraldehyde has also been identified as a photooxidation product derived from 1-hexene (NLM, 1996). Valeraldehyde has very low soil adsorptivity and can readily volatilize or leach from soil (NLM, 1996). It will also volatilize readily from water to which it has been discharged, with a volatilization half-life from a model river reported to be 8.3 hours (NLM, 1996). Atmospheric valeraldehyde can be expected to readily biodegrade. Some reported sources of valeraldehyde detected in the environment include the following:

- emissions from building materials, including particle board with glued-on carpet and plywood coated with polyurethane, and from decorating and finishing materials such as ceiling tiles, wallcoverings, flooring, wood veneer, and carpeting materials (NLM, 1996)
- indoor air contaminant from tobacco smoke (Florin *et al.*, 1980)
- outdoor ambient atmospheric samples, including ice fog in Fairbanks, Alaska, and cloud mist and fog in various locations in California (Grosjean & Wright, 1983)
- emissions from gasoline, diesel and turbine engines (NRC, 1981; Jonsson *et al.*, 1985; Koert *et al.*, 1987)
- woodburning emissions from fireplaces and forest fires (NLM, 1996)
- wastewater and waste gases from poultry processing plant and industrial waste disposal site (Pellizzari, 1982; Wachter *et al.*, 1982)
- effluent water streams from industrial plants (NRC, 1981)

- drinking water contaminant as a result of ozonation processes (Matsui *et al.*, 1989).

Some measurements of specific pollutant levels of valeraldehyde reported in the available literature include the following:

- Valeraldehyde was measured in a range of 0-38 &g/m<sup>3</sup> in ambient air surrounding a waste disposal site in New Jersey (Pellizzari, 1982; NLM, 1996)
- In the EPA headquarters building, 18 of 20 air samples analyzed contained valeraldehyde at levels ranging from 0.5 to 1.9 &g/m<sup>3</sup> (NLM, 1996).
- Valeraldehyde was one of the top five VOCs recovered during the initial one hour exposure period from oak veneer heated to 70°C at a concentration of 342 &g/m<sup>3</sup> (Muller & Black, 1995).
- Valeraldehyde was detected in drinking water at a concentration of 0.5 &g/L at an Ottumwa, Iowa, water treatment plant (NRC, 1981).
- Valeraldehyde levels from peroxidation of fatty acids commonly found in foods were measured at 3.5 Å 1.9, 13.3 Å 4.1 and 7.3 Å 3.9 nmol/mg of arachidonic acid, linoleic acid and linoleic acid, ethyl ester, respectively (Tamura *et al.*, 1991).
- Valeraldehyde was a major carbonyl compound present at 13 to 36% in the headspace of five Burley chewing tobacco samples and at 31-67% in the headspace of 13 flue-cured tobacco samples (Chou & Que Hee, 1994).

Regulatory Status: Valeraldehyde was established as a generally recognized as safe (GRAS) substance by the Flavor and Extract Manufacturing Association (FEMA) and assigned FEMA #3098; and it is approved for direct food use by the US Food and Drug Administration (FDA § 121.1164) under the Federal Food, Drug, and Cosmetic Act (CFR 172.515) (Furia, 1972; Opdyke, 1979).

The ACGIH-recommended threshold limit value-time weighted average (TLV-TWA) for valeraldehyde is 50 ppm (176 mg/m<sup>3</sup>) based on acute and subchronic animal data and clinical experience with valeraldehyde. No short term exposure limit (STEL) has been recommended to date (ACGIH 1992, 1995). The Occupational Safety and Health Administration (OSHA) has established a permissible exposure limit-time weighted average (PEL-TWA) of 50 ppm for valeraldehyde; and the National Institute for Occupational Safety and Health (NIOSH) has established a recommended exposure limit (REL) of 50 ppm (NIOSH, 1992).

Valeraldehyde is one of 89 aldehydes added as a chemical group to the Priority List prepared for the EPA Administrator in the 27th Report of the Interagency Testing Committee (ITC). The aldehydes group was recommended with intent to designate (USEPA, 1991).

The following action has been taken by the TSCA Interagency Testing Committee (ITC) on valeraldehyde (Walker, 1995b):

- recommended for algal toxicity, aquatic invertebrates acute and chronic toxicity and fish chronic toxicity testing as part of a substructure-based class study (aldehydes);
- still under active consideration for health effects, chemical fate or ecological effects testing.

### EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to valeraldehyde and cancer risk in humans were identified in the available literature. Valeraldehyde liquid and vapor are capable of causing irritation of the skin, eyes, nose, and respiratory tract. Very high vapor exposure may cause nausea, vomiting, and headaches (Eastman Kodak Co., 1991). When tested at 2% in petrolatum, valeraldehyde produced no irritation in human subjects after a 48-hour closed-patch test. The same concentration was also negative for sensitization reactions in a maximization test on 25 volunteers (Opdyke, 1979).

Animal Data: No 2-year carcinogenicity studies of valeraldehyde were identified in the available literature. Toxicity information identified was limited to acute studies which are summarized in Table 3.

Table 3. Acute toxicity data for valeraldehyde

Route	Species	Toxicity value	Reference
Oral	Rat	LD <sub>50</sub> = 3200 - 6400 mg/kg	Eastman Kodak Co., 1991
Oral	Mouse	LD <sub>50</sub> = 6400 - 12800 mg/kg	Eastman Kodak Co., 1991
Intraperitoneal	Rat	LD <sub>50</sub> = 400 - 800 mg/kg	Eastman Kodak Co., 1991
Intraperitoneal	Mouse	LD <sub>50</sub> = 200 - 400 mg/kg	Eastman Kodak Co., 1991
Dermal	Guinea pig	LD <sub>50</sub> = 20 g/kg	Opdyke, 1979
Dermal	Rabbit	LD <sub>50</sub> = 4.86 g/kg	ACGIH, 1992
Inhalation	Rat	4000 ppm for 4 hours killed 3 of 6 rats	ACGIH, 1992

Fifty mice, 20 guinea pigs, and 5 rabbits were exposed to 670 ppm valeraldehyde aerosol for 10 hours or until death. Two mice died during exposure and 2 additional mice and 5 guinea pigs died subsequent to cessation of exposure. All animals had expanded, edematous, hemorrhagic lungs and fluid in the pleural cavity. The livers were enlarged and there was fluid in the peritoneal cavity of the animals that died on the days following exposure (Salem & Cullumbine, 1960).

Sensory irritation potential of valeraldehyde was assessed in mice by measuring respiratory rate depression during 10-minute exposures in a head-only exposure chamber. The concentrations which elicited a 50% decrease in respiratory rate ( $RD_{50}$ ) were 1121 and 1190 ppm in Swiss-Webster and B6C3F1 mice, respectively (Steinhagen & Barros, 1984).

Undiluted valeraldehyde held in covered contact with the depilated skin of guinea pigs for a period of 24 hours proved to be a strong primary irritant, and there was some evidence that it might be absorbed directly through the intact skin since animals in the highest dose groups failed to gain weight during the 14-day observation period. A standardized skin sensitization test in guinea pigs failed to sensitize any of the 5 test animals (Eastman Kodak Co., 1991).

Following instillation of 1 drop of valeraldehyde into rabbit eyes as both the undiluted compound and as a 50% solution in propylene glycol, the animals showed signs of immediate irritation and evidence of corneal injury (Eastman Kodak Co., 1991).

Short-Term Tests: Valeraldehyde was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 when assayed in the spot test at 3 & mol/plate both with and without activation (Florin *et al.*, 1980). It was also inactive in strains TA98 and TA100 when assayed using preincubation with and without activation (doses not stated) (Sasaki & Endo, 1978). The NTP also reported negative results for valeraldehyde in the Ames assay (NTP, 1996a).

Valeraldehyde concentrations ranging from 3 to 30 mM induced dose-dependent increases in the mutation frequency at both the HGPRT and Na/K loci in Chinese hamster V-79 lung cells (Brambilla *et al.*, 1989).

Valeraldehyde had no effect on the rate of sister chromatid exchanges (SCE) in human lymphocytes *in vitro*. Tested concentrations were 0.002% (v/v) in ethanol for 24 or 48 hours and 0.003% (v/v) in ethanol for 48 hours (Obe & Beek, 1979). Following their analysis of the preceding study, Tucker and coworkers (1993) classified valeraldehyde as insufficiently studied for SCE.

In the unscheduled DNA synthesis (UDS) assay, valeraldehyde concentrations of 3-30 mM produced a modest but statistically significant increase of net nuclear grains, i.e., induction of DNA repair synthesis in rat hepatocytes. The UDS assay with human hepatocytes was negative (Martelli *et al.*, 1994).

At a dose of 492.6 µg/ml with activation, valeraldehyde was weakly positive for the induction of DNA repair in the *umu* test using *S. typhimurium* strain TA1535/psk1002. No genotoxicity was seen in the absence of activation (Ono *et al.*, 1991).

Valeraldehyde showed no DNA damaging potential in the *Bacillus subtilis*/microsome rec-assay both with and without S9 activation (Matsui *et al.*, 1989).

In an alkaline elution study, valeraldehyde (0.5 - 4.5 mM) produced a dose-dependent increase in DNA single-strand breaks in Chinese hamster ovary (CHO) KI cells (Marinari *et al.*, 1984).

Valeraldehyde was not toxic toward cultured human endothelial cells or diploid fibroblasts at concentrations of 10-100 µM or 10-50 µM, respectively (Kaneko *et al.*, 1987, 1988).

Metabolism: Aldehydes are readily metabolized by three principal routes: oxidation to acids; reduction to alcohols; and conjugation with sulfhydryls, such as glutathione. The existence of an array of dehydrogenase isozymes and oxidases results in the ability of an organism to oxidize a range of substrates, including valeraldehyde. The acid oxidation products of aldehydes may be either excreted or condensed with coenzyme A to produce the acyl-CoA derivative. Reduction to alcohols may occur by the action of aldehyde reductases. These enzymes require NADP as a coenzyme and are located in both mitochondrial and cytoplasmic compartments of the cell and may have biogenic amines as the endogenous substrate. Aldehydes tend to react with cell sulfhydryl groups. The reaction of aldehydes with glutathione produces thiohemiacetals. Under conditions that

either deplete glutathione levels or result in an inhibition of aldehyde dehydrogenase, the acute and chronic effects of aldehyde toxicity might be more fully expressed (Brabec, 1993).

It has been reported that various aliphatic aldehydes are likely to be produced as a result of lipid peroxidation of biological samples such as rat liver microsomes. Yoshino and coworkers (1990) demonstrated that valeraldehyde could be produced easily in plasma and liver of vitamin E-deficient rats. Male Wistar rats were fed either a vitamin E-supplemented diet or a vitamin E-deficient diet. After 5 or 8 weeks, aliphatic aldehydes were determined in liver and plasma. Valeraldehyde contents in the livers of the E-deficient diet group were significantly higher than those of the E-supplemented diet group ( $P < 0.05$  and  $P < 0.001$  at 5 and 8 weeks, respectively). Levels in plasma increased slightly but not significantly.

Structure/Activity Relationships: Six compounds, structurally similar to valeraldehyde or identified as a possible metabolite, were screened for relevant information associating these related chemicals with a mutagenic or carcinogenic effect. No information was found on carcinogenicity or mutagenicity for n-pentanol [71-41-0]. Information on carcinogenicity was identified for only one of the compounds, isobutyraldehyde. Mutagenicity data were available for five of the structurally related compounds; butyraldehyde, isobutyraldehyde, isovaleraldehyde, propionaldehyde, and hexaldehyde.

#### *Carcinogenicity*

The NTP has conducted two-year bioassays of isobutyraldehyde in rats and mice. Although the reports have not been completed, the Pathology Working Group (PWG) review of the rat study provided the following information. Male and female F344 rats were exposed to isobutyraldehyde by whole-body inhalation at concentrations of 0, 500, 1000, or 2000 ppm for 6 hours/day, 5 days/week for 104 weeks. The PWG reviewed a variety of lesions from this study and noted an increased incidence of mononuclear cell leukemia in female rats exposed to 2000 ppm isobutyraldehyde. They recommended evaluation of the significance of this lesion in light of the statistical evaluation and the historical control data. The PWG also noted a number of compound-related nasal lesions including: degeneration of the olfactory epithelium, squamous metaplasia of the respiratory epithelium, and suppurative inflammation of the nasal cavity (NTP, 1996b).

#### *Mutagenicity/Genotoxicity*

A summary of the mutagenicity/genotoxicity data on valeraldehyde and five structurally related compounds is shown in Table 2. Briefly, all compounds tested negative in the *Salmonella typhimurium* assay; one compound was tested in the mouse lymphoma assay with positive results; all compounds except isovaleraldehyde tested positive for induction of at least one of the following: sister chromatid exchanges, chromosomal aberrations, or DNA damage.

Table 4. Summary of information on valeraldehyde and structurally related compounds

Chemical [CAS No.]	Genotoxicity Data	Reference
Valeraldehyde [110-62-3]  <b>CH<sub>3</sub>(CH<sub>2</sub>)<sub>3</sub>CH O</b>	<p><i>Mutation</i></p> <p>negative in <i>S. typhimurium</i> strains TA98, TA100, TA1535, TA1537 with and without activation (spot test)</p> <p>negative in <i>S. typhimurium</i> strains TA98 and TA100 with and without activation (preincubation)</p> <p>negative NTP <i>S. typhimurium</i> studies</p> <p>positive at the HGPRT and Na/K loci in Chinese hamster V-79 cells</p> <p><i>Sister Chromatid Exchange</i></p> <p>negative in human lymphocytes <i>in vitro</i></p> <p><i>DNA Damage</i></p> <p>positive for induction of UDS in rat hepatocytes</p> <p>negative for induction of UDS in human hepatocytes</p> <p>weakly positive for DNA repair in <i>umu</i> test in <i>S. typhimurium</i> TA1535/PSK1002 with activation but not without</p> <p>negative for DNA damage in <i>Bacillus subtilis</i>/microsome rec-assay with and without activation</p> <p>positive for single strand breaks in CHO K1 cells</p>	<p>Florin <i>et al.</i>, 1980</p> <p>Sasaki &amp; Endo, 1978</p> <p>NTP, 1996a</p> <p>Brambilla <i>et al.</i>, 1989</p> <p>Obe &amp; Beek, 1979</p> <p>Martelli <i>et al.</i>, 1994</p> <p>Martelli <i>et al.</i>, 1994</p> <p>Ono <i>et al.</i>, 1991</p> <p>Matsui <i>et al.</i>, 1989</p> <p>Marinari <i>et al.</i>, 1984</p>
Hexaldehyde [66-25-1]  <b>CH<sub>3</sub>(CH<sub>2</sub>)<sub>4</sub>CH O</b>	<p><i>Mutation</i></p> <p>negative in <i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 with and without activation (spot test)</p> <p><i>DNA Damage</i></p> <p>positive for induction of UDS in rat hepatocytes</p> <p>negative for induction of UDS in human hepatocytes</p> <p>positive for single strand breaks in CHO K-1 cells</p> <p>weakly positive for DNA repair in <i>umu</i> test in <i>S. typhimurium</i> TA1535/PSK1002 with activation but not without</p>	<p>Florin <i>et al.</i>, 1980</p> <p>Martelli <i>et al.</i>, 1994</p> <p>Martelli <i>et al.</i>, 1994</p> <p>Marinari <i>et al.</i>, 1984</p> <p>Ono <i>et al.</i>, 1991</p>
Butyraldehyde [123-72-8]	<p><i>Mutation</i></p> <p>negative in <i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 with</p>	<p>Mortelmans <i>et al.</i>, 1986</p>

$\text{CH}_3(\text{CH}_2)_2\text{CHO}$	and without activation (preincubation)	
	negative in TA98, TA100, TA1535, TA1537 with and without activation (spot test)	Florin <i>et al.</i> , 1980
	negative in TA98, TA100 with and without activation (preincubation)	Sasaki & Endo, 1978

Table 4. Summary of information on valeraldehyde and structurally related compounds (cont.)

Chemical [CAS No.]	Genotoxicity Data	Reference
Butyraldehyde (cont.)	<i>Mutation (cont.)</i>	
	negative in <i>Drosophila melanogaster</i> for sex-linked recessive lethals/reciprocal translocations	NTP, 1996a
	positive at the HGPRT and Na/K loci in Chinese hamster V-79 cells	Brambilla <i>et al.</i> , 1989
	<i>Sister Chromatid Exchange</i>	
	positive in CHO cells with and without activation	Galloway <i>et al.</i> , 1987
	negative in human lymphocytes <i>in vitro</i>	Obe & Beek, 1979
	<i>Chromosomal Aberrations</i>	
	negative in CHO cells with and without activation	Galloway <i>et al.</i> , 1987
Isobutyraldehyde [78-84-2]	<i>DNA Damage</i>	
	positive for induction of UDS in rat hepatocytes	Martelli <i>et al.</i> , 1994
	negative for induction of UDS in human hepatocytes	Martelli <i>et al.</i> , 1994
	<i>Micronuclei</i>	
	negative in NTP micronucleus assay	NTP, 1996a
	$(\text{CH}_3)_2\text{CHCHO}$	<i>Mutation</i>
negative in <i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 with and without activation (preincubation)		Mortelmans <i>et al.</i> , 1986
negative in TA98, TA100 with and without activation (preincubation)		Sasaki & Endo, 1978
positive in NTP mouse lymphoma assay		NTP, 1996a
negative in <i>Drosophila melanogaster</i> for sex-linked recessive lethals		Woodruff <i>et al.</i> , 1985
		Obe & Beek, 1979
<i>Sister Chromatid Exchange</i>		
negative in human lymphocytes <i>in vitro</i>		NTP, 1996a
positive in NTP <i>in vitro</i> assay		NTP, 1996a
<i>Chromosomal Aberrations</i>		
positive in NTP <i>in vitro</i> assay	NTP, 1996a	



	<i>Micronuclei</i>	
	negative in NTP <i>in vivo</i> assay	
Isovaleraldehyde [590-86-3]	<i>Mutation</i>	Aeschbacher <i>et al.</i> , 1989
	negative in <i>S. typhimurium</i> TA98, TA100, TA102 with and without activation (preincubation)	
<b>(CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CHO</b>	<i>Sister Chromatid Exchange</i>	
	negative in human lymphocytes <i>in vitro</i>	Obe & Beek, 1979
Propionaldehyde [78-84-2]	<i>Mutation</i>	Mortelmans <i>et al.</i> , 1986
	negative in <i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 with and without activation (preincubation)	
<b>CH<sub>3</sub>CH<sub>2</sub>CHO</b>	negative in <i>S. typhimurium</i> TA98, TA100, TA102 with and without activation (preincubation)	Aeschbacher <i>et al.</i> , 1989
	negative in <i>S. typhimurium</i> TA98, TA100, TA1535, TA1537 with and without activation (spot test)	Florin <i>et al.</i> , 1980
	negative in <i>S. typhimurium</i> TA98, TA100 with and without activation (preincubation)	Sasaki & Endo, 1978
	positive at the HGPRT and Na/K loci in Chinese hamster V-79 cells	Brambilla <i>et al.</i> , 1989
	negative in Chinese hamster V-79 cells using 6-thioguanine resistance	Smith <i>et al.</i> , 1990
	<i>Sister Chromatid Exchange</i>	
	negative in human lymphocytes <i>in vitro</i>	Obe & Beek, 1979
	positive in NTP <i>in vitro</i> assay	NTP, 1996a
	<i>Chromosomal Aberrations</i>	
	positive in NTP <i>in vitro</i> assay	NTP, 1996a
	<i>DNA Damage</i>	
	positive for induction of UDS in rat hepatocytes	Martelli <i>et al.</i> , 1994
	negative for induction of UDS in human hepatocytes	Martelli <i>et al.</i> , 1994
	positive for DNA single strand breaks in CHO K-1 cells	Marinari <i>et al.</i> , 1984
	weakly positive for DNA repair in <i>umu</i> test in <i>S. typhimurium</i> TA1535/PSK1002 with activation but not without	Ono <i>et al.</i> , 1991

## REFERENCES

- ACGIH (1992) *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 6th ed., Cincinnati, OH, American Conference of Governmental Industrial Hygienists, pp. 1675-1676
- ACGIH (1995) *1996-1996 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*, Cincinnati, OH, American Conference of Governmental Industrial Hygienists, p. 35
- Aeschbacher, H.U., Wolleb, U., Loliger, J., Spadone, J.C. & Liardon, R. (1989) Contribution of coffee aroma constituents to the mutagenicity of coffee. *Food Chem. Toxicol.*, **27**(4), 227-232
- Aldrich Chemical Co., Inc. (1996a) *Aldrich Catalog/Handbook of Fine Chemicals 1996-1997*, Milwaukee, WI, p. 1521
- Aldrich Chemical Co., Inc. (1996b) *Aldrich Flavors and Fragrances*, Milwaukee, WI, p. 97
- Amoore, J.E. & Hautala, E. (1983) Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J. Appl. Toxicol.*, **3**(6), 272-290
- Brabec, M.J. (1993) Aldehydes and acetals. In: Clayton, G.D. & Clayton, F.E., eds., *Patty's Industrial Hygiene and Toxicology*, 4th ed., Vol. IIA, New York, John Wiley & Sons, Inc., pp. 283- 327
- Brambilla, G., Cajelli, E., Canonero, R., Martelli, A. & Marinari, U.M. (1989) Mutagenicity in V79 Chinese hamster cells of n-alkanals produced by lipid peroxidation. *Mutagenesis*, **4**(4), 277-279
- Budavari, S., ed. (1989) *The Merck Index*, 11th ed., Rahway, NJ, Merck & Co., Inc. p. 1558
- Chemical Information Services, Inc. (1994) *Directory of World Chemical Producers 1995/96 Standard Edition*, Dallas, TX, p. 703
- Chou, C-C. & Que Hee, S.S. (1994) Saliva-available carbonyl compounds in some chewing tobaccos. *J. Agric. Food Chem.*, **42**, 2225-2230
- Chun, H.N. & Kim, Z.U. (1992) Evaluation of vegetable oil rancidity by headspace gas chromatographic analysis. *Han'guk Nonghwa Hakhoechi*, **35**(1), 36-41 [STN Abstract: 117-46992]
- CIS (1995) The Chemical Information System, TSCATS database, Towson, MD, PSI International, Inc.
- Collins, D.E. & Richey, F.A., Jr. (1992) Synthetic organic chemicals. In: Kent, J.A., ed., *Riegel's Handbook of Industrial Chemistry*, 9th ed., NY, Van Nostrand Reinhold, pp. 800, 805
- Crescent Chemical Co., Inc. (undated) *Crescent Laboratory Chemicals: The Riedel-de Haën Catalogue*. Hauppauge, NY, p. 1366

- De Vincenzi, M., Castriotta, F., Di Folco, S., Dracos, A., Magliola, M., Mattei, R., Purificato, I., Stacchini, A., Stacchini, P. & Silano, V. (1987) A basis for estimation of consumption: Literature values for selected food volatiles. Part II. *Food Addit. Contam.*, **4**(2), 161-218
- Eastman Chemical Co. (1993) *Eastman Laboratory Chemicals*,, Catalog No. 55, 93-94 ed., Rochester, NY, p. 999
- Eastman Kodak Co. (1991) Toxicity and health hazard summary, material safety data sheet, and toxicity report on pentanal (EPA/OTS Doc. #86-920000053), Eastman Kodak Health and Safety Laboratory, 16 pp
- Falbe, J., Lappe, P. & Weber, J. (1985) Aldehydes, aliphatic and araliphatic. In: *Ullmann's Encyclopedia of Industrial Chemicals*, 5th ed., Vol. A1, pp. 321-327, 349
- Fisher Scientific (undated) *Acros Organics Handbook of Fine Chemicals 1996-1996*, Pittsburgh, PA, p. 1763
- Florin, I., Rutberg, L., Curvall, M. & Enzell, C.R. (1980) Screening of tobacco smoke constituents for mutagenicity using the Ames test. *Toxicology*, **18**, 219-232
- Fluka Chemical Corp. (1995) *Fluka Chemika - Biochemika 1995/96*, Ronkonkoma, NY, p. 1549
- Frankel, E.N., Selke, E., Neff, W.E. & Miyashita, K. (1992) Autoxidation of polyunsaturated triacylglycerols. IV. Volatile decomposition products from triacylglycerols containing linoleate and linolenate. *Lipids*, **27**(6), 442-446 [STN Abstract: 117-190413]
- Furia, T.E., ed. (1972) *CRC Handbook of Food Additives*. Cleveland, OH, CRC Press, p. 510
- Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B. & Zeiger, E. (1987) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. *Environ. Mol. Mutagen.*, **10**(Suppl. 10), 1-175
- Gorbatov, V.M., Sinitsyn, K.D., Krylova, N.N., Lyaskovskaya, Y. N., Volovinskaya, V.P., Bazarova, K.I., Khlamova, R.R.I. & Solomev'a, L.I. (1982) Treating meat products to impart the taste and smell of a smoked product. *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnuye Znaki*, **9**, 294 [STN Abstract: 119- 202736]
- Grosjean, D. & Wright B. (1983) Carbonyls in urban fog, ice fog, cloudwater and rainwater. *Atmos. Environ.*, **17**(10), 2093-2096
- Hunter, D., ed. (1994) *Chemical Week 1995 Buyers' Guide*, New York, Chemical Week Associates, p. 342
- Janssen Chimica (1992) *1993-1994 Janssen Chimica Catalog Handbook of Fine Chemicals*, New Brunswick, NJ, Spectrum Chemical Mfg. Corp., p. 1410
- Jonsson, A., Persson, K.A. & Grigoriadis, V. (1985) Measurements of some low-molecular-weight oxygenated, aromatic, and chlorinated hydrocarbons in ambient air and in vehicle emissions. *Environ. Int.*, **11**, (2-4), 383-392 [STN Abstract: 104-38948]

- Kaneko, T., Honda, S., Nakano, S.I. & Matsuo, M. (1987) Lethal effects of linoleic acid hydroperoxide and its autoxidation products, unsaturated aliphatic aldehydes, on human diploid fibroblasts. *Chem.-Biol. Interact.*, **63**, 127-137
- Kaneko, T., Kaji, K. & Matsuo, M. (1988) Cytotoxicities of a linoleic acid hydroperoxide and its related aliphatic aldehydes toward cultured human umbilical vein endothelial cells. *Chem.-Biol. Interact.*, **67**, 295-304
- Koert, D.N., Wilk, R.D., Partridge, P.A. & Cernansky, N.P. (1987) Carbonyl formation from a model diesel fuel. *Proceedings APCA Annual Meeting*, **80th**(1), 22 pp [STN Abstract: 108-115392]
- Lancaster Synthesis Inc. (1995) *The 1995/96 Catalog*, Windham, NH, p. 1413
- Lewis, R.J., Sr. (1993) *Hawley's Condensed Chemical Dictionary*, 12th ed., New York, Van Nostrand Reinhold Co., p. 1207
- Lin, Y., Dueker, S.R., Jones, A.D., Ebeler, S.E. & Clifford, A.J. (1995) Protocol for collection and HPLC analysis of volatile carbonyl compounds in breath. *Clin. Chem.*, **41**(7), 1028-1032
- Mallinckrodt Specialty Chemicals Co. (1989) *Reagent and Laboratory Chemicals Catalog 1990-91*, Paris, KY, p. 259
- Marinari, U.M., Ferro, M., Sciaba, L., Finollo, R., Bassi, A.M. & Brambilla, G. (1984) DNA-damaging activity of biotic and xenobiotic aldehydes in Chinese hamster ovary cells. *Cell Biochem. Funct.*, **2**(4), 243-248
- Martelli, A., Canonero, R., Cavanna, M., Ceradelli, M. & Marinari, U.M. (1994) Cytotoxic and genotoxic effects of five *n*-alkanals in primary cultures of rat and human hepatocytes. *Mutat. Res.*, **323**, 121-126
- Matsui, S., Yamamoto, R. & Yamada, H. (1989) The *Bacillus subtilis*/microsome rec-assay for the detection of DNA damaging substances which may occur in chlorinated and ozonated waters. *Water Sci. Technol.*, **21**(8-9), 875-887
- McNeal, T.P. & Hollifield, H.C. (1993) Determination of volatile chemicals released from microwave-heat-susceptor food packaging. *J. AOAC Int.*, **76**(6), 1268-1275
- Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B. & Zeiger, E. (1986) Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ. Mutagen.*, **8**(Suppl. 7), 1-119
- Muller, W.J. & Black, M.S. (1995) Sensory irritation in mice exposed to emissions from indoor products. *Am. Ind. Hyg. Assoc. J.*, **56**, 794-803
- NIOSH (1990) *National Occupational Exposure Survey (NOES) as of 12/06/90*, Cincinnati, OH, p. 35
- NIOSH (1992) *NIOSH Recommendations for Occupational Safety and Health. Compendium of Policy Documents and Statements (DHHS (NIOSH) Publ. No. 92-100)*, Cincinnati, OH, Division of Standards Development and Technology Transfer, p. 131

- NLM (1996) *Hazardous Substances Data Bank (HSDB)* Bethesda, MD, National Library of Medicine, searched 6/11/96 [HSN 851]
- NRC (1981) *Formaldehyde and other aldehydes*. National Research Council Report, Washington, D.C., National Academy Press, pp. 5-20 to 5-25, 5-31, 5-42
- NTP (1996a) *NTP Results Report, Results, Status, and Publication Information on All NTP Chemicals*, Research Triangle Park, NC, National Toxicology Program, May 8, 1996, pp. 10, 29, 142
- NTP (1996b) *NTP Pathology Working Group Review of the Two-Year Chronic Inhalation Toxicity/Carcinogenicity Study of Isobutyraldehyde (IBA) (C60968B/60968-01) in F344 Rats*. Research Triangle Park, NC, National Toxicology Program, May 29, 1996
- Obe, G. & Beek, B. (1979) Mutagenic activity of aldehydes. *Drug Alcohol Depend.*, **4**(1-2), 91-94
- Ono, Y., Somiya, I. & Kawamura, M. (1991) The evaluation of genotoxicity using DNA repairing test for chemicals produced in chlorination and ozonation processes. *Water Sci. Technol.*, **23**(1-3), 329-338
- Opdyke, D.L. (1979) Monographs on fragrance raw materials: *n*-Valeraldehyde. *Food Cosmet. Toxicol.*, **17** (Suppl.), 919-921
- Oswald, A.A., Jermasen, T.G., Westner, A.A. & Huang, I.D. (1987) Selective hydroformylation process using alkyl diaryl phosphine rhodium carbonyl hydride catalysts. Assignee: Exxon Research and Engineering Co. (Patent No. US 4687874 A) 61 pp. [STN Abstract: CA108-40088]
- Pellizzari, E.D. (1982) Analysis for organic vapor emissions near industrial and chemical waste disposal sites. *Environ. Sci. Technol.*, **16**(11), 781-785 [STN Abstract: 97-168024]
- Pellizzari, E.D., Hartwell, T.D., Harris, B.S., III, Waddell, R.D., Whitaker, D.A. & Erickson, M.D. (1982) Purgeable organic compounds in mother's milk. *Bull. Environ. Contam. Toxicol.*, **28**, 322- 328
- Pfaltz & Bauer, Inc. (undated) *Pfaltz & Bauer Chemicals Catalog*, Waterbury, CT, Aceto Corp., p. 999
- Rogers, J.A. (1981) Oils, essential. In: Grayson, M. & Eckroth, D., eds., *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., New York, John Wiley & Sons, Vol. 16, pp. 312, 327
- Salem, H. & Cullumbine, H. (1960) Inhalation toxicities of some aldehydes. *Toxicol. Appl. Pharmacol.*, **2**, 183-187
- Sasaki, Y. & Endo, R. (1978) Mutagenicity of aldehydes in *Salmonella*. *Mutat. Res.*, **54**, 251-252

- Schultz, T.W., Bryant, S.E. & Lin, D.T. (1994) Structure-toxicity relationships for *Tetrahymena*: aliphatic aldehydes. *Bull. Environ. Contam. Toxicol.*, **52**, 279-285
- Shibamoto, T. (1990) A new analytical method for low-molecular-weight aldehydes. In: Charalamboris, G., ed., *Developments in Food Science, Flavors and Off-Flavors*. Amsterdam, Elsevier Science Publishers B.V., pp. 471-484
- Smith, R.A., Cohen, S.M. & Lawson, T.A. (1990) Acrolein mutagenicity in the V79 assay. *Carcinogenesis*, **11**(3), 497-498
- Snyder, J.M. (1995) Volatile analysis of oxidized oils by a direct supercritical fluid extraction method. *J. Food Lipids*, **2**, 25-33
- Steinhagen, W.H. & Barrow, C.S. (1984) Sensory irritation structure-activity study of inhaled aldehydes in B6C3F1 and Swiss-Webster mice. *Toxicol. Appl. Pharmacol.*, **72**(3), 495-503
- STN International (1996) STN database: Registry, CA. Columbus, OH, Chemical Abstracts Service
- Tamura, H., Kitta, K. & Shibamoto, T. (1991) Formation of reactive aldehydes from fatty acids in a Fe<sup>2+</sup>/H<sub>2</sub>O<sub>2</sub> oxidation system. *J. Agric. Food Chem.*, **39**, 439-442
- TCI America (1996) *TCI America Organic Chemicals 96/97 Catalog*, Portland, OR, p. 1444
- Tucker, J.D., Auletta, A., Cimino, M.C., Dearfield, K.L., Jacobson-Kram, D., Tice, R.R. & Carrano, A.V. (1993) Sister-chromatid exchange: second report of the Gene-Tox program. *Mutat. Res.*, **297**, 101-180
- Urbach, G. (1987) Dynamic headspace gas chromatography of volatile compounds in milk. *J. Chromatogr.*, **404**, 163-174
- USEPA (1991) Environmental Protection Agency, Part VIII: Twenty-seventh report of the interagency testing committee to the administrator; receipt of report and request for comments regarding priority list of chemicals. *Fed. Regist.*, **56**(44), 9534-72 [6 Mar 1991]
- USITC (1993, 1994a, 1994b) *Synthetic Organic Chemicals: US Production and Sales, 1991/1992/1993*, (USITC Publications 2607/2720/2810), Washington, DC, US Government Printing Office, pp. 15-25/3-58/3-58
- Van, H. (1994) *1995 Chemical Buyers Directory*, 82nd annual ed., New York, Schnell Publishing Co., p. 785
- Verschueren, K. (1983) *Handbook of Environmental Data on Organic Chemicals*, 2nd ed., New York, Van Nostrand Reinhold Company, p. 1180

- Wachter, J.K., Andelman, J.B., Beck, J.M. & Nolle, S. (1982) Organic chemicals and other factors in water reuse at a poultry processing plant. *Proceedings Water Reuse Symposium*, **2**, 862-880 [STN Abstract: 100-56292]
- Walker, J. (1995a) Personal communication [facsimile transmittal] from John Walker Ph.D., M.P.H., Executive Director, TSCA Interagency Testing Committee, Environmental Protection Agency, Washington, DC, to Victor Fung, Ph.D., National Cancer Institute, Division of Cancer Biology, 4/26/95
- Walker, J. (1995b) Personal communication [facsimile transmittal] from John Walker Ph.D., M.P.H., Executive Director, TSCA Interagency Testing Committee, Environmental Protection Agency, Washington, DC, to Victor Fung, Ph.D., National Cancer Institute, Division of Cancer Biology, 6/8/95
- Williams, R.E., Armstrong, D.W., Murray, W.D. & Welsh, F.W. (1988) Enzyme and whole cell production of flavor and fragrance compounds. *Ann. N.Y. Acad. Sci.*, **542**, 406-412
- Woodruff, R.C., Mason, J.M., Valencia, R. & Zimmering, S. (1985) Chemical mutagenesis testing in *Drosophila*. V. Results of 53 coded compounds tested for the National Toxicology Program. *Environ. Mutagen.*, **7**, 667-702
- Yoshino, K., Sano, M., Fujita, M. & Tomita, I. (1990) Studies on the formation of aliphatic aldehydes in the plasma and liver of vitamin E-deficient rats. *Chem. Pharm. Bull.*, **38**(8), 2212-2215