

CHEMICAL SUMMARY FOR VANILLIN

This summary is based on information retrieved from a systematic search limited to secondary sources (see Appendix A). The only exception is summaries of studies from unpublished TSCA submissions that may have been included. These sources include online databases, unpublished EPA information, government publications, review documents, and standard reference materials. No attempt has been made to verify information in these databases and secondary sources.

I. CHEMICAL IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

The chemical identity and physical/chemical properties of vanillin are summarized in Table 1.

TABLE 1. CHEMICAL IDENTITY AND CHEMICAL/PHYSICAL PROPERTIES OF VANILLIN

| Characteristic/Property | Data | Reference |
|-----------------------------------|--|------------------------|
| CAS No. | 121-33-5 | |
| Common Synonyms 1996 | 4-hydroxy-3-methoxybenzaldehyde; methyl- protocatechuic aldehyde; vanillic aldehyde; 3-methoxy-4-hydroxybenzaldehyde | Budavari et al. |
| Molecular Formula | $C_8H_8O_3$ | |
| Chemical Structure | $(CH_3O)C_6H_3(OH)CHO$ | Kirwin and Galvin 1993 |
| Physical State | white or slightly yellow needles | Budavari et al. 1996 |
| Molecular Weight | 152.15 | Budavari et al. 1996 |
| Melting Point | 80-81°C | Budavari et al. 1996 |
| Boiling Point | 285°C | Budavari et al. 1996 |
| Water Solubility | 1 g/100 mL | Budavari et al. 1996 |
| Density | 1.056 g/mL | Budavari et al. 1996 |
| Vapor Density (air = 1) | 5.2 | HSDB 1996 |
| K_{oc} | not found | |
| Log K_{ow} | not found | |
| Vapor Pressure | 2.2×10^{-3} mm Hg @ 25°C | HSDB 1996 |
| Reactivity Walters 1985 | can react violently with bromine, potassium tert-butoxide, tert-chlorobenzene + NaOH, formic acid + $Tl(NO_3)_3$ and perchloric acid | Keith and |
| Flammability | not found | |
| Flash Point | not found | |
| Dissociation Constant | pK_{a1} 7.40, pK_{a2} 11.4 (25°C) | Chapman and Hall 1995 |
| Henry's Law Constant | not found | |
| Molecular Diffusivity Coefficient | not found | |
| Air Diffusivity Coefficient | not found | |
| Fish Bioconcentration Factor | not found | |
| Odor Threshold | 2×10^{-1} ppm, water; 1.10×10^{-8} ppb, air | Kirwin and Galvin 1993 |
| Conversion Factors | 1 ppm = 6.2 mg/m ³ 1 mg/m ³ = 0.161 ppm | Brabec 1993 |

II. ENVIRONMENTAL FATE

A. Environmental Release

No information was found in the secondary sources searched regarding the environmental release of vanillin. The chemical occurs naturally in vanilla, potato parings, and Siam benzoin (Budavari et al. 1996).

B. Transport

No information was found in the secondary sources searched regarding the environmental transport of vanillin. The vapor pressure (2.2×10^{-3} mm Hg [HSDB 1996]) for the chemical indicates that little volatilization from soil or water could occur. Vanillin is soluble in water (1 g/100 mL [Budavari et al. 1996]) and may move through the soil, possibly to groundwater.

C. Transformation/Persistence

1. Air — Vanillin oxidizes to some extent when exposed to moist air and is "affected" by light (Budavari et al. 1996). Vanillin absorbs UV light at wavelengths of 308 and 278 nm (Kirwin and Galvin 1993), suggesting that phototransformation is possible. Decomposition of vanillin under strict anaerobic conditions has been observed (HSDB 1996).
2. Soil — No information was found in the secondary sources searched regarding the fate of vanillin in soil.
3. Water — No information was found in the secondary sources searched regarding the fate of vanillin in the aquatic environment. Based on its absorption of UV light at wavelengths of 308 and 278 nm, vanillin in surface water could undergo some phototransformation.
4. Biota — No information was found in the secondary sources searched regarding the bioaccumulation of vanillin.

III. HUMAN HEALTH EFFECTS

A. Pharmacokinetics

The absorption of vanillin orally and by intraperitoneal, subcutaneous, and intravenous injections, may be inferred from acute toxicity observed in animals exposed by those routes and from systemic effects observed following subchronic oral exposure. Major metabolites of vanillin include vanillic acid and glucuronide and sulfate conjugates that are excreted, along with other metabolites in the urine. Ninety-four percent of an oral dose of 100 mg/kg vanillin was excreted as urinary metabolites and unchanged vanillin within 48 hours of treatment.

1. Absorption — No information was found in the secondary sources searched regarding the absorption of vanillin. The acute toxicity of vanillin in animals exposed

orally and by intraperitoneal, subcutaneous, and intravenous injections indicates that the chemical is absorbed by those routes. Systemic effects observed in animals following oral subchronic treatment with vanillin further indicates that gastrointestinal absorption of the chemical occurs.

2. Distribution — No information was found in the secondary sources searched regarding the distribution of vanillin.
3. Metabolism — Vanillin yields vanillic acid in humans (HSDB 1996). Rats given oral doses of 100 mg/kg vanillin excreted mainly glucuronide and sulfate conjugates in the urine within the first 24 hours (Kirwin and Galvin 1993). By 48 hours, 94% of the dose was accounted for: 7% as vanillin, 19% as vanillyl alcohol, 47% as vanillic acid, 19% as vanilloylglycine, 8% as catechol, 2% as 4-methylcatechol, 0.5% as guaiacol, and 0.6% as 4-methylguaiacol (Kirwin and Galvin 1993).

Vanillin administered intraperitoneally to rats gave rise to several urinary metabolites, consisting mainly of vanillic acid in both free and conjugated forms, and smaller amounts of conjugated vanillin, conjugated vanillyl alcohol, and catechol (Kirwin and Galvin 1993).

4. Excretion — Rats treated with vanillin either orally or intraperitoneally excreted vanillin and its metabolites in the urine (Kirwin and Galvin 1993). Ninety-four percent of an oral dose of 100 mg/kg was excreted as urinary metabolites and unchanged vanillin within 48 hours of treatment (Kirwin and Galvin 1993).

B. Acute Toxicity

Vanillin is known to cause dermal reactions in people previously sensitized to other compounds. Vanillin is considered a moderate skin allergic sensitizing agent in animals. Vanillin has a low oral toxicity in animals with LD₅₀'s ranging from 1.4 g/kg in guinea pigs to 3.0 g/kg in rabbits.

1. Humans — In closed-patch tests, vanillin caused no primary skin irritation when tested at concentrations of 20 and 2 % on normal subjects, and at 0.4 % on subjects with dermatoses. Concentrations of 2 and 5 % in petrolatum produced no sensitization reactions. Vanillin applied undiluted for 48 hours in the standard aluminum-patch test did not produce any irritation or sensitization in a 62-year-old subject with a perfume dermatitis (Kirwin and Galvin 1993).

Positive reactions to vanillin were reported in 8 out of 142 patients already sensitized to balsam of Peru. In studies of sensitization to balsam of Peru and its components, vanillin, pure or 10 %, produced positive patch-test reactions in 21 out of 164 patients sensitive to the balsam. In these studies, vanillin was considered to be a secondary allergen. Vanillin is not responsible for most cases of sensitivity to natural vanilla. Vanillin is known to cause reactions in people previously sensitized to balsam of Peru, benzoin, rosin, benzoic acid, orange peel, cinnamon, and clove (Kirwin and Galvin 1993).

2. Animals — Oral LD₅₀ values reported for vanillin in animals were 3.0 g/kg for rabbits, 1.58-2.8 g/kg for rats, and 1.4 g/kg for guinea pigs, indicating low oral toxicity for

these animals (Kirwin and Galvin 1993). Vanillin was found to be a moderate skin allergic sensitizing agent in animals (Kirwin and Galvin 1993).

C. Subchronic/Chronic Effects

Vanillin can cause dermal reactions in people previously sensitized to other compounds. In rats, dietary levels of vanillin as low as 64 mg/kg/day fed for 10 weeks have caused such chronic symptoms as growth depression and damage to the myocardium, liver, kidney, lung, spleen, and stomach. Most studies, however, indicate that chronic symptoms are not evident below dietary levels of 500 mg/kg/day.

1. Humans — No information was found in the secondary sources searched regarding the chronic effects of vanillin in humans. However, vanillin can cause dermal reactions in people previously sensitized to other compounds (Kirwin and Galvin 1993).
2. Animals — Intra-gastric administration of 300 mg of vanillin/kg to rats, twice weekly, for 14 weeks produced no adverse effects. Rats fed diets containing vanillin at levels of 20 mg/kg/day for 18 weeks had no adverse effects, while 64 mg/kg/day for 10 weeks caused growth depression and damage to the myocardium, liver, kidney, lung, spleen, and stomach. Rats fed diets containing vanillin for 13 weeks exhibited growth depression and enlargement of the liver, kidney, and spleen at dosage levels of 5% (2500 mg/kg/day)¹, mild changes at 1% (500 mg/kg/day)¹, and no changes at 0.3% (150 mg/kg/day)¹. Four to six week old rats maintained for 91 days on diets containing vanillin exhibited no adverse effects at rates of 3000 ppm (150 mg/kg/day)¹, mild adverse effects at 10,000 ppm (500 mg/kg/day)¹, and growth depression and enlargement of the liver, kidneys, and spleen at 50,000 ppm (2500 mg/kg/day)¹. Rats fed dietary levels of vanillin of 10,000 ppm (500 mg/kg/day)¹ for 16 weeks, 1000 ppm (50 mg/kg/day)¹ for 27-28 weeks, 20,000 or 50,000 ppm (1000 or 2500 mg/kg/day)¹ for 1 year, or 5000, 10,000, or 20,000 ppm (250, 500, or 1000 mg/kg/day)¹ for 2 years exhibited no adverse effects on growth or hematology and produced no macroscopic or microscopic changes in tissues. Rats fed for 5 weeks on a diet of vanillin at 0.5 g/kg of the diet showed symptoms of intoxication, including decreases in adrenal vitamin C and in liver protein (Kirwin and Galvin 1993).

D. Carcinogenicity

Vanillin did not cause tumors in mice injected intraperitoneally. Neither EPA nor the International Agency for Research on Cancer (IARC) have classified vanillin as to its carcinogenicity. Vanillin is not listed among the chemicals studied or to be studied by the National Toxicology Program (NTP 1996).

1. Humans — No information was found in the secondary sources searched regarding the carcinogenicity of vanillin in humans.

¹ Based on a food factor of 0.05 for a 0.35 kg rat (U.S. EPA 1985).

2. Animals — Vanillin injected intraperitoneally into strain A mice at total doses of 3.6 to 18.0 g/kg over a period of 24 weeks produced no excesses of lung tumors and was not considered to be carcinogenic (HSDB 1996).

E. Genotoxicity

In two experiments, chromatid aberrations in human lymphocytes did not differ significantly from ethanol solvent controls at vanillin concentrations of 1, 2, or 4 mM. Chromosome aberrations were also not significant at these three doses if chromosome gaps were excluded from the analysis. With gaps, a significant increase was observed only at the 4 mM concentration (HSDB 1996).

F. Developmental Toxicity

No information was found in the secondary sources searched regarding the developmental toxicity of vanillin in humans or animals.

G. Reproductive Toxicity

Although the reproductive system is reported in Material Safety Data Sheets (Sigma 1995, Lockheed Martin 1995) for vanillin as a target system, no information was found in the secondary sources searched regarding the reproductive toxicity of vanillin in humans or animals.

H. Neurotoxicity

No information was found in the secondary sources searched regarding the neurotoxicity of vanillin in humans or animals.

IV. ENVIRONMENTAL EFFECTS

LC₅₀ values for vanillin in Pimephales promelas (fathead minnows) range from 57 mg/L for 96 hours to 370 mg/L for 1 hour, indicating moderate to low toxicity to this aquatic species. Laboratory animal tests suggest that vanillin poses no toxic threat to terrestrial organisms. The low vapor pressure of vanillin makes it an unlikely air pollutant.

A. Toxicity to Aquatic Organisms

Reported LC₅₀ values for vanillin in fathead minnows are varied as follows: 370-173 mg/L for 1 hour (Verschueren 1996), 109-112 mg/L for 24 hours (U.S. EPA 1996), 125-131 mg/L for 24 hours (Verschueren 1996), 65 mg/L for 48 hours (U.S. EPA 1996), 116-123 mg/L for 48 hours (Verschueren 1996), 112-121 mg/L for 72 hours (Verschueren 1996), 112-121 mg/L for 96 hours (Verschueren 1996), and 57-123 mg/L for 96 hours (U.S. EPA 1996).

B. Toxicity to Terrestrial Organisms

No information was found in the secondary sources searched regarding the toxicity to terrestrial animals. However, laboratory animal acute toxicity tests suggest that vanillin will have a low toxicity to these organisms.

C. Abiotic Effects

According to the definition provided in the Federal Register (U.S. EPA 1992), vanillin is a volatile organic carbon (VOC) substance. As a VOC, vanillin can contribute to the formation of photochemical smog in the presence of other VOC's. However, due to the very low vapor pressure of vanillin, it is not likely that this chemical will be a significant air pollutant.

V. EPA/OTHER FEDERAL/OTHER GROUP ACTIVITY

The Clean Air Act Amendments of 1990 do not list vanillin as a hazardous air pollutant. Occupational exposure to vanillin is not regulated by the Occupational Safety and Health Administration or the National Institute for Occupational Safety and Health. Other federal agencies and groups (listed in Table 2) may develop recommendations to assist in controlling workplace exposure and should be contacted regarding workplace exposures and for additional information on vanillin.

**TABLE 2. OTHER FEDERAL OFFICES/OTHER GROUP CONTACT
NUMBERS FOR INFORMATION ON VANILLIN**

| Other Agency/Department/Other Group | Contact Number |
|---|-----------------------|
| Consumer Product Safety Commission ^a | (301) 504-0994 |
| Food & Drug Administration ^b | (301) 443-3170 |

^a Used in perfumes (Budavari 1996).

^b Used as a flavoring agent in foods (Budavari 1996).

VI. CITED REFERENCES

Budavari S, O'Neil MJ, Smith A, Heckelman PE, Kinneary JF, Eds. 1996. The Merck Index, 12th ed. Merck & Co., Inc., Whitehouse Station, NJ, p. 1693.

Chapman and Hall. 1995. Chapman and Hall Chemical Database. DIALOG(R)File 303. Retrieved online 8/29/96.

Brabec MJ. 1993. Aldehydes and Acetals. In: Clayton GD, Clayton FE, Eds. 1993. Patty's Industrial Hygiene and Toxicology, Vol.2, Part A, 4th ed. New York: John Wiley & Sons, 318.

HSDB. 1996. Hazardous Substances Data Bank. MEDLARS Online Information Retrieval System, National Library of Medicine. Retrieved 8/30/96.

Keith LH, Walters DB, Eds. 1985. Compendium of Safety Data Sheets for Research and Industrial Chemicals. VCH Publishers, Deerfield Beach, pp. 1726-1727.

Kirwin CJ, Galvin JB. 1993. Ethers. In: Clayton GD, Clayton FE, Eds. 1993. Patty's Industrial Hygiene and Toxicology, Vol.2, Part A, 4th ed. New York: John Wiley & Sons, pp. 445-525.

Lockheed Martin Energy Systems, Inc. 1995. Material Safety Reference Sheet for Vanillin. 3 pp.

NTP. 1996. National Toxicology Program. Management Status Report. Produced from NTP Chemtrack system. August 8, 1996. National Toxicology Program, Research Triangle Park, NC.

Sigma Chemical Company. 1995. Material Safety Data Sheet for Vanillin. 4 pp.

U.S. EPA. 1985. Reference Values for Risk Assessment. Environmental Criteria and Assessment Office, U.S. EPA, Cincinnati, OH, Table 1-2.

U.S. EPA. 1992. U.S. Environmental Protection Agency. Part 51 - Requirements for Preparation, Adoption, and Submittal of Implementation Plans. Fed. Reg. 57:3945.

U.S. EPA. 1996. AQUIRE: Aquatic Toxicity Information Retrieval. 1996. U.S. EPA Office of Research and Development. Searched online 9-3-96.

Verschuere, K. 1996. Handbook of Environmental Data on Organic Chemicals. 3rd ed. New York: Van Nostrand Reinhold, p. 1883.

APPENDIX A. SOURCES SEARCHED FOR CHEMICAL SUMMARY PREPARATION

ACGIH. 1991. American Conference for Governmental Industrial Hygienists, Inc. TLVs®. Documentation of the Threshold Limit Values and Biological Exposure Indices, 6th ed. ACGIH, Cincinnati, OH.

ACGIH. 1996. American Conference of Governmental Industrial Hygienists. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. ACGIH, Cincinnati, OH.

AQUIRE. 1996. Aquatic Information Retrieval online data base. Chemical Information Systems, Inc., a subsidiary of Fein-Marquart Assoc.

ATSDR. 1996. Agency for Toxic Substances and Disease Registry. Toxicological Profiles. Chamblee, GA: ATSDR.

Budavari S, O'Neil MJ, Smith A, Heckelman PE (Eds.). 1996. The Merck Index, 12th ed. Rahway, N.J.: Merck & Co., Inc.

CHEMFATE. 1996. Syracuse Research Corporation's Environmental Fate Data Bases. Syracuse Research Corporation, Syracuse, NY.

Clayton GD, Clayton FE. 1993. Patty's Industrial Hygiene and Toxicology, 4th ed. New York: John Wiley & Sons.

HSDB. 1996. Hazardous Substances Data Bank. MEDLARS Online Information Retrieval System, National Library of Medicine.

IARC. 1996. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Lyon: IARC.

NIOSH. 1992. National Institute for Occupational Safety and Health. NIOSH Recommendations for Occupational Safety and Health. Compendium of Policy Documents and Statements. Cincinnati, OH: NIOSH.

NIOSH. 1994. National Institute for Occupational Safety and Health. 1990. NIOSH Pocket Guide to Chemical Hazards. NIOSH, Cincinnati, OH.

NTP. 199... National Toxicology Program. Toxicology and Carcinogenesis Studies. Tech Rep Ser.

NTP. 1996. National Toxicology Program. Management Status Report. Produced from NTP Chemtrack system. August 8, 1996. National Toxicology Program, Research Triangle Park, NC.

OSHA. 1993. Occupational Safety and Health Administration. Table Z-2. Limits for Air Contaminants.

TRI93. 1995. 1992 Toxics Release Inventory. Public Data Release. Office of Pollution Prevention and Toxics (7408), U.S. Environmental Protection Agency, Washington, D.C.

TSCATS. 1996. Toxic Substances Control Act data submissions. MEDLARS Online Information Retrieval System, National Library of Medicine.

U.S. Air Force. 1989. The Installation Restoration Toxicology Guide, Vols. 1-5. Wright-Patterson Air Force Base, OH.

U.S. EPA. 1991. U.S. Environmental Protection Agency. Table 302.4 List of Hazardous Substances and Reportable Quantities 40 CFR, part 302.4:3-271.

U.S. EPA. Most current. U.S. Environmental Protection Agency. Drinking Water Regulations and Health Advisories. Office of Drinking Water, U.S. Environmental Protection Agency, Washington, D.C.

U.S. EPA. Most Current. U.S. Environmental Protection Agency. Health Effects Assessment Summary Tables. Cincinnati, OH: Environmental Criteria and Assessment Office, U.S. EPA.

U.S. EPA reviews such as Health and Environmental Effects Documents, Health and Environmental Effect Profiles, and Health and Environmental Assessments, HERD Analogue Profiles, ITC Documents.

U.S. EPA. Most current. U.S. Environmental Protection Agency. Integrated Risk Information System (IRIS) Online. Cincinnati, OH: Office of Health and Environmental Assessment.

Verschueren, K. (Ed.). 1996. Handbook of Environmental Data on Organic Chemicals, 3rd. ed. Van Nostrand Reinhold, New York.