SUMMARY OF DATA FOR CHEMICAL SELECTION

Diphenolic Acid

126-00-1

BASIS OF NOMINATION TO THE CSWG

Diphenolic acid is brought to the attention of the CSWG because a new, cost effective manufacturing process is expected to make this chemical an attractive substitute for bisphenol A.

Since diphenolic acid is a close structural analog of bisphenol A, environmental releases and consumer exposures from use in baby bottles, dental resins, and lacquers to coat food cans would be similar to those for bisphenol A. Very little information on the toxicity of diphenolic acid was found in the available literature. The chronic effects of diphenolic acid are not well characterized.

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 annual production range of levulinic acid, the precursor chemical of diphenolic acid.

SELECTION STATUS

ACTION BY CSWG: 9/28/00

Studies requested:

Subchronic (90-day) tests

Battery of genetic toxicity tests

Priority: High

Rationale/Remarks:

Presently a medium production volume chemical (<1 million lb/yr)

A new manufacturing process is expected to greatly reduce the cost of producing diphenolic acid, thus increasing its use.

Potential substitute for bisphenol A

Virtually no information on toxicity of diphenolic acid

CSWG, through NCI, will alert the EPA's endocrine disruption program about the need for testing diphenolic acid because of its structural similarity to bisphenol A.

NCI will conduct Ames and mouse lymphoma assays.

CHEMICAL IDENTIFICATION

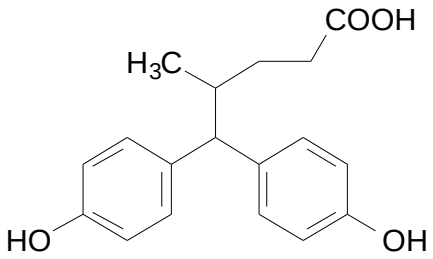
CAS Registry Number: 126-00-1

Chemical Abstracts Service Name: Benzenebutanoic acid, 4-hydroxy-γ-(4-hydroxyphenyl)-γ-methyl- (9CI); valeric acid, 4,4-bis(*p*-hydroxyphenyl)-(8CI)

Synonyms: 4,4-Bis(4-hydroxyphenyl)pentanoic acid; CTFA 00879; diphenolic acid; DPA

Structural Class: Phenol

Structure, Molecular Formula and Molecular Weight:



$C_{17}H_{18}O_4$ Mol. wt.: 286.33

Chemical and Physical Properties:

Description: Light tan granules (Lewis,1993); pink powder (Aldrich, 1998)

Prepared for NCI by Technical Resources International, Inc., under contract no. N022-CB-50511 (4/00)

Melting Point:	167-170 °C (Aldrich, 1998); 170-173 °C (Lewis, 1993)
Solubility:	Slightly soluble in water; soluble in acetic acid, acetone and ethanol, isopropanol and methyl ethyl ketone (Lewis, 1993; Merck, 1997)
Density/Specific Gravity:	1.30-1.32 (Lewis, 1993)
Flash Point:	No data found in available literature
Reactivity:	Incompatible with strong oxidizing agents and strong bases; releases toxic fumes of carbon monoxide and carbon dioxide (Aldrich, 1998)
Octanol/Water Partition Coefficient:	No data found in available literature

Technical Products and Impurities: Diphenolic acid is available in research quantities at a purity of 95% from Aldrich Chemical Co., Inc. (Aldrich, 1998).

Prepared for NCI by Technical Resources International, Inc., under contract no. N022-CB-50511 (4/00)

EXPOSURE INFORMATION

Production and Producers: Diphenolic acid is derived by condensing phenol with levulinic acid in the presence of hydrochloric acid (EPA, 2000; Merck, 1997).

Biofine, Inc. developed a high-temperature, dilute acid hydrolysis process that converts cellulosic biomass to levulinic acid and derivatives. Celluose is initially converted to soluble sugars, which are then transformed to levulinic acid (Fitzpatrick, 1990).

As of 1999, levulinic acid had a worldwide market of about one million lbs. per year at a price of $4-6 per pound. Large-scale commercialization of the Biofine process could produce levulinic acid for as little as $0.32 per pound, spurring increased demand for levulinic acid and its derivatives (EPA, 2000).

The Biofine process produces diphenolic acid at one third the cost of bisphenol A, making it an attractive substitute for the production of plastics, such as LEXAN, in which bisphenol A is a main ingredient (Adams, 1998).

Diphenolic acid is listed in the EPA's Toxic Substances Control Act (TSCA) Inventory (NLM, 2000). Based on non-confidential data received by the EPA, diphenolic acid is a medium production volume chemical used as an adhesive and in coatings. There is a potential of 35 million pounds per year of levulinic acid to make this product (Walker, 1999). No other quantitative information was found in the available literature for diphenolic acid, including the impact of the Biofine process on production volume of diphenolic acid.

According to recent issues of chemical directories, diphenolic acid is manufactured and/or distributed by DSM Fine Chemicals, Inc.; Langfang Triple Well Chemicals Co., Ltd.; Chemicals Incorporated; Chiminord SRL; KIC Chemicals, Inc.; TCI, Pfaltz & Bauer, Inc.; and Lancaster Synthesis, Ltd. (Hunter, 1999; Tilton, 1999; Walker, 1999).

Prepared for NCI by Technical Resources International, Inc., under contract no. N022-CB-50511 (4/00)

The Port Import/Export Reporting Service (PIERS) reported diphenolic acid imports of 1,301 pounds over the 18 month period from October 1998 to April 2000 (Dialog Information Service, 2000).

Use Pattern: Diphenolic acid is widely used as a chemical intermediate in paint formulations, protective and decorative coatings and finishes, lubricating oil additives, cosmetics, surfactants, plasticizers, and textile chemicals (Lewis, 1993; Merck, 1997; US Patent and Trademark Office, 2000). Brominated diphenolic acid shows promise as an environmentally-acceptable marine coating, while dibrominated diphenolic acid may find use as a fire retardant (EPA, 2000). Since diphenolic acid is a close structural analog of bisphenol A, diphenolic acid has the potential to displace bisphenol A. A possible endocrine disruptor, bisphenol A is used in polymer applications such as for use in baby bottles, dental resins, and lacquers to coat food cans (EPA, 2000).

Currently 116 patents on file with the US Patents and Trademark Office use diphenolic acid in some capacity (US Patents and Trademark Office, 2000).

Human Exposure: No information regarding diphenolic acid was available from The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983.

Diphenolic acid is listed in the Toxic Substances Act Chemical Inventory (NLM, 2000).

Environmental Occurrence: No information on the natural or environmental occurrence of diphenolic acid was identified in the available literature.

Prepared for NCI by Technical Resources International, Inc., under contract no. N022-CB-50511 (4/00)

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace allowable levels of diphenolic acid. Diphenolic acid was not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a threshold limit value (TLV) or biological exposure index (BEI) are made.

Prepared for NCI by Technical Resources International, Inc., under contract no. N022-CB-50511 (4/00)

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to diphenolic acid and cancer risk in humans were identified in the available literature.

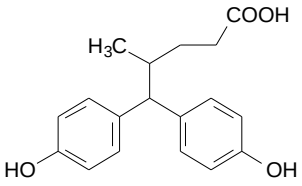
Animal Data: No acute toxicity studies of diphenolic acid in animals were identified in the available literature.

No 2-year carcinogenicity studies of diphenolic acid in animals were identified in the available literature.

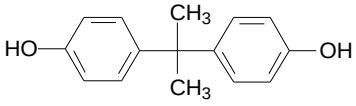
Short-TermTests: No short-term test studies of diphenolic acid were identified in the available literature.

Metabolism: No metabolism studies of diphenolic acid were identified in the available literature.

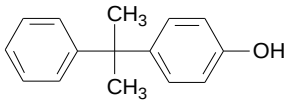
Structure-Activity Relationships: Two chemicals structurally similar to diphenolic acid were screened for relevant information associating these chemicals with a mutagenic or carcinogenic effect. Structures of diphenolic acid and these structurally similar compounds, bisphenol A and 2-phenyl-2-(4-hydroxyphenyl)propane, are shown below.



Diphenolic Acid



Bisphenol A
[80-05-7]



2-phenyl-2-(4- hydroxyphenyl) propane
[599-64-4]

Prepared for NCI by Technical Resources International, Inc., under contract no. N022-CB-50511 (4/00)

Exposure to bisphenol A yielded negative results for carcinogenicity in female Fischer 344 rats and B6C3F1 mice and equivocal results in male Fischer 344 rats in a two-year feed study (NTP, 1982).

Evaluation of genotoxicity data in the available literature showed that *in vitro* exposure to bisphenol A led to DNA strand breaks in rat hepatocytes (Storer *et al*, 1996), and *in vivo* exposure to bisphenol A led to DNA adduct formation when administered to CD1 male rats intraperitoneally or orally (Atkinson & Roy, 1995). Exposure to bisphenol A interfered with cell-free assembly of microtubules, disruption of the cytoplasmic microtubule complex, disruption of the mitotic spindle, induction of metaphase arrest, and induction of micronuclei in Chinese hamster V79 cells (Pfeiffer *et al*., 1997). In addition, inhibition of DNA synthesis was observed following exposure to bisphenol A in Chinese hamster ovary (CHO) cells (Galloway *et al*., 1998).

However, as reported in the National Toxicology Program database (NTP, 1982), exposure to bisphenol A yielded negative results in the following tests: *in vitro* cytogenetics tests in CHO cells including chromosome aberrations and sister chromatid exchanges (inconclusive) (Ivett *et al*., 1989); sex-linked recessive lethal/reciprocal translocation tests in *D. melanogaster*; mutagenicity at the TK locus in L5178Y mouse lymphoma cells (Myhr & Caspary, 1991); mammalian micronucleus test; and *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 with and without S-9 activation (Haworth *et al*., 1983).

Although 2-phenyl-2-(4-hydroxyphenyl)propane is an HPV chemical (with production exceeding 1 million pounds annually in the United States) (Environmental Defense, 2000), no data on carcinogenicity or mutagenicity were found in the available literature for 2-phenyl-2-(4-hydroxyphenyl)propane.

Prepared for NCI by Technical Resources International, Inc., under contract no. N022-CB-50511 (4/00)

References

Adams, B. (1998) *Don't Call It Garbage*. [http://www.eng.rpi.edu/dept/News Comm/Review/ dec98 /plastics.html]

Aldrich Chemical Co., Inc. (1998) *Aldrich Catalog/Handbook of Fine Chemicals 1998/1999,* Milwaukee, WI, p 205

Atkinson, A. & Roy, D. (1995) *In vivo* DNA adduct formation by bisphenol A. *Environ. Mol. Mutagen.*, **26**, 60-66

Dialog Information Service (2000) Piers Imports Database (File 573), Palo Alto, CA, searched April, 2000 [Record No. 11353568]

EDF (2000) *Environmental Defense (2000) Scorecard for 2-Phenyl-2(4-hydroxyphenyl)propane* [http://www.scorecard.org/chemical-profiles]

EPA (2000) *Presidential Green Chemisty Challenge 1999 Small Business Award. Biofine, Incorporated.* [http://www.epa.gov/opptomtr/greenchemistry/sba99.htm]

Fitzpatrick, S.W. (1990) Lignocellulose degradation to furfural and levulinic acid. Assignee: Biofine Incorporated, (US Patent 4,897,497), 8 pp

Galloway, S.M., Miller, J.E., Armstrong, M.J., Bean, C.L., Skopek, T.R. & Nichols, W.W. (1998) DNA synthesis inhibition as an indirect mechanism of chromosome aberrations: comparison of DNA-reactive and non-DNA-reactive clastogens. *Mutat. Res.*, **400**, 169-186

Ghorpade, W.M. & Hanna, M.A. (1999) Method and apparatus for production of levulinic acid via reactive extrusion. Assignee: Board of Regents Univeristy of Nebraska Lincoln, (US Patent 5,859,263), 11 pp

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W. & Zeiger, E. (1983) Salmonella mutagenicity test results for 250 chemicals. *Environ. Mutagen.*, **5**(Suppl 1), 3-142

Hunter, D., ed. (1999) *Chemical Week 2000 Buyers Guide*, New York, Chemical Week Associates, p 308

Ivett, J.L., Brown, B.M., Rodgers, C., Anderson, B.E., Resnick, M.A. & Zeiger, E. (1989) Chromosomal aberrations and sister chromatid exchange tests in Chinese hamster ovary cells *in vitro*. IV. Results with 15 chemicals. *Environ. Mol. Mutagen.*, **14**, 165-187

Lewis, R.J., ed. (1993) *Hawley's Condensed Chemical Dictionary,* 12th ed., New York, Van Nostrand Reinhold, Co., p 150

Merck (1997) Diphenolic acid. 3370. *The Merck Index*, 12th ed. on CD-ROM, New York, Chapman & Hall

Myhr, B.C. & Caspary, W.J. (1991) Chemical mutagenesis at the thymidine kinase locus in L5178Y mouse lymphoma cells: Results for 31 coded compounds in the National Toxicology Program. *Environ. Mol. Mutagen.*, **18**, 51-83

NLM (2000) *ChemID*, Bethesda, MD, searched April 2000 [Record Nos. 126-00-1, 80-05-7, 599-64-4]

NTP (1982) *Carcinogenesis Bioassay of Bisphenol A (CAS No. 80-05-7) in F344 rats and B6C3F$_1$ mice (feed study) (Technical Report Series No. 215; NIH Publ. No. 82-184060)*, Research Triangle Park, NC, National Toxicology Program

Pfeiffer, E., Rosenberg, B., Deuschel, S. & Metzler, M. (1997) Interference with microtubules and induction of micronuclei *in vitro* by various bisphenols. *Mutat. Res.*, **390**, 21-31 [abstract]

Storer, R.D., McKelvey, T.W., Kraynak, A.R., Elia, M.C., Barnum, J.E., Harmon, L.S., Nichols, W.W. & DeLuca, J.G. (1996) Revalidation of the *in vitro* alkaline elution/rat hepatocyte assay for DNA damage: improved criteria for assessment of cytotoxicity and genotoxicity and results for 81 compounds. *Mutat. Res.*, **368**, 59-101 [abstract]

Tilton, H., ed. (1999) *2000 OPD Chemical Buyers Directory*, New York, Schnell Publishing Co., p. 447

US Patent and Trademark Office (2000) Results of Search in 1976-2000 db for: Diphenolic acid: 116 Patents. *Welcome to the USPTO Web Patent Databases.* [http://www.uspto.gov/patft/index.html]

Walker, J. (1999) Personal communication [electronic mail] from John Walker, Ph.D., M.P.H., Executive Director, TSCA Interagency Testing Committee, Environmental Protection Agency, Washington, DC, to Jean Sevin, Ph.D., Technical Resources International, Inc. (TRI), October 18, 1999