SUMMARY OF DATA FOR CHEMICAL SELECTION

Dibenzofuran

132-64-9

BASIS OF NOMINATION TO CSWG

Dibenzofuran is presented to CSWG for consideration based on the potential for widespread human exposure and a lack of information on toxicity.

Worker exposure to dibenzofuran may occur through inhalation and dermal contact at sites where coal tar, coal tar derivatives, or creosote are handled. The general population may be exposed to dibenzofuran through contact with creosote-treated wood or inhalation of fly ash particulates and emissions from municipal waste incinerators. Since dibenzofuran is a contaminant often found in waste dumps and in water supplies, exposure through ingestion of contaminated food products, e.g., fish, may also occur.

Despite significant human exposure, very little information on the toxicity of dibenzofuran was found in the available literature. This limited information suggests that dibenzofuran may not exhibit "dioxin-like" behavior.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dibenzofuran was originally presented to the CSWG as a result of the Furans Class Study. In August 1978, dibenzofuran was dropped as a candidate chemical for testing because it was being studied by Litton Bionetics under contract to the Environmental Protection Agency (EPA). The CSWG members felt that the Litton protocol was sufficient to meet the NCI standards since it addressed both carcinogenicity and reproductive effects via the oral route of administration with an adequate number of animals. Unfortunately, the Litton study was terminated several months after exposure was initiated due to lack of funds (Beliles, 2000).

SELECTION STATUS

ACTION BY CSWG: 12/12/00

Studies requested:

Carcinogenicity

Short-term tests for chromosome aberrations

Priority: High

Rationale/Remarks:

Widespread human exposure as an environmental pollutant

Exposure as a contaminant of several products handled in the occupational setting

Human exposure occurs via multiple routes

Potential for carcinogenicity via epigenetic mechanisms not related to TCDD toxicity

CSWG suggested skin painting studies using the TGAC mouse, with the recommendation that the FVB/N strain also be added

NCI will conduct the mouse lymphoma assay

CHEMICAL IDENTIFICATION

CAS Registry Number: 132-64-9

<u>Chemical Abstract Service Name</u>: Dibenzofuran (8CI; 9CI)

Synonyms: 2,2-Biphenylene oxide, dibenzo(b,d)furan, diphenyl-

ene oxide

Structural Class: Polycyclic aromatic hydrocarbon (PAH); cyclic

ether

Structure, Molecular Formula and Molecular Weight:

C₁₂H₈O Mol. wt.: 168.19

Chemical and Physical Properties:

<u>Description</u>: White solid (Sigma-Aldrich, 2000)

Melting Point: 86.5 °C (Lide, 1995)

Boiling Point: 287 °C (Lide, 1995)

Solubility: Slightly soluble in water; soluble in ethanol and

acetone; very soluble in ether, benzene, and acetic

acid; sublimable (Elvers, 1989; Lide, 1995)

<u>Density</u>: 1.0886 at 99°C (Lide, 1995)

Reactivity: Strong oxidation agent; stable at room temperature

in closed container (Fisher Scientific Canada, 1999)

Octanol/Water Partition Coefficient: Log $K_{o/w} = 4.12$ (NLM, 2000a)

<u>Vapor Pressure</u>: 0.0044 mm Hg at 25 °C (NLM, 2000a)

<u>Technical Products and Impurities</u>: Dibenzofuran is available at 99+% purity from Sigma-Aldrich (Sigma-Aldrich, 2000). Research grade dibenzofuran is also available from Acros, Alfa Aesar, and TCI America (Alfa Aesar, 1999; Fisher Scientific, 2000; TCI America, 1998).

EXPOSURE INFORMATION

<u>Production and Producers</u>: Dibenzofuran is recovered from a wash oil fraction of coal tar that boils between 275 °C and 290 °C. Redistillation separates dibenzofuran from acenaphthene, which boils at a lower temperature. Crystallization of the redistilled fraction then produces technically pure dibenzofuran (Elvers *et al.*, 1989).

Dibenzofuran is supplied by twelve companies within the United States (Chemical Sources International, 2000).

Dibenzofuran is listed in the EPA's Toxic Substances Control Act (TSCA) Inventory (NLM, 1999).

<u>Use Pattern</u>: Dibenzofuran is found in various percentages in coal tars and coal tar creosotes. Coal tar creosote is a complex mixture typically composed of 85% PAHs and 2-17% phenolics. Typical wood preservative creosote is approximately 3.5% dibenzofuran. Dibenzofuran occurs at levels of 0.19-1.50 wt % of dry tar in commercial coal tars (ATSDR, 1990; NLM, 2000a).

Due to its high heat resistance, dibenzofuran, together with biphenyl, is a component of heat-transfer oils. When combined with methylnaphthalenes, it is suitable as a carrier for dyeing and printing textiles. A range of polymers can be produced from dibenzofuran, e.g., heat-resistant polyarylacetylene and quinoxaline polymers or photoconductive polymers for electrophotography (Elvers *et al.*, 1989).

As a combustion product, dibenzofuran may be released from the incomplete combustion of coal biomass, refuse, diesel fuel and residual oil, as well as from tobacco smoke (NLM, 2000a).

<u>Human Exposure</u>: Humans are exposed to dibenzofuran through inhalation of contaminated air, ingestion of contaminated food, or dermal contact with some treated wood products (NLM, 2000a).

Occupational Exposure. The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981-1983, estimated that 3,292 workers were potentially exposed to dibenzofuran in the workplace. (NLM, 1999). Occupational exposure to dibenzofuran may occur through dermal contact and inhalation, particularly at sites where coal tar and coal tar derivatives, especially creosote, are used (NLM, 2000a).

General Population Exposure. The general population may be exposed to dibenzofuran through inhalation of air which has been contaminated by a variety of combustion sources. Assuming an average ambient air concentration of 19 ng/m³, the average daily air intake of dibenzofuran is 380 ng (NLM, 2000a).

There should be very little exposure of the average homeowner to creosote solutions [containing dibenzofuran] used for wood treatment because they can only be sold to certified applicators. However, homeowners can be exposed to creosote-treated products (ATSDR, 1990).

In the EPA's National Human Adipose Tissue Survey, 46 composite samples of human adipose tissue representing various age groups and locations were analyzed. Three percent of these samples contained dibenzofuran (NLM, 2000a).

Environmental Exposure. Exposure to dibenzofuran may occur through consumption of contaminated food and drinking water. Dibenzofuran was qualitatively detected in catfish from the Black River near Lorain, Ohio, and in Potomac River bass. Dibenzofuran was qualitatively identified in drinking water collected from Cincinnati, Ohio in October 1978 and Philadelphia, Pennsylvania in February 1976 (NLM, 2000a).

The concentration of dibenzofuran detected in Finnish margarines and vegetable oils ranged from 0.08 to 0.64 μ g/kg. The mean concentration in various Finnish cereal products ranged from 1.0 (wheat) to 4.7 μ g/kg (bran) (NLM, 2000a).

Environmental Occurrence:

Dibenzofuran is a common component of environmental pollutants, and has been identified in air, ground water, fuel gas, fly ash from municipal incinerators, and diesel exhaust gas particulates, and cigarette smoke (Watanabe, 1992).

Water. Dibenzofuran has been detected in the surface waters of Lake Erie and is one of 28 aromatic compounds regularly detected in surface sediments from the Elizabeth River, which flows into the Chesapeake Bay. Dibenzofuran (1.70 and 9.50 ppm) was found in sediment from two of five Great Lakes tributaries. Dibenzofuran has also been found in sediments collected from Lake Pontchartrain, Eagle Harbor (Puget Sound area), the Black River, the Martha's Vineyard area, and in sediment cores in various northern New Jersey waterways (NLM, 2000a; Padma et al., 1999).

Dibenzofuran was also found in tissue of snails obtained from two different sites in Pensacola, Florida as well as in sediment taken from the Black River (Rostad & Pereira, 1987; West *et al.*, 1988).

Concentrations of dibenzofuran ranging 0.008 - 0.42 ppm were detected in ground water beneath an abandoned creosote plant in Texas. Dibenzofuran was also found at concentrations of 0.01 - 0.49 ppm beneath a wood preserving facility in Florida and was detected qualitatively in ground water beneath a coal-tar distillation facility in Minnesota (NLM, 2000a).

Hazardous waste sites. Dibenzofuran is a component of coal tar. Prior to the development of a nationwide gas pipeline system, gas was produced locally by coal distillation. The coal tar residue not sold for roofing and road surfacing materials was

disposed of at sites near the gasification plants. There are approximately 1,500 coal tar waste sites in the United States (Culp *et al.*, 1998).

Air. The total releases and transfers of dibenzofuran listed in EPA's Toxic Release Inventory for 1994 were reported as 26,116 pounds and 53,744 pounds, respectively (EPA, 1994). In 1998, the Toxic Release Inventory reported that total on-site releases of dibenzofuran were 150,929 pounds (air emissions - 94,230 pounds; releases to land - 56,670 pounds; surface water discharges - 29 pounds) and total off-site releases were 13,304 pounds. For creosote, total on-site releases in 1998 were 3,072,169 pounds and total offsite releases were 1,263,532 pounds (EPA, 1998).

Atmospheric sampling of dibenzofuran was performed between November 1988 and February 1989 in Minneapolis and Salt Lake City. Levels ranged from 6.5 - 31 ng/m³ in Minneapolis and 10 -76 ng/m³ in Salt Lake City. The concentration of dibenzofuran in the gas-phase in the ambient air of Portland, Oregon in February to April 1984 was 13 - 25 ng/m³ (mean 19 ng/m³) but the concentration in the particulate phase was only 0 - 0.35 ng/m³ (mean 0.1 ng/m³) (NLM, 2000a).

Regulatory Status: Dibenzofuran is cited in the Clean Air Act 1990 Amendments - Hazardous Air Pollutants as a volatile hazardous air pollutant of potential concern. The Superfund Amendment Reauthorization Act (SARA) Section 110 placed dibenzofuran on the revised Agency for Toxic Substances and Disease Registry (ATSDR) priority list of hazardous substances to be the subject of a toxicological profile. The listing was based on the substance's frequency of occurrence at Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) National Priorities List sites, its toxicity, and/or its potential for human exposure. Dibenzofuran is also listed in the Massachusetts Substance List for Right-to-Know Law, the New Jersey Department of Health Hazard Right-to-Know Program Hazardous Substance List, and the Pennsylvania Department of Labor and Industry Hazardous Substance List. California's Air Toxics "Hot Spots" List (Assembly Bill

2588) and EPA's Toxic Release Inventory Chemicals also list dibenzofuran as a hazardous air pollutant (EDF, 1998; EPA, 1998; STN, 2000).

No standards or guidelines have been set by NIOSH or the Occupational Safety and Health Administration (OSHA) for occupational exposure to or workplace allowable levels of dibenzofuran. Dibenzofuran 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. The OSHA standard for coal-tar pitch volatiles (which contain a small amount of dibenzofuran) in workroom air is a 0.2 mg/m³ time-weighted average (ATSDR, 1990).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

<u>Human Data</u>: No epidemiological studies or case reports investigating the association of exposure to dibenzofuran and cancer risks in humans were identified in the available literature.

<u>Animal Data</u>: No 2-year carcinogenicity studies of dibenzofuran in animals were identified in the available literature.

According to the International Agency for Research on Cancer (IARC), the available data indicate that coal-tars and coal-tar pitches are causally associated with cancer in humans and that creosotes derived from coal-tars are probably carcinogenic to humans (IARC, 1984).

To determine the contribution of benzo[a]pyrene to the carcinogenicity of coal tar, mice were fed two coal tar mixtures or benzo[a]pyrene in a 2-year bioassay. The coal tar diets induced a dose related increase in tumors at multiple sites. Although the benzo[a]pyrene present in the two coal tar mixtures could have accounted for the forestomach tumors observed, the lung and liver tumors appeared to be due to other components in the coal tar mixture and the small intestine tumors may have resulted from chemically-induced cell proliferation that occurred at high doses of coal tar. Although the coal tar mixtures contained 1,504 or 1,810 mg/kg of dibenzofuran, respectively, they also contained mutagenic PAHs which could have accounted for the observed lung and liver tumors (Culp *et al.*, 1998; Goldstein *et al.*, 1998).

Short-Term Tests:

Dibenzofuran has been evaluated for mutagenic activity in the Ames assay. Dibenzofuran did not induce genotoxicity with or without metabolic activation in *Salmonella* TA98 at concentrations from 0.025-1.6 µmol/plate and TA100 at concentrations from 0.05- 4.0 µmol/plate (Matsumoto *et al.*, 1988). In a separate study by Mortelmans and coworkers (1984), dibenzofuran did not induce

mutagenicity in *Salmonella* strains TA98, TA100, TA1535, or TA1537 in the absence and presence of S-9. These results are consistent with the results reported by Uno and coworkers (1991), as well as Schoeny (1982).

<u>Metabolism</u>: No information on the metabolism of dibenzofuran in mammalian organisms was found in the available literature. The bacteria *Sphingomonas*, *Brevibacterium*, *Terrabacter*, and *Staphylococcus auricularis* degrade dibenzofuran to 2,2',3-trihydroxybiphenyl via dibenzofuran 4,4a-dioxygenase (Bunz & Cook, 1993; Ouelette & McLeish, 2000).

Other Biological Effects:

Enzyme Induction. The P450 superfamily contains the principal enzymes responsible for the metabolic activation of carcinogens. In the P4501A family, CYP1A1 and CYP1B1 metabolize and participate in the metabolic activation of PAHs. CYP1A2 catalyzes aromatic and heterocyclic amine *N*-oxidation, and has been implicated as a risk factor in urinary bladder and colorectal cancer (Gonzalez & Kimura, 1999; MacLeod *et al.*, 1997).

Chaloupka and coworkers investigated manufactured gas plant PAH mixtures in B6C3F₁ mice. This residue contained a complex mixture of 2-ring, 3-ring and 4-ring PAHs which induced hepatic CYP1A1 and CYP1A2 gene expression. However, the 3-ring mixture, which contained dibenzofuran and five other PAHs induced only CYP1A2. All six tricyclic PAHs significantly induced hepatic microsomal methoxyresorufin *O*-de-ethylase (MROD) activity, a more specific indicator of CYP1A2 activity than ethoxyresorufin *O*-de-ethylase (EROD) activity, although acenaphthylene and anthracene were more active than dibenzofuran (Chaloupka *et al.*, 1994; Chaloupka *et al.*, 1995).

Aryl Hydrocarbon (Ah) Receptor Binding Studies. An important criterion to define whether dibenzofurans and dibenzodioxins exhibit "dioxin-like" toxicity is Ah receptor binding (EPA, 2000).

In competitive binding studies using mouse hepatic cytosol, the tricyclic PAHs, including dibenzofuran, did not displace TCDD from the Ah receptor or benzo[a]pyrene from the 4S carcinogen binding protein. Thus, tricyclic PAHs appear to induce hepatic CYP1A2 gene expression in mice by an Ah receptor-independent pathway (Chaloupka *et al.*, 1994; Chaloupka *et al.*, 1995).

Immunotoxicity. A reconstituted PAH mixture containing 17 congeners, including dibenzofuran, and the 2-, 3-, and 4-ring PAH fractions all caused a dose-dependent decrease in the splenic plaque-forming cell response of B6C3F₁ mice to sheep red blood cells or trinitrophenyl-lipopolysaccharide antigens (Harper *et al.*, 1996). While this response may occur with "dioxin-like" PAHs, it cannot be attributed to dibenzofuran because of the other PAHs present in the mixtures.

<u>Structure-Activity Relationship</u>: Chemicals structurally similar to dibenzofuran were screened for relevant information associating these chemicals with mutagenic or carcinogenic effects. Dibenzo-*p*-dioxin was found to be the most structurally related compound to dibenzofuran. The structure of dibenzo-*p*-dioxin is shown below:

A bioassay of unsubstituted dibenzo-*p*-dioxin was conducted in Osborne-Mendel rats and B6C3F₁ mice. Groups of 35 rats of each sex were administered dibenzo-*p*-dioxin at 5,000 or 10,000 ppm in feed for 110 weeks. Groups of 50 mice of each sex were administered the same doses in feed for 87 or 90 weeks. Controls consisted of groups of 35 untreated rats of each sex and 50 untreated mice of each sex. No tumors were induced in rats or mice of either sex at incidences that were significantly higher in the dosed groups than in the corresponding control groups. Thus, it was concluded that

under the conditions of the bioassay, dibenzo-*p*-dioxin was not carcinogenic (NTP, 1979).

Dibenzo-p-dioxin was negative in the Ames *Salmonella* strains TA98 and TA100 with or without S-9 activation (NLM, 2000b).

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