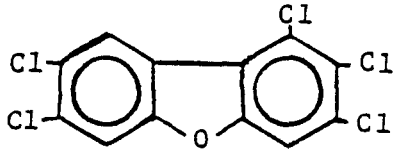
NTP Chemical Nomination

I. Chemical Identification

a. 1,2,3,7,8-Pentachlorodibenzofuran



b. Common or generic names and synonyms

Penta CDF

c. CAS Registry Number

57117-41-6

d. Polychlorinated dibenzofurans (PCDFs) are a series of tricylic aromatic compounds which are chemically similar to polychlorinated dibenzo-p-dioxins (PCDD). The PCDFs occur as undesired trace contaminants in certain industrial chemicals, such as polychlorinated biphenyls, chlorophenols and polychlorinated benzenes. There are 135 PCDFs which include 28 pentachloro isomers.

e. Physical and chemical properties

Purified PCDFs are high melting, white solids. Little information is available on the general physical, chemical and solubility properties of penta CDF. Dibenzofuran is soluble in ethanol, acetone, acetic acid and n-hexane, but almost insoluble in water.[1,2,3,4]

Vapor pressures of PCDFs have not been measured directly, but estimates derived from gas chromatographic data range from 4 to 20 mm Hg X 10^{-7} at 25°C for the tetra- to hepta-CDFs.[5] The PCDFs display ultraviolet (UV) absorption maxima in the range of 250 to 270 nm and 300 to 330 nm. UV data are not available for many PCDF congeners.

f. Commercial product(s) composition - Not applicable.

g. References

1. Beilstein's Handbook der Organischen Chemie Sys. No. 2370.

2. Weast, R.C. (Ed.), CRC Handbook of Chemistry and Physics, 6th ed. CRC Press, Boca Raton, Florida, 1979.

3. Greenlee, W. and Poland, A. in Dioxin:Toxicological and Chemical Aspects, F. Cattabeni et al., SP Medical and Scientific Books, Halsted Press, New York, 1978, p. 118.

4. Helling, C. et al., J. Environ. Qual., 2:171, 1973.

5. Report of the Ad Hoc Study Group on Pentachlorophenol Contaminants, U.S. EPA, Science Advisory Board, 1978, Table 7.13, p. 64.

II. Production, Use, Occurrence, and Analysis

a. Production

A number of synthetic routes have been employed for preparation of specific PCDFs. They include (1) chlorination of dibenzofuran and its chlorinated homologues; (2) reduction of chlorinated o-nitrodiphenyl ethers followed by internal diazo coupling; (3) internal cyclization of o-chloro-substituted diphenyl ethers by either chemical or photolytic techniques; (4) pyrolysis of PCBs, chlorinated phenols and derived products, and chlorinated diphenyl ethers; (5) coupling of a chlorinated anisidine with a chlorinated benzene followed by demethylation and internal cyclization; and (6) coupling of a chlorinated aniline to a chloroanisole followed by demethylation and internal cyclization.[1,2]

PCDFs are formed during the manufacture and subsequent heating and pyrolysis of PCBs and chlorophenols. Human exposure to PCDFs is due to the widespread use of PCBs and chlorophenols and may also be due to specific exposure in the workplace or accidental exposure such as that which occurred from contaminated (Yusho) vegetable oil in Japan (1968) and Taiwan (1979).

b. Uses - Not applicable.

c. Occurrence in the environment

Between 1930 and 1975 (when production was terminated) approximately 630 million kg of PCBs were produced in the U.S. With a content of about 1.5 mg/kg of PCDFs in the PCBs, it is estimated that 945 kg of PCDFs were present in the PCBs. The amount of environmental exposure is impossible to determine, however, since additional PCDFs can be produced by pyrolysis of the PCBs and PCDFs are subject to environmental degradation by photolysis (sunlight). Extensive analysis of environmental samples is required to determine the general background levels of PCDFs which also are contaminants in chlorophenols and have been identified in fly ash and other products from municipal incinerators and accidental fires.[3]

With respect to PCP, the major chlorophenol containing trace levels of PCDFs, 22.5 million kg are produced annually in the U.S. Assuming a total PCDF level of 200 mg/kg in commercial PCP, 4,500 kg of PCDFs are generated annually in the U.S. from PCP manufacture. These figures merely suggest the potential for human exposure which must actually be determined by direct analyses of food and tissue samples.

d. Analysis

Sensitive and highly specific analytical methods are required for detection and quantitation of PCDF levels in environmental, biological and food samples. These procedures generally involve preliminary steps (extraction, column chromatography, HPLC) to isolate the analytes (chromatographic techniques such as absorption, partition, exclusion or ion-exchange chromatography may be used), which are generally followed by low or high resolution mass spectrometry coupled with high or low resolution gas chromatography to identify and quantitate particular PCDFs. Sample extracts may be examined by high resolution gas chromatography to tentatively identify and quantitate individual PCDFs or PCDDs prior to confirmatory gas chromatography-mass spectrometry. In addition, biological procedures (e.g., enzyme induction and radioimmunoassays) may be applied to sample screening in order to minimize the demand for mass spectrometric screening or to determine if significant amounts of biologically active PCDFs are present.

c. References

1. Kende, A.S. et al., 167th Nat. Meeting ACS, Los Angeles, CA, 4-4-74, paper ORGN 130.

2. Safe, S.H. and L.M. Safe, J. Agric. Food Chem., 32, 68, 1984.

3. Rappe, C. and Buser, H. in Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products, R. Kimbrough (Ed.), Elsevier/North Holland Biomedical Press, New York, 1980, p. 64.

III. Toxicology

a. Human data, case reports, and epidemiological studies

1. "Yusho poisoning" occurred in western Japan in 1968. Approximately 1600 people consumed rice oil which had been contaminated with Kanechlor 400, a commercial polychlorinated biphenyl compound which was contaminated with a mixture of PCDFs.[1,2] The PCDFs are thought to be responsible in large part for the toxic symptoms seen in this incident. These included chloracne, excessive secretion from the Meibomian glands, and pigmentation of

face, eyelids, gingiva and nails. A critical dose of 2.5 mg (46 ug/kg) of PCDF for induction of dermal symptoms has been estimated from studies of Yusho victims.[3]

2. In the spring of 1979, similarly contaminated rice oil was consumed by about 2000 people in central Taiwan. Symptoms resembled those of Yusho victims. In an analysis of tissue samples from a deceased patient, concentration of PCDFs was found to be highest in the liver - about 3 times greater than the level in intestinal fat, the tissue with the next highest level. All retained PCDF congeners had at least 3 chlorine atoms in the 2,3,7 and 8 positions.[2]

3. The Environmental Protection Agency has not set a "level of concern" for CDFs in hazardous wastes. The Agency stated that, as biological availability of these toxicants is expected to be dependent on waste matrix characteristics, a generic risk estimation for all wastes would be difficult to perform. Similarly, it would not be feasible to set the lower limit at the limit of detection, since the limit of detection is not fixed, but rather is dependent on sample and matrix characteristics. However, the Agency has stated that "Because of the high acute and chronic toxicity properties of many of the CDDs and CDFs, ...if a lower limit of concern were to be developed it would be very low."[4]

b. Experimental animal information

1. A PCDF mixture containing 49% 1,2,3,7,8-penta CDF was administered orally to 2 adult Rhesus monkeys (one male, one female), and i.p. to young, male Wistar rats (N=4). Upon analysis of the livers of the animals it was found that the 2,3,4,7,8-penta CDF isomer was the most readily accumulated. 1,2,3,7,8-penta CDF followed by 2,3,7,8-tetra CDF were next most readily accumulated.[5]

2. 1,2,3,7,8-penta CDF significantly increased aryl hydrocarbon hydroxylase (AHH) activity in the lung but not in the liver, while the 2,3,4,7,8-penta isomer significantly increased AHH activity in both organs. Both chemicals were administered to young, male Wistar rats (N=4) in a single i.p. injection at a dose level of 5 ug/kg.[6] A dose response study in the rat of 2,3,4,7,8-penta CDF demonstrated that the minimum dosages of this congener were 1 ug/kg for inductive effects and 10 ug/kg for acute toxicity.[1]

An earlier study of the effects of 1,2,3,7,8-penta CDF on male Wistar rats (N=3) demonstrated significant increases in both AHH and DT-diaphorase activity in the liver. However, the dosage in this experiment was 10 mg/kg in a

single i.p. injection. Severe atrophy of the thymus and hypertrophy of the liver were also noted.[7]

3. Investigations were made on the effects of OCDF and dibenzofuran on *in vitro* absorption of solutes and concomitant fluid transfer in the mouse everted small intestine. Prior to sacrifice, mice (inbred strain CD-1, N=4) received a single, oral dose of 2.0 mg/kg body weight of one chemical. Absorption of D-glucose decreased 7 days after treatment with both chemicals, as did final D-glucose content of tissue homogenates. D-glucose malabsorption was abolished by an exogenous energy supply, D-mannose. Intestinal absorption of D-galactose and several amino acids was unchanged. Fluid transfer was unaltered. Lowered D-glucose absorption probably resulted from increased intracellular metabolism effects rather than from impaired function of the D-glucose carrier at the brush border. Apparent malabsorption was unrelated to chlorine content,[8] so similar results might be expected from penta CDF.

c. *In vitro* and other short-term tests - None.

d. Other relevant information

1. While few studies have been performed on 1,2,3,7,8-penta CDF *per se*, numerous tests have been conducted on the toxic effects of fly ash and transformer fluids which contain penta CDFs as contaminants. Species tested include rats, mice, guinea pigs, and rabbits. TCDD- or TCDF-like syndromes are usually induced. Common findings include weight loss, decreased thymus weight, and liver hypertrophy. However, because the samples contain a mixture of PCDDs and PCDFs in various concentrations, it is impossible to attribute the effects to any particular chemical species.[9,10,11,12,13,14]

2. The mechanism of action of halogenated aryl hydrocarbon toxicity is unknown. There does appear to be a correlation between AHH inducing ability and toxicity, the biochemical basis of which is that the AHH induction and halogenated aryl hydrocarbon-induced toxicity require binding to a cytosolic receptor. There is no evidence that a disturbance in energy metabolism is the cause, despite pronounced weight loss associated with PCDF intoxication. Limited data indicate no relationship between altered nucleic acid or protein metabolism and toxicity. PCDFs decrease serum albumin levels and increase the globulin/albumin ratio, but not to such an extent as to cause the toxic syndrome.[15]

The toxicity of the PCDFs is believed to be mediated through stereospecific recognition and binding by a cytosolic receptor species as it is for TCDD and TCDF.[16]

There appears to be no correlation between π-electron density and toxicity of PCDFs; therefore, it is unlikely that charge-transfer complexes play an important role in explaining relative toxicities of PCDFs.[8]

3. 2,3,4,7,8-penta CDF, which is structurally quite similar to the compound of interest, was able to selectively increase 7 alpha-hydroxylation, but strongly suppressed 2 alpha-, 6 beta-, and 16 alpha-hydroxylation and 5 alpha-reduction of progesterone and testosterone in the liver microsomes of rats. This change in the metabolic pattern was accompanied by a marked decrease in total metabolism of both steriods and appeared to correlate with toxic potency. The change in steroid metabolism may be responsible, at least in part, for endocrine symptoms caused by this compound via disturbance of steroid homeostasis.[17]

e. References

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3. S. Hori et al., Toxicology, 24:123-139, 1982.

4. Federal Register, 48(65):14514-14529, 1983.

5. H. Kurski et al., Fd. Cosmet. Toxicol., 18:387-392, 1980.

6. J. Nagayama et al., Arch. Toxicol., 53:177-184, 1983.

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15. A. Parkinson and S. Safe, Toxicol. Environ. Chem., 4:1-46, 1981.

16. A. Poland et al., Annals of N.Y. Academy of Sci., 320:214-230, 1979.

17. S. Yoshihara et al., J. Pharmacobiodynamics, 5(12):994-1004, 1982.

IV. Disposition and structure-activity relations

a. Absorption, distribution, metabolism and excretion

1. The furans are quite insoluble in all media, and solubility tends to decrease further as the degree of halogenation increases. Insolubility may act to selectively limit the rate and degree of absorption of the more highly halogenated furans. The less halogenated furans are usually metabolized and excreted more rapidly. Therefore, once absorbed, the highly halogenated compounds may be more persistent and thus have greater potential for bioaccumulation.[1]

2. A diet containing 0.6 ppm of a mixture of PCDFs having 4,5, or 6 chlorine atoms was fed to female ddN mice (N=15-20) for 18 days after mating or for 14 days after delivery. Dams, fetuses, and offspring were analyzed for PCDFs. PCDFs were transferred to the fetuses across the placenta and to the offspring through milk. Transfer was greater through the milk than via the placenta. While 0.26% of the amount ingested was found in the dam, only 0.003% of the ingested amount was transferred to the fetus. Of the amount ingested by the dam, suckling mice accumulated 0.07% after 1 week, and 0.14% after 2 weeks.[2]

3. PCDF degradation patterns are less specific and more dependent on chlorine substitution pattern than are the degradation patterns of the similarly-structured PCDDs. Preferential enzymatic attack would occur at the 1,2 positions.[3]

b. Structure-activity correlations and considerations

1. PCDF congeners which induce AHH and δ-amino levulinic acid synthetase activity and bind to the cytosol binding protein have halogen atoms in at least 3 of the lateral

ring positions (2,3,7 and 8)[4] and have at least one unsubstituted ring position.

2. Addition of chlorine in the 1-position of PCDFs has little effect on toxicity and any lowering of toxicity is less than an order of magnitude, relative to 2,3,7,8-TCDF.[5]

3. Analysis of liver samples from 2 deceased Yusho patients determined that none of the PCDF isomers retained had 2 vicinal hydrogenated carbons in the dibenzofuran rings.[6] In addition, most had all lateral positions chlorinated. Some higher chlorinated PCDFs were still present in the liver 44 months after consumption,[7] demonstrating slower excretion than the tetra isomers.

4. In rats and mice, retention of PCDF congeners increases with increasing number of chlorine atoms in the Cl_4-Cl_6 range. PCDFs are generally retained to a greater degree than corresponding PCDDs.[8,9]

5. For halogenated aromatic hydrocarbons congeners, the correlation between toxicity and the ability to bind to the receptor and induce enzyme activity suggests (a) that the parent compounds, not metabolites, are responsible for toxicity, and (b) that the capacity of a congener to elicit a single toxic response indicates the potential to produce the complete syndrome.[10]

IV. References.

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9. M. Van den Berg et al., Chemosphere, 12(4/5):537-544, 1980.

10. A. Poland and J.C. Knutson, Ann Rev. Pharmacol. Toxicol., 22:517-554, 1982.

V. Ongoing toxicological and environmental studies in the government, industry, and academia

None.

VI. Rationale for recommendation and suggested studies

The 1,2,3,7,8-penta CDF is recommended for study because it is a ubiquitous environmental contaminant which is structurally similar to the 2,3,7,8-TCDF and of which very little is known of its toxicity. The accidental contaminations in Japan, Taiwan, and New York, coupled with the presence of 1,2,3,7,8-penta CDF in transformer fluids, fly ash, and aquatic samples, indicate significant past and potential human exposure. Since 1,2,3,7,8-penta CDF possesses the ability to accumulate in tissue, an investigation and determination of its toxicological profile is considered to be of the utmost importance.

The types of studies to be performed initially should include a mutagenesis screen and acute and short-term toxicity testing. If this penta CDF demonstrates activity in these tests then serious consideration should be given to additional testing of its ability to elicit teratogenic, reproductive and chronic, including carcinogenic, effects.