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Project Summary

Health Assessment Document for Polychlorinated Dibenzo-*p*-Dioxins

The full health assessment document on polychlorinated dibenzo-*p*-dioxins discusses multimedia environmental issues pertaining to the most toxic chlorinated dioxins, namely 2,3,7,8-tetrachloro-; 1,2,3,7,8-pentachloro-; 1,2,3,6,7,8-hexachloro-; and 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxins. Scientifically valid data essential for human health risk assessment purposes from an extensive literature search were compiled and discussed critically. Discussions are based on physiochemical properties and analytical methodologies; stability and degradation; production, use, synthesis; environmental resources and environmental levels; environmental fate and transport; degradation; bioaccumulation and bioconcentration factors; ecological effects; various aspects of toxic effects from acute, subchronic and chronic exposure in experimental animals and humans; pharmacokinetics and mechanism of toxic effects; teratogenicity and reproductive effects; mutagenicity and carcinogenicity. Based on this review, critical studies have been identified and utilized for estimating the unit risk.

This Project Summary was developed by EPA's Environmental Criteria and Assessment Office, Cincinnati, OH, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

Dioxins are a class of compounds that contain the dibenzo-*p*-dioxin nucleus. In chlorinated dioxins, the dibenzo-*p*-dioxin nucleus is substituted with chlorine at different positions of the fused benzene rings. Depending on the number and position of chlorine substitution, 75 congeners are possible for the chlorinated dioxins. The full document deals with the most toxic chlorinated dioxins, namely, 2,3,7,8-tetrachloro-, 1,2,3,7,8-pentachloro-, 1,2,3,6,7,8-hexachloro- and 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin. Of these four congeners, the 2,3,7,8-tetrachlorodibenzo-*p*-dioxin has been studied extensively and is often described in both popular and technical literature as "TCDD" or simply "dioxin".

Few documents exist at the present time that deal with selected aspects of polychlorinated dibenzo-*p*-dioxins in the environmental media. The full document, however, provides comprehensive multimedia assessment of the analytical methodologies, environmental levels and ecological and health effects of the four chlorinated dioxins Table 1 lists the acronyms used when discussing the polychlorinated dibenzo-*p*-dioxins

Discussion

Polychlorinated dibenzo-*p*-dioxins are a class of chlorinated tricyclic aromatic hydrocarbons consisting of two benzene rings connected by a pair of oxygen atoms. According to the position and number of chlorine atoms it is possible to form 75 different congeners of chlorinated dioxins. The word "dioxins" is often used to refer to this class of compounds, especially with respect to the highly toxic and environmentally widely distributed 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). This class of compounds is rather stable toward heat, acids and alkalis. The solubility of 2,3,7,8-TCDD in water is 0.2 µg/l. This isomer and the three other PCDDs discussed in the full

Table 1. *Acronyms for polychlorinated dibenzo-p-dioxins*

Acronym	Full name
PCDDs	Polychlorinated dibenzo-*p*-dioxions
2,3,7,8-TCDD	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
1,2,3,7,8-PeCDD	1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin
1,2,3,6,7,8-HxCDD	1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin
1,2,3,7,8,9-HxCDD	1,2,3,7,8,9-Hexachlorodibenzo-*p*-dioxin

document are soluble in certain aromatic and aliphatic solvents. The PCDDs are chemically relatively stable and start to decompose at temperatures >500°C; the percent of decomposition depends upon the residence time in the high temperature zone and the proportion of oxygen in the heated zone.

The commonly used method for the determination of these compounds in different samples consists of solvent extraction, followed by sulfuric acid and base washes to remove lipids and other impurities from the solvent extract. The extract is then subjected to two liquid chromatographic clean-up procedures. The cleaned-up extract is finally analyzed for the PCDDs by the gas chromatographic-mass spectrometric methods. Despite the specialized methods used for the determination of PCDDs, the results of analysis at very low levels (possibly <9 ppt in biological matrices) can be questionable unless special precautions including addition of internal standards, are made.

None of the PCDDs are either commercially manufactured or have any known use. They are produced as unwanted contaminants primarily during the manufacture of chlorophenols and their derivatives. The primary sources of PCDD contamination in the environment result from the industrial manufacture of chlorophenols and their derivatives and the subsequent disposal of wastes from these industries. Municipal incineration may also produce some environmental emission of PCDDs. From the available data, it is difficult to ascertain the comparative importance of these three sources in contributing to environmental emissions. The 1,2,3,7,8-PeCDD found in environmental samples has only been reported in emissions from incinerators.

The monitoring data to date indicate that the maximum level of PCDDs is likely to be found in soil and drainage sediment samples near chlorophenol manufacturing industries and chemical waste disposal sites.

The environmental fates of the four PCCDs are not known with certainty. Most of the investigations in this field have been conducted with 2,3,7,8-TCDD, and the conclusions regarding the environmental fate of the other three PCDDs have been drawn by analogy. Few data exist in the literature that would indicate significant chemical and biological transformation of these compounds in atmospheric, aquatic or soil media. The role of photochemical transformation in determining the fates of these chemicals in various ambient media is not known with certainty, but the PCDDs are susceptible to photochemical reactions in the presence of hydrogen donors. In the aquatic media, a substantial proportion of the PCDDs may be present in the sediment-sorbed state or in the biota. In the atmosphere, the PCDDs are expected to be present in the vapor-phase and particulate-sorbed states. The atmospheric transport of these compounds can be predicted from dispersion modeling equations. In the case of the accidental release of 2,3,7,8-TCDD at Seveso, Italy, it has been estimated from laboratory experiments that 2,3,7,8-TCDD deposition from air to soil follows an exponential decay pattern along the downward wind direction. The most probable transport mechanisms of the PCDDs from soils are transport to atmosphere by contaminated dust particles, direct volatilization from the surface or near surface zones (≤ 5 cm), and transport to surface water by eroded soil.

Both the calculated and the experimental results show that the PCDDs will concentrate in sediments and biota present in aquatic media. In mammals, 2,3,7,8-TCDD is readily absorbed through the gastrointestinal tract, and absorption through intact skin has also been reported. Absorption may decrease dramatically if 2,3,7,8-TCDD is absorbed to particulate matter such as activated carbon or soil. After absorption, 2,3,7,8-TCDD is distributed to tissues high in lipid content; however, in many species, the liver is a major storage site. Metabolism of 2,3,7,8-TCDD occurs slowly, with the polar metabolites excreted in the urine and feces Unmetabolized 2,3,7,8-TCDD can be eliminated in the feces and in the milk. I is metabolized by the P-450 mono oxygenase system through a reactive epoxide intermediate. The metabolism o 2,3,7,8-TCDD seems to be detoxification process resulting in the production of metabolites that are less toxic than the parent compound. Avail able scientific data support the contention that the toxic response to 2,3,7,8-TCDD exposure is mediation through cytosoli Ah-receptor site binding.

The PCDDs discussed in the fu document are among some of the mos toxic compounds known, with the lowes LD_{50} level for male guinea pigs, the mos sensitive species, being 0.6 µg/kg fo 2,3,7,8-TCDD. The other congeners ar somewhat less toxic; however, the LD_5 values are still in the µg/kg range Although 2,3,7,8-TCDD is highly toxic i all species tested, there are large specie differences in sensitivity, with the LD_5 for hamsters being 1157-5052 µg/kg The characteristic signs and symptom of lethal poisoning are severe weight los and thymic atrophy. Death usually occu many days after the exposure. In rat rabbits and mice, 2,3,7,8-TCDD pro duces an acute liver injury that is n observed in either monkeys, hamsters, guinea pigs. In mice, the immun response is also suppressed. After sub chronic or chronic exposure to 2,3,7, TCDD in rats or mice, the liver appears be the most severely affected orga although systemic hemorrhage, eden and suppressed thymic activity are al observed. The limited data available f the other PCDDs indicate that the chemicals produce the same symptom as 2,3,7,8-TCDD in a given specie however, the doses required are higher.

Humans have been exposed herbicides and other chlorinated chem icals containing 2,3,7,8-TCDD as contaminant. The symptoms of toxicity many cases are similar to those observ in animals, with exposure leading altered liver function and lip metabolism, porphyria cutanea tarc

neurotoxicity and pathologic changes in hematologic parameters. In addition, exposure of humans to 2,3,7,8-TCDD produces skin lesions such as chloracne and hyperpigmentation. Although some signs such as chloracne are attributed to the PCDDs, the other signs of toxicity may arise, at least in part, from the other chemical of which PCDDs are a minor contaminant.

Animal studies have demonstrated that 2,3,7,8-TCDD is teratogenic and fetotoxic in rats, mice, rabbits and ferrets; and fetotoxic in monkeys. Exposure to 2,3,7,8-TCDD in mice produces facial clefts, while exposure in rats results in edema, hemorrhage and kidney anomalies; rabbits have a higher incidence of extra ribs. In rats, a reduction in the gestation index, decreased fetal weight, increased liver-to-body weight ratio and increased incidence or dilated renal pelvis in the offspring have been observed. Certain human epidemiology studies have shown positive associations with exposure to chemicals contaminated with 2,3,7,8-TCDD and birth defects and abortions, while others have not.

There is a limited data base with conflicting evidence for 2,3,7,8-TCDD's mutagenic potential; therefore, the available evidence is judged to be inconclusive. There are no studies in the published literature regarding the mutagenicity of HxCDD or any other congeners of PCDD.

There is evidence from chronic animal cancer bioassay studies that 2,3,7,8-TCDD and HxCDD are probable human carcinogens. There are no chronic cancer bioassay studies available that evaluate the carcinogenic potential for the other PCDDs. The available data for 2,3,7,8-TCDD and HxCDD come from gavage and feeding studies, there being no studies available for inhalation exposure. The epidemiologic evidence for the carcinogenicity of 2,3,7,8-TCDD alone is inadequate while the evidence for phenoxyacetic herbicides and/or chlorophenols with 2,3,7,8-TCDD as an impurity is limited. There have been no epidemiologic evaluations, as yet, for HxCDD as the sole compound of concern.

A number of chronic animal cancer bioassays show that 2,3,7,8-TCDD is an animal carcinogen. In rats, oral exposure to 2,3,7,8-TCDD resulted in an increased incidence of hepatocellular carcinomas, squamous cell carcinomas of the tongue and hard palate/nasal turbinates, and squamous cell carcinomas of the lung. In both male and female mice, increased incidences of liver tumors were observed. A mixture of the two isomers of HxCDD, discussed in the full document has been tested for carcinogenicity and shows increased incidences of liver tumors in rats and mice. Also, 2,3,7,8-TCDD has produced fibrosarcomas at the site of application after dermal administration, although there was no significant increase in dermal tumors when the mixture of HxCDDs was tested. Since both compounds produce statistically significant increased incidences of tumors in two species of animals, there is sufficient evidence, according to the EPA weight-of-evidence classification criteria, to conclude that both 2,3,7,8-TCDD and HxCDD are animal carcinogens. The 2,3,7,8-TCDD has been shown to be a promoter as well as an initiator in rodent test systems. Evidence is available from epidemiologic studies that implicate exposure to herbicides contaminated with 2,3,7,8-TCDD with a significantly elevated risk of soft tissue sarcomas and to a lesser extent non-Hodgkins lymphomas; however, the exposures to 2,3,7,8-TCDD were always compounded with exposures to the herbicides chemicals.

Assuming that 2,3,7,8-TCDD and HxCDD are carcinogenic in humans, upper bound incremental unit cancer risks have been estimated for both ingestion and inhalation exposure. The unit risks have been estimated using a multistage extrapolation model that is linear at low doses. Available metabolism and pharmacokinetic data are insufficient to alter typically used assumptions for estimating the human equivalent dose. Since incidence data exist only for oral studies in animal test systems, the inhalation risk estimates are based upon the cancer potency derived from the oral studies along with appropriate conversion assumptions.

Using data from a feeding study with female rats, the upper limit incremental cancer risk for 2,3,7,8-TCDD is estimated to be 1.56×10^{-1} per ng/kg/day. The upper limit estimate of incremental cancer risk is 4.5×10^{-3} for a continuous lifetime exposure to 1 ng/l of 2,3,7,8-TCDD in drinking water and 3.3×10^{-5} for a continuous lifetime exposure to 1 pg/m^3 of 2,3,7,8-TCDD in ambient air.

Using data from an ingestion study with female rats and male mice, the cancer potency for HxCDD is estimated to be 6.2×10^{-3} per ng/kg/day. The upper limit estimate of incremental cancer risk is 1.8×10^{-4} for a continuous lifetime exposure to 1 ng/l of HxCDD in drinking water and 1.3×10^{-6} for a continuous lifetime exposure to 1 pg/m^3 of HxCDD in ambient air.

Conclusions

The PCDDs, 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,6,7,8- and 1,2,3,7,8,9-HxCDD, are highly toxic following acute exposure. All animal species administered high levels of these compounds developed weight loss and thymic atrophy. In some species liver damage, edema, hair loss and immunosuppression were also observed. Chronic toxicity studies were conducted only on 2,3,7,8-TCDD and a mixture of the two isomers of HxCDD. In these studies, the primary nonneoplastic lesion was fatty and necrotic change in the liver.

In the species studied, the fetus has been shown to be highly sensitive to the toxic effects of 2,3,7,8-TCDD. In rats the fetotoxicity observed included hemorrhage, edema and kidney anomalies, while in mice the predominant lesions were cleft palate and kidney anomalies. The lowest reported exposure in rats, 1 ng/kg, produced a significant (by some analyses but not others) effect on the fetus, and was similar to the lowest-observed-adverse-effect level (LOAEL) observed in chronic studies.

Evidence from oral animal cancer bioassays is "sufficient" (according to EPA and IARC criteria) to conclude that 2,3,7,8-TCDD and a mixture of the two isomers of HxCDD are animal carcinogens. The 2,3,7,8-TCDD has increased the incidence of a variety of tumors, including liver tumors in rats and mice, while the mixture of HxCDD tested increased the incidence of liver tumors in both sexes of rats and mice. In addition, squamous cell carcinomas of the tongue and hard palate/nasal turbinate and squamous cell carcinomas of the lung were observed in rats. The available epidemiologic evidence for the carcinogenicity of 2,3,7,8-TCDD alone is inadequate and there have been no epidemiologic evaluations, as yet, for HxCDD as the sole compound of concern. Considering the animal evidence together with the epidemiologic data, the overall weight-of-evidence classification for 2,3,7,8-TCDD using EPA's classification scheme is category B2 meaning that 2,3,7,8-TCDD should be regarded as a "probable" human carcinogen. The overall weight-of-evidence classification for HxCDD is also category B2 meaning that it should be regarded as a "probable" human carcinogen. In terms of low dose potency, 2,3,7,8-TCDD and the HxCDD mixture are the two most potent

carcinogens evaluated by the EPA's Carcinogen Assessment Group. Epidemiologic studies of workers exposed to chemicals contaminated with 2,3,7,8-TCDD such as 2,4,5-trichlorophenoxyacetic acid and 2,4,5-trichlorophenol have produced positive findings that are suggestive of an elevated risk of cancer in humans. These epidemiologic findings are not inconsistent with the premise that 2,3,7,8-TCDD is probably carcinogenic for humans. There are no chronic studies available regarding the carcinogenicity of 1,2,3,7,8-PeCDD.

Needs for Future Research

- The basic physical properties such as water solubilities and vapor pressures of the PeCDDs and HxCDDs need to be determined. These parameters are important in predicting the environmental fate of these compounds.
- New analytical methodologies must be established to determine the low levels of these compounds in environmental matrices without ambiguity.
- More monitoring data, particularly in air aquatic media as well as in vegetables grown near urban incinerators, should be developed by a diversity of research groups.
- Isotopically labeled internal standard compounds (^{37}Cl or ^{13}Cl) should be prepared for PeCDDs and HxCDDs.
- More research efforts should be directed to determining the environmental fate of the PeCDDs and HxCDDs. The determination of the fate of these chemicals with respect to the possibility of photochemical transformations in different environmental matrices needs special attention.
- Pharmacokinetic studies should be conducted to demonstrate more clearly the degree of absorption of the PCDDs by all routes. In particular, studies are needed on respiratory absorption and on PCDDs absorbed to environmental media.
- Although a number of studies demonstrate that 2,3,7,8-TCDD is a teratogen, the other congeners should be tested for teratogenic potential.
- There is no information on the effects of chronic exposure to 1,2,3,7,8-PeCDD, and studies should be conducted to determine both the toxic effects of this compound and its carcinogenic potential.
- Further epidemiology data on the effects in human populations to PCDDs might assist in determining which effects observed in animals are also present in humans. In these studies, careful quantitation of PCDD levels in humans and industrial hygiene samples might provide dose-response data necessary for health assessment.
- Bioavailability studies from contaminated soil, fly ash, etc., are needed.
- Mechanism-of-action studies should be conducted to determine the fundamental mode of action of the PCDDs.
- New destruction methods should be investigated in order to provide feasible methods for decontaminating environmental sites where PCDDs have been detected.
- Determine the BCF for all the most toxic PCDDs in state-of-the-art test systems.

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The complete report, entitled "Health Assessment Document for Polychlorinated Dibenzo-p-Dioxins," (Order No. PB 86-122 546/AS; Cost: $50.95, subject to change) will be available only from:

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