Scand J Work Environ Health 1989;15(6):377-382

<https://doi.org/10.5271/sjweh.1837>

Issue date: Dec 1989

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This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/2482540

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Chlorinated dioxins and dibenzofurans in the environment — a hazard to public health?

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VAINIO H, HESSO A, JÄPPINEN P. Chlorinated dioxins and dibenzofurans in the environment — a hazard to public health? *Scand J Work Environ Health* 1989;15:377-382. Polychlorinated dibenzodioxins (PCDD) and polychlorinated dibenzofurans (PCDF) are globally distributed, are persistent in the environment, and tend to accumulate in human tissues. Several 2,3,7,8-substituted PCDD and PCDF have been found at parts-per-trillion levels in human milk and adipose tissue. Food is the major source for the general population. Above-average exposures may be caused by the incineration of various wastes, certain industries (eg, metal and paper and pulp), and traffic exhaust. PCDD and PCDF have been of great public concern because one of the congeners, 2,3,7,8-tetrachlorodibenzodioxin, is an extremely potent carcinogen and teratogen in rodents. Although epidemiologic studies on cancer are too few for conclusions, animal studies and documented human exposure suggest that humans may be at increased risk. Human exposure is generally low when compared with the effective levels for rodents. However, part of the population can be more exposed and, consequently, also be potentially at higher risk.

Key terms: occurrence in the environment, polychlorinated dibenzofurans, polychlorinated dioxins, risk estimates, toxicity.

Polychlorinated dibenzodioxins (PCDD) consist of a large series of almost planar tricyclic aromatic compounds which have repeatedly attracted attention during the last 15 years, first in connection with industrial accidents and later as by-products of industrial and traffic emissions. There are 75 different PCDD, with varying degrees and location of chlorine substitution. Furthermore, there are 135 polychlorinated dibenzofurans (PCDF) with appearance, chemical properties, and effects similar to those of PCDD.

Recently, there has been a lively public discussion about PCDD, especially after they were found in various consumer products and in breast milk (1-3). The purpose of this paper is to review briefly the occurrence of PCDD and PCDF in the environment, their toxic effects, and populations at potential risk.

Occurrence of PCDD and PCDF in the environment

PCDD and PCDF are primarily released into the environment through combustion processes, exhaust gases, solid wastes, and waste water. Even though PCDD and PCDF have no industrial use or commercial

value, they have spread extensively in the environment in the same manner as polychlorinated biphenyls and some chlorinated pesticides have. During the last few years, PCDD and PCDF have been detected in human tissues in many industrialized countries. The concentrations of PCDD vary from low (about 1-10 ppt) to high (about 1000 ppt), depending on the degree of chlorination. The PCDF levels usually range between 1 and 100 ppt (4, 5).

An isomer-specific analysis of PCDD and PCDF has suggested that the food chain is the major source of human exposure to these chemicals (6).

Commercial and technical products as sources of PCDD and PCDF

Some commercial and technical products contain PCDD and/or PCDF as impurities or as by-products of the synthetic process. Such known products are, eg, 2,4,5-trichlorophenoxyacetic acid, other chlorinated phenoxy acids, pentachlorophenol, and other chlorophenols. The concentrations of impurities have decreased over the years in many industrialized countries, and in some cases the product itself has been replaced (7).

Incineration plants as sources of PCDD and PCDF

Municipal and industrial incineration plants have spread PCDD and PCDF rather extensively into the environment. The first studies on PCDD and PCDF concentrations in emissions date from the late 1970s when there was 0.1-0.5 ppm of PCDD and PCDF in fly ash. As sample-collecting techniques developed, it became possible to assess the quantity and quality

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of total incinerator emissions. Isomer-specific analyses have indicated that almost all possible PCDD and PCDF compounds (210 in all) are present in fly ash and that the isomer profiles of different incineration plants are similar (7).

High-temperature industrial processes

Some high-temperature industrial processes, as in the copper and steel industries, cause PCDD and PCDF emissions. When copper and iron scrap contaminated with polyvinyl chloride, chlorinated paraffin, or other compounds is processed for reuse, PCDD and PCDF are emitted. In one study (8), PCDD concentrations of 1–15 pg/m³ were measured in the work environment, and the total emissions were estimated to be 0.2–9 µg/t of scrap iron.

The pulp and paper industry as a source of PCDD and PCDF

The first doubts about possible PCDD emissions from the pulp and paper industry were expressed in 1974 by Sandermann (9). Many aquatic organisms, including fish, selectively accumulate PCDD and PCDF which are substituted at the 2,3,7 and 8 positions (10, 11). The isomer profile in crabs, however, differs from that in salmon (7).

Isomers other than the 2,3,7,8-substituted PCDD and PCDF were also detected in crabs, and the same isomers were found in the bottom sediment. The highest concentrations were measured in the mouths of rivers below pulp mills using chlorine bleaching. The isomer profiles in the waste water of these mills were analogous with the profiles in crabs (7).

According to Swedish and Canadian studies, PCDD and PCDF are formed in all pulp bleaching stages using chlorine. The amounts of PCDF and PCDD formed are strongly dependent on the amount of chlorine used per ton of pulp (12).

Finished products, like coffee filters, milk cartons, cosmetic tissues, and ladies' tampons, have been found to contain small concentrations (a few picograms per gram of product) of 2,3,7,8-substituted congeners (13).

When pulp is bleached with chlorine, many chlorine compounds other than PCDD and PCDF are also formed. For example, alkylated PCDF (PCDD-like aromatic chlorine compounds) have been found in both pulp and paper products. The toxicity of alkylated PCDF is so far unknown (14).

Traffic exhausts

Used motor oil may contain measurable amounts of PCDD and PCDF (15). The isomer profiles, especially those for PCDF, closely resemble those of incineration plants. Analyses of car exhaust show that motor traffic is a major PCDD and PCDF source. Various chlorine-containing additives have a crucial effect on PCDD and PCDF emissions (16). It has been esti-

mated that in Sweden the annual traffic emissions are 5–15 g of tetrachlorodibenzodioxin equivalents; this amount is one-tenth of the emissions (estimated as 50–150 g of tetrachlorodibenzodioxin equivalents) from the iron and steel industry (17).

Long-distance migration

According to recent studies, ambient air in urban and industrialized areas contains measurable amounts of PCDD and PCDF (0.01–10 pg/m³) (18). The concentrations are 5 to 10 times lower in rural areas. The isomer profiles closely resemble those of incineration plants and traffic (7). According to measurements made on the west coast of Sweden, it is clear that PCDD and PCDF migrate from the industrial areas in central Europe. Long-distance migration is probably one reason for the PCDD concentrations in seal fat in the Spitzbergen (19).

Enrichment of PCDD and PCDF in the food chain

The bottom sediment in the Stockholm archipelago and the Gulf of Bothnia contains PCDD and PCDF in concentrations above the parts-per-trillion level, and the isomer profiles resemble those of incineration plants and traffic emissions. In fish and seal fat specimens, 2,3,7,8-substituted PCDD and PCDF have been measured in background concentrations of 0.1–100 ppt (5, 7). Elevated PCDD and PCDF concentrations are inevitably found in the sediment and water animals found downstream from pulp mills using chlorine bleaching. Rather low PCDD concentrations have been found in mammalian and domestic animal fat. However, chlorinated phenol contamination in feed has caused elevated concentrations in chicken and pork meat (4), and other isomers in addition to the 2,3,7,8-substituted ones have been found.

The background concentrations of PCDD and PCDF in human adipose tissue have been measured in some industrialized countries. They have been assessed among populations in China, Japan, and Canada (20). The concentrations in China, which can be considered a partly industrialized country, were for hexa-, hepta-, and octachlorodibenzodioxins only, and they were about one-fifth to one-tenth of the concentrations measured in Canada and Japan. As for PCDF, industrialization does not cause such marked differences in concentration levels. The concentrations of pentachlorodibenzofurans and hexachlorodibenzofurans are two to three times higher in Japan than in China, but there are only small differences between Canada and China.

According to an on-going study in the Federal Republic of Germany, human fat concentrations of most PCDD and PCDF isomers are 2 to 100 ppt. Higher concentrations have been found only for hexachlorodibenzodioxins (40–200 ppt) and octachlorodibenzodioxins (200–1100 ppt). However, concentra-

tions in subjects with workplace exposure to PCDD and PCDF can be 10 to 100 times higher (21). Recently, high levels of 2,3,7,8-tetrachlorodibenzodioxin (2,3,7,8-TCDD) were measured in the adipose tissue of production workers who had made products contaminated with 2,3,7,8-TCDD (22).

PCDD and PCDF in human milk

Data on PCDD and PCDF in human milk have been summarized recently by Astrup Jensen (23). In industrialized countries, human milk fat contains a concentration of 2,3,7,8-TCDD of about 2 ppt. Of the total PCDD content, of 150–450 ppt, more than 50 % consists of the less toxic octachlorodibenzo-p-dioxin.

Among the PCDF, the most abundant component is not the octachloro isomer, but penta- (PeCDF) or hexachlorodibenzofurans (HxCDF). All of the PeCDF and HxCDF detected in human milk fat have the 2,3,7,8-chlorine substitution. The average background concentration of HxCDF is 10–100 ppt, and that of PeCDF is 20–50 ppt (23). The total PCDD levels in human milk fat are usually significantly higher than the content of PCDF.

The isomer patterns of PCDD and PCDF in the fat of mother's milk and human blood correlate well with the concentrations in adipose tissue. Cow's milk contains the same PCDD and PCDF compounds, but the concentrations are one to two orders of magnitude lower.

Toxicity of PCDD and PCDF

The toxicity of PCDD and PCDF is dependent on the degree of halogenation and on the location of the halogen atoms (24). Typically, the toxic isomers of PCDD and PCDF produce the same spectrum of toxic and biochemical effects, including the induction of specific cytochrome P-450 isoenzymes and other enzymes, thymic atrophy, teratogenesis, and carcinogenesis. The activity of the aryl hydrocarbon hydroxylase enzyme has been used as an indicator of their biological effect (25). Although the mechanism of toxicity of halogenated aromatics is not well understood, it appears to be mediated by reversible binding to a protein receptor and is manifested through alterations in gene expression rather than mutation or a direct cytotoxic effect (26, 27).

Some of the PCDD and PCDF, especially 2,3,7,8-TCDD and 2,3,7,8-tetrachlorodibenzofuran, have a high acute toxicity in rodents, with a remarkable species difference. The median lethal dose of 2,3,7,8-TCDD is 0.6 µg/kg of body weight for guinea pigs, 280 µg/kg for mice, and 5000 µg/kg for hamsters. (For reviews, see references 26 and 28.)

2,3,7,8-TCDD is excreted slowly from the body, with a half-time of three to four weeks in rodents and even longer in humans (29). A half-time of 4.95 years

was reported for humans after the ingestion of a single dose of ³H-labeled TCDD (30). No systematic toxicokinetic data are available on the elimination of other PCDD and PCDF from humans.

2,3,7,8-TCDD is not mutagenic, but is strongly teratogenic, and also carcinogenic in experimental animals (26, 29). It is the most potent animal carcinogen that has been tested. In rodents, it is about a million times more potent than vinyl chloride (31). In susceptible rodents, rats and mice, 2,3,7,8-TCDD causes neoplasms, especially hepatic ones, even with daily doses as low as a nanogram per kilogram of body weight. Recently, it has been shown that 2,3,7,8-TCDD is a complete carcinogen also in the hamster, the species most resistant to the acute toxic effect of this compound (32).

In addition to its carcinogenic potency, 2,3,7,8-TCDD is also the most potent animal teratogen known, and it causes other reproductive and immune system effects in animals at very low doses as well (24, 33).

While sufficient evidence does not exist to link 2,3,7,8-TCDD to human reproductive or developmental toxicity (see, eg, references 28 and 34), it has been shown to be a reproductive or developmental toxicant in a wide variety of animal species (35, 36). Animal studies have also shown that extended periods of exposure are not necessary for developmental toxicity to result.

2,3,7,8-TCDD also causes immunologic abnormalities in humans. According to a recent report (37), 18 workers exposed accidentally to 2,3,7,8-TCDD 17 years earlier had more natural killer cells, antinuclear antibodies, and immune complexes in their peripheral blood than referents had. Eight of the workers suffered from chloracne.

Cancer epidemiology — inconclusive findings

In the well-known chemical accident in 1976 near Seveso, Italy, an explosion caused the contamination of a populated area with 2,3,7,8-TCDD (38). The 10-year mortality experience of the population in the contaminated areas has recently been published (39). The population revealed an increased mortality from cardiovascular diseases. However, the authors attributed this increased mortality more to "incident-related stressors" than to 2,3,7,8-TCDD exposure. The relative risks for malignancies as a whole were not raised. Mortality from several specific cancers was elevated. This finding was, however, often based on small numbers. Nevertheless, some of the increases warrant further attention, such as those of liver and hepatobiliary tract cancers in women and of lymphatic and hematopoietic neoplasms (particularly leukemia in men) and the suggestive increases in soft-tissue tumors and melanoma. The 10-year follow-up of the population near Seveso thus provides some hypotheses as to the effects of 2,3,7,8-TCDD on humans.

Many incidents resembling the Seveso accident occurred earlier but did not reach the ears of the general public until much later (40). In 1949, 250 workers were exposed to 2,3,7,8-TCDD in an explosion at a Monsanto chemical plant, and 121 of them later developed chloracne. By 1978, 32 of these workers had died [versus 46.4 expected deaths, standardized mortality ratio (SMR) 69; 95 % confidence interval (95 % CI) 47–97]. There were nine deaths from cancer in this group versus 9.0 expected, five deaths occurring from lung cancer versus 2.9 expected (SMR 172, 95 % CI 56–402), three from lymphomas and neoplasms of the hematopoietic tissues versus 0.9 expected (SMR 333, 95 % CI 69–974), and one from soft-tissue sarcoma versus 0.2 expected (41). It is obvious that the 2,3,7,8-TCDD exposure in the Monsanto accident was rather high, because chloracne developed in approximately 50 % of the exposed workers. However, as the level of exposure is uncertain and the number of cases small, this study is far from conclusive.

In 1953, there was an explosion in Ludwigshafen at the BASF AG plant, and 74 workers were exposed to 2,3,7,8-TCDD. Chloracne developed in 66 of them. By 1979, 21 of the exposed had died, 7 of them from cancer versus 4.3 expected (SMR 163, 95 % CI 66–335) (42). There were three observed deaths from lung cancer versus 1.1 expected (SMR 273, 95 % confidence interval 56–797), three deaths from stomach cancer versus 0.5 expected (SMR 600, 95 % CI 124–1753), and one from colon cancer.

In 1977, a working group of the International Agency for Research on Cancer (43) concluded that no evaluation of carcinogenicity of PCDD could be made on the basis of the available data. In 1987 (44), 2,3,7,8-TCDD was evaluated as showing sufficient evidence of carcinogenicity in animals but inadequate evidence for carcinogenicity in humans, and in the overall evaluation 2,3,7,8-TCDD was classified as possibly carcinogenic to humans.

International and national risk estimates

The risks caused by PCDD and PCDF have been assessed by several international and national study groups. (For references, see, eg, reference 28.) A “tolerable weekly intake” has been set for 2,3,7,8-TCDD by the International Programme on Chemical Safety (IPCS) (2) on the basis of rodent cancer studies. The proposal from the IPCS was based on the cancer responses at doses 1, 10 and 100 $\text{ng} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ in an animal lifetime feeding study (45). An uncertainty factor of 200 was applied to the “non-observed effect” level of 1 $\text{ng} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, and thus a “tolerable weekly intake” for man turned out to be 0–35 $\text{pg} \cdot \text{kg}^{-1}$ of body weight $\cdot \text{week}^{-1}$. This value coincides with the value of 5 $\text{pg} \cdot \text{kg}^{-1}$ of body weight $\cdot \text{d}^{-1}$ given by a Nordic Council working group (46). The long biological half-time of 2,3,7,8-TCDD was the reason for

the IPCS group making their recommendation in the form of weekly rather than daily intake. The toxicity of different PCDD and PCDF isomers is typically expressed in terms of toxic equivalents, which relate the toxicity of all PCDD/PCDF compounds to the known toxicity of 2,3,7,8-TCDD according to one of several weighing schemes (46). Hence a mixture of PCDD and PCDF expressed in toxic equivalents is assumed to have the same toxic effect as 2,3,7,8-TCDD.

The Environmental Protection Agency in the United States (47) has used the same long-term animal cancer data but applied linearized multistage model extrapolation from the lowest dose to show a significant elevated response (10 $\text{ng} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ caused a statistically significant increase in liver tumors) to humans at still lower levels. The “virtually safe dose” derived by this extrapolation model was 0.006 $\text{pg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, a daily dose corresponding to an additional 10^{-6} risk of cancer in the course of a lifetime (47).

The differences in the magnitude of these two estimates (IPCS and Nordic Group on one hand and the Environmental Protection Agency on the other) are due to the adoption of different risk estimation philosophies. The Environmental Protection Agency has used the no-threshold model, and the IPCS and Nordic Group the threshold model. The IPCS and Nordic Group treated 2,3,7,8-TCDD as a promoter and used an uncertainty factor approach, whereas the Environmental Protection Agency treated 2,3,7,8-TCDD as a complete carcinogen and applied a no-threshold approach. At the moment, because of inadequate knowledge on the mechanisms of cancer induced by 2,3,7,8-TCDD, it is not possible to tell which of these approaches is scientifically more correct.

Who are the people potentially at risk?

PCDD and PCDF are widespread in the environment at very low levels, but they have a strong tendency to accumulate in aquatic organisms. Therefore, people eating fish contaminated with PCDD and PCDF are potentially at risk, although the levels detected in fish to date have rarely been high enough for recommendations on the limitation of fish intake to be considered.

Some emergency situations may entail high exposures to PCDD and/or PCDF. In situations where polychlorinated biphenyls have been heated to high temperatures (eg, fires or explosions in capacitors) high concentrations are emitted into the air (3). Waste incinerators can also emit high levels of PCDD and PCDF, depending on the quality and mode of operation (48).

Several 2,3,7,8-chlorinated PCDD and PCDF are present in human milk at concentrations much higher than those in cow milk. The intake of human milk varies greatly between individual infants. Because of

the relatively short period of intake and the universally accepted benefits of breastfeeding, an expert group of the World Health Organization did not suggest any limitations on breastfeeding (29).

Acknowledgments

We want to thank Dr K L'Abbe for her critical comments and Dr J Cheney for his editorial help. Ms L Kuusela is thanked for typing the manuscript.

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Received for publication: 28 September 1989