5. Summary of Data Reported and Evaluation

5.1 Exposure data

Polychlorinated dibenzofurans (PCDFs) are formed as inadvertent by-products in the production and use of polychlorinated biphenyls (PCBs) and, in combination with polychlorinated dibenzo-*para*-dioxins (PCDDs), in the production of chlorophenols and have been detected as contaminants in these products. PCDFs and PCDDs also may be produced in thermal processes such as incineration and metal processing and in the bleaching of paper pulp with free chlorine. PCDFs are also found in residual waste from the production of vinyl chloride and the chloralkali process for chlorine production. The relative amounts of PCDF and PCDD congeners produced depend on the production or incineration process and vary widely.

Like PCDDs, PCDFs are ubiquitous in soil, sediments and air. Excluding occupational or accidental exposures, most background human exposure to PCDFs occurs as a result of eating meat, milk, eggs, fish and related products, as PCDFs are persistent in the environment and accumulate in animal fat. High exposures have occurred in relation to incidents in Japan (*yusho*) and Taiwan (*yucheng*) involving contamination of rice oil and in accidents involving electrical equipment containing PCBs. Occupational exposures also may occur in metal production and recycling, and in the production and use of chlorophenols and PCBs.

Based on limited data, the sum of the mean background levels of the penta- and hexachlorinated PCDF congeners commonly found in human tissues is generally in the range of 10–100 ng/kg fat, and the PCDF contribution to tissue international toxic equivalent (I-TEQ) values is typically of the same order of magnitude as that of the PCDDs. Since the mid-1980s, mean tissue levels of total PCDFs and PCDDs (measured as I-TEQ) in the general population have decreased by two- to three-fold. Five-fold higher tissue levels have been found in subpopulations consuming large amounts of PCDF-contaminated fish. Accidental exposures to PCDFs have led to tissue levels one or more orders of magnitude higher than background levels.

5.2 Human carcinogenicity data

In the *yusho* and *yucheng* incidents, each involving about 2000 cases, people were exposed to sufficient PCBs and PCDFs to produce symptoms. Fatal liver disease is 2–3 times more frequent than national rates in both cohorts. In Japan, at 22 years of follow-up, there is a three-fold excess of liver cancer mortality in men, which was already detectable and even higher at 15 years of follow-up. In Taiwan, at 12 years of follow-up, there is no excess of liver cancer mortality. This difference does not appear to be the result of study design, differences in diagnostic habits, exposure or age at exposure, but may be related to differences in the time of follow-up.

5.3 Animal carcinogenicity data

There are no long-term carcinogenicity studies on PCDFs.

2,3,7,8-Tetrachlorodibenzofuran (2,3,7,8-TCDF) treatment following a single dose of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) resulted in an increased incidence of mouse skin papillomas.

2,3,4,7,8-Pentachlorodibenzofuran (2,3,4,7,8-PeCDF) treatment following a single dose of MNNG resulted in an increased incidence of mouse skin papillomas. 2,3,4,7,8-PeCDF treatment following four weeks' treatment with *N*-nitrosodiethylamine (NDEA) resulted in an increased incidence of hepatocellular carcinomas and hyperplastic nodules in male rats. Treatment with the same compound after a single dose of NDEA increased the incidence of focal hepatic lesions in female rats.

1,2,3,4,7,8-Hexachlorodibenzofuran (1,2,3,4,7,8-HxCDF) treatment following a single dose of MNNG resulted in an increased incidence of mouse skin papillomas. 1,2,3,4,7,8-HxCDF treatment following four weeks' treatment with NDEA resulted in an increased incidence of hepatocellular carcinomas and hyperplastic nodules in male rats. Treatment with the same compound after a single dose of NDEA increased the incidence of focal hepatic lesions in female rats.

5.4 Other relevant data

Kinetics

The half-lives of PCDFs in humans are much longer than those in experimental animals.

In most vertebrate species, the 2,3,7,8-substituted PCDFs are the congeners which are preferentially retained in tissues. Oxidation by cytochrome P450 primarily occurs at the 4 and 6 positions in the molecule and the presence of chlorine atoms at these positions reduces metabolism more than substitution at the 1 and 9 positions. Consequently, chlorine substitution on these positions strongly hinders elimination. In rodents, some PCDFs, e.g. 2,3,4,7,8-PeCDF, show an extremely high affinity for liver tissue, which has been attributed to binding to the CYP1A2 protein. As Ah-receptor-mediated effects are primarily caused by the parent compound, biotransformation should be considered as a detoxification process.

Toxic effects

In animal experiments, 2,3,7,8-substituted PCDFs exhibit the same pattern of toxicity as those documented for PCDDs.

Studies of adults in Japan (*yusho*) and Taiwan (*yucheng*) who ingested rice oil contaminated with PCBs, PCDFs and other by-products of PCB thermal degradation have observed effects in multiple systems. In both situations the poisonings were characterized by chloracne, elevated triglyceride levels, abnormal neurological symptoms, ophthalmic changes and alterations in immune parameters. In *yucheng*, porphyrin levels were also elevated.

Biochemical responses and mechanism of action

2,3,7,8-Substituted PCDFs bind to the Ah receptor and, as documented for PCDDs, induce *CYP1A1* and *CYP1A2* gene expression. Ah-receptor-binding affinities of 2,3,7,8-TCDF, 1,2,3,7,8- and 2,3,4,7,8-PeCDF are of the same order of magnitude as that observed for 2,3,7,8-TCDD. With increasing chlorination, receptor binding affinity decreases. The enzyme induction follows the same structure–activity relationship.

Reproductive and developmental effects

In the *yucheng* population, eight of 39 children exposed *in utero* died before birth. Surviving children showed signs of intra-uterine growth retardation and congenital anomalies at birth, a deficit of cognitive development up to seven years of age, and defects in musculoskeletal development and pigmentation.

Several PCDFs have been shown to be teratogenic in mice, causing cleft palate and hydronephrosis. 2,3,4,7,8-PeCDF leads to persistent reproductive effects (reduced sperm count, structural alterations of the female genital tract) following prenatal exposure. It also promotes the growth of surgically induced endometriosis in mice. All of these effects are also observed with 2,3,7,8-TCDD.

Genetic and related effects

2,3,4,7,8-PeCDF increased the frequencies of sister chromatid exchange and micronucleus formation in human lymphocytes *in vitro*.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of polychlorinated dibenzofurans.

There is *inadequate evidence* in experimental animals for the carcinogenicity of 2,3,7,8-tetrachlorodibenzofuran.

There is *limited evidence* in experimental animals for the carcinogenicity of 2,3,4,7,8-pentachlorodibenzofuran.

---

[1] For definition of the italicized terms, see Preamble, pp. 26–27.

There is *limited evidence* in experimental animals for the carcinogenicity of 1,2,3,4,7,8-hexachlorodibenzofuran.

Overall evaluation

Polychlorinated dibenzofurans *are not classifiable as to their carcinogenicity to humans (Group 3).*