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INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

ENVIRONMENTAL HEALTH CRITERIA 88

POLYCHLORINATED DIBENSO- *PARA*-DIOXINS AND DIBENZOFURANS

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The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

Every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors that may have occurred to the Manager of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

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A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone No. 7988400 - 7985850).

ENVIRONMENTAL HEALTH CRITERIA FOR POLYCHLORINATED DIBENZO-PARA-DIOXINS AND DIBENZOFURANS

A WHO Task Group on Environmental Health Criteria for Polychlorinated Dibenzo-para-dioxins and Dibenzofurans met at the Monitoring and Assessment Research Centre, London, United Kingdom, from 9 to 13 February, 1987. Dr M. Berlin opened the meeting and welcomed the members on behalf of the host Institute and on behalf of the United Kingdom Department of Health and Social Security, who sponsored the meeting. Dr G.C. Becking addressed the meeting on behalf of the three cooperating organizations of the IPCS (UNEP, ILO, and WHO). The Task Group reviewed and revised the draft criteria document and made an evaluation of the risks for human health and for the environment from exposure to polychlorinated dibenzo-p-dioxins and dibenzofurans.

The drafts of this document were prepared by Dr U.G. Ahlborg, Dr H. Hakensson, and Dr B. Holmstedt, all of the National Institute of Environmental Medicine, Stockholm, Sweden, and by Professor C. Rappe of the University of Umea, Umea, Sweden.

The efforts of all who helped in the preparation and finalization of the document are gratefully acknowledged.

* * *

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ABBREVIATIONS

AHH	aryl hydrocarbon hydroxylase
ALA	aminolevulinic acid
BGG	bovine gammaglobulin
BHA	butylated hydroxyanisole
BP	benzo(a)-pyrene
CMI	cell-mediated immunity
DEN	diethylnitrosamine
diCDD	dichlorinated dibenzo-p-dioxin
diCDF	dichlorinated dibenzofuran
DMBA	dimethylbenzathraline
ECOD	7-ethoxycoumarin-o-deethylase
EGF	epidermal growth factor
EH	epoxide hydratase
EI	electron impact
EROD	7-ethoxyresurofin-o-deethylase
ETG	epidermal transglutaminase
fg	femtogram (10^{-15}g)
GC	gas chromatography
heptaCDD	heptachlorinated dibenzo-p-dioxin
heptaCDF	heptachlorinated dibenzofuran
hexaCDD	hexachlorinated dibenzo-p-dioxin
hexaCDF	hexachlorinated dibenzofuran
HMI	humoral-mediated immunity
HPLC	high pressure liquid chromatography
IARC	International Agency for Research on Cancer
ip	intraperitoneal
IR	infrared
LOEL	lowest-observed-effect level
MCPA	4-chloro-o-tolyloxyacetic acid
MFO	mixed-function oxidase
MS	mass spectrometry
MSW	municipal solid waste
ng	nanogram (10^{-9}g)
NMR	nuclear magnetic resonance
NOEL	no-observed-effect level
octaCDD	octachlorinated dibenzo-p-dioxin
octaCDF	octachlorinated dibenzofuran
PAH	polyaromatic hydrocarbons
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzo-p-dioxin

PCDF	polychlorinated dibenzofuran
PCDPE	polychlorinated diphenylether
PCPY	polychlorinated pyrene
PCQ	polychlorinated quaterphenyl
pentaCDD	pentachlorinated dibenzo-p-dioxin
pentaCDF	pentachlorinated dibenzofuran
pg	picogram (10^{-12}g)
SC	subcutaneous
SCE	sister chromatid exchange
SD	standard deviation
SEM	standard error of the mean
SIM	selected ion monitoring
TCDD	2,3,7,8-tetrachlorinated dibenzo-p-dioxin
TCDF	2,3,7,8-tetrachlorinated dibenzofuran
TCP	trichlorophenol
tetraCDD	tetrachlorinated dibenzofuran
tetraCDF	tetrachlorinated dibenzofuran
TPA	12-o-tetradecanoylphorbol-13-acetate
triCDD	trichlorinated dibenzo-p-dioxin
triCDF	trichlorinated dibenzofuran
t3	triiodothyronine
t4	thyroxine
UDPGT	UDP-glucuronosyltransferase
UV	ultraviolet
2,4-D	2,4-dichlorophenoxyacetic acid
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
3-MC	3-methylcholanthrene

1. SUMMARY AND RECOMMENDATIONS

1.1 Summary

1.1.1 Sources

Polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are two series of tricyclic aromatic compounds with similar chemical and physical properties; they are ubiquitous in the environment. They do not occur naturally, nor are they intentionally produced. There are 75 positional isomers of PCDDs and 135 isomers of PCDFs.

The most important sources of contamination with PCDDs and PCDFs include:

- contaminated commercial chemical products, such as chlorinated phenols and their derivatives, and PCBs;
- incineration of municipal, hazardous, and hospital wastes, and of sewage sludges;
- automobile operation;
- fossil fuel combustion;
- overheating and emissions from fires involving PCBs;
- disposal of industrial wastes resulting from processes such as the production of chlorophenols and

their derivatives, chlorophenol wood treatment, use of PCB fluids in electrical equipment, and wastes from pulp and paper processing.

1.1.2 Ambient levels and routes of exposure

The limited data available indicate that ambient levels of these compounds are very low in air, soil, and sediment, i.e. fg/m^3 in air, ng/kg in soil and sediment. Levels of PCDDs and PCDFs up to 50 ng/kg have been found in aquatic organisms in the general environment.

Data on contamination of drinking water and commercial food are very limited.

Exposure to these compounds in the general population probably occurs mainly through the food-chain.

Some workers engaged in the production, use, and destruction of materials containing PCDDs and PCDFs and their precursors may receive high exposure. For these persons, inhalation and dermal contact are the primary exposure routes of concern.

1.1.3 Toxicokinetics, biotransformation, and biological monitoring

The bioavailability of PCDDs and PCDFs depends on the matrix they are in and the route of exposure. Data on bioavailability through inhalation are not available for any species.

The quantity absorbed by humans after any route of exposure is not known.

Studies on rodents given single or repeated oral doses of 2,3,7,8-TCDD have shown that about half of the administered dose is absorbed from the gastrointestinal tract. The reported half-lives for elimination were between 12 and 94 days for rodents. The half-life of 2,3,7,8-TCDD in adipose tissue of the rhesus monkey is about 1 year.

Animal data on the toxicokinetics of PCDDs other than 2,3,7,8-TCDD are limited. The half-life for 2,3,7,8-TCDD has been reported to be in the range of 2 and 8 days for rats, mice, and monkeys and more than 20 days for guinea-pigs. Studies on rats have shown that 2,3,4,7,8-pentaCDF is more highly retained than is 2,3,7,8-TCDD.

Data on the retention of PCDDs and PCDFs in tissues of various species, exposed to synthetic mixtures or to environmental samples containing PCDDs and PCDFs, show a high variability in retention time

between congeners with or without chlorine substitution in the 2,3,7, and 8 positions.

Limited human data indicate half-lives for some 2,3,7,8-substituted PCDDs and PCDFs in the range of 2-6 years.

The PCDDs and PCDFs are predominately stored in fat, but they are also excreted in milk and pass through the placenta. They also appear in the blood and vital organs at lower concentrations.

The tissue distribution in humans is not clear at present, although it has been suggested that the ratio between fatty tissue and liver is higher in humans than in rodents.

In human fat, background levels of TCDD up to 20 ng/kg have been found in the general population, with no known specific exposure, but higher levels have been reported in some cases without evidence of disease. None of these populations were randomly sampled. The more highly chlorinated PCDDs and PCDFs, particularly octaCDD, are also present in these samples. Average tissue levels of TCCD tend to increase with age.

1.1.4 Health effects

1.1.4.1 Animals

The toxic and biological effects resulting from exposure to 2,3,7,8-TCDD are dependent on a number of factors, which include the species, strain, age, and sex of the animals used. The toxic responses observed in several animal species include body weight loss, hepatotoxicity, porphyria, dermal toxicity, gastric lesions, thymus atrophy and immunotoxicity, teratogenicity, reproductive effects, and carcinogenicity. TCDD induces a wide spectrum of biological effects including enzyme induction and vitamin A depletion. Not all of these effects are observed in any single animal species. The most characteristic toxic effects observed in all laboratory animals are body weight loss, thymus atrophy, and immunotoxicity. Chloracne and related dermal lesions are the most frequently noted signs of 2,3,7,8-TCDD toxicosis in humans; dermal lesions are also observed in rhesus monkeys, hairless mice, and rabbits. In contrast, most rodents do not develop chloracne and related dermal toxic lesions after exposure to 2,3,7,8-TCDD. Many of the toxic lesions are noted primarily in epithelial tissues.

Reproductive effects have been reported in rhesus monkeys and rats. The lowest-observed-effect levels have been reported to be approximately 1-2 ng/kg body weight per day. In two cancer studies in rats, hepatocellular carcinomas were produced at approximate dose levels of 0.1 µg/kg body weight per day and 0.01 µg/kg body weight per day. Doses of 0.001 µg/kg body weight resulted in foci or areas of hepatocellular alteration. The incidence of certain hormone-dependent tumours was lower than in the control animals.

TCDD does not appear to have mutagenic properties, and is therefore not likely to be genotoxic. Thus, it is assumed to be carcinogenic through an indirect mechanism.

Several other PCDDs and PCDFs cause signs and symptoms similar to those of 2,3,7,8-TCDD, but there is a wide variation with regard to potency. There are 12 isomers that display higher toxicity, i.e., the tetra-, penta-, hexa-, and heptaCDDs and CDFs with four chlorine atoms in the symmetrical lateral positions 2,3,7, and 8. A mixture of two hexachlorodibenzo-p-dioxins (1,2,3,7,8,9- and 1,2,3,6,7,8-hexaCDD) has been demonstrated to possess carcinogenic properties in long-term animal studies, but at higher doses than those used in the study of TCDD. Dibenzo-p-dioxin and 2,7-diCDD failed to demonstrate carcinogenic properties. The relative toxic and biological potencies of PCDDs and PCDFs have been estimated using short-term studies in rats and mammalian cell cultures.

There are marked species differences in the susceptibility of animals to the biological and toxic effects elicited by 2,3,7,8-substituted PCDDs and PCDFs. For example, the oral LD50 values range from 0.6 µg/kg body weight in guinea-pigs, to 5051 µg/kg body weight in Golden Syrian hamsters for 2,3,7,8-TCDD. The tremendous variation in species and strain sensitivity to 2,3,7,8-TCDD and related compounds cannot be explained by the observed toxicokinetic differences. The toxicity and toxicokinetics of TCDD in monkeys most closely resemble the effects observed in humans. There is evidence in inbred mice that the cellular levels of the Ah receptor correlate, in part, with susceptibility to the biological and toxic effects of these compounds. The receptor has also been identified in other species including man. However, interspecies comparison of cellular Ah receptor levels do not explain fully the differences in sensitivity.

1.1.4.2 Humans

For occupational and accidental exposures to PCDDs and PCDFs, in spite of many clinical and follow-up studies, no clear-cut persistent systemic effects have been delineated except for chloracne. Other effects have been noted, but, apart from chloracne and perhaps minor functional disorders, none has been persistent.

In some epidemiological studies of people exposed to a mixture of dioxins, furans, and other chemicals, an increased incidence of cancer at different sites has been claimed, but a number of factors limits confidence in the findings.

In the Seveso accident, the only clear-cut adverse health effect recorded has been chloracne. Chloracne (193 cases) occurred in 1976 and 1977, and 20 of those individuals still had active chloracne in 1984. Many studies have been performed to find possible links between exposure to Agent Orange and health effects in civilians or military personnel in Viet Nam. However, the information available to date does not allow definite conclusions to be drawn with regard to effects on human reproduction or any other significant health effects.

In the Missouri incident, children who showed acute illness when the contamination occurred in 1971 are now reportedly in good health. Furthermore, epidemiological studies in Missouri on populations exposed to lower concentrations of dioxins over longer periods of time have so far not revealed any significant health effects. Although no clinical symptoms were observed, there were indications of an effect on the cell-mediated immune system.

The only documented intoxications with PCDFs in humans are the two instances of contamination of rice oil with PCDFs, PCBs, and PCQs, i.e., Yusho in Japan, 1968, and Yu-cheng in Taiwan, 1979. In total, several thousand people were acutely intoxicated. From the data it appears most likely that the causative agent was the PCDFs. The general symptomatology was similar to that seen in intoxications with TCDD, with the differences reflecting the intensity of exposure and the ages and sex of those exposed.

The average daily intake of 2,3,7,8-substituted PCDFs by Yusho

patients was estimated to be 0.1-0.2 µg/kg body weight for a period of several months, while the lowest dose causing disease was estimated to be 0.05-0.1 µg/kg body weight per day over a period of 30 days.

1.1.5 Conclusion

PCDDs and PCDFs occur throughout the environment and we all probably carry a body burden of them. They have sometimes produced complex toxic effects following occupational and accidental exposure.

Based on the Yusho disease and experiments in sensitive species of monkeys, and making assumptions about the relative potencies of PCDDs and PCDFs, man and certain monkeys may have comparable sensitivity to these compounds. However, the uncertainties related to the real dose received by humans and the difficulties of assessing toxic effects other than chloracne in humans prevents a firm conclusion as to the relative resistance of humans to the toxic effects of these compounds. Exposure should be reduced to levels as low as reasonably practicable.

1.2 Recommendations

1. Analytical interlaboratory validation and "round-robin" studies using standardized quality assurance and quality control procedures are needed to improve analytical methodology.

Sampling strategy and analytical procedures and data interpretation should be optimized and standardized before undertaking surveys.

2. Further information is required about the origins and environmental distributon and fate of PCDDs and PCDFs.

Further monitoring data, including time trends and determinations of isomer patterns, are required for environmental levels of PCDDs and PCDFs, especially for food, ambient air, and sediments.

3. Data should be obtained about the effects of PCDDs and PCDFs on environmental biota.

4. More information is required on the bioavailability of PCDDs and PCDFs from different matrices in the environment and from the diet. Exposure from these sources should be correlated with agricultural and industrial practices.

5. Simpler and less expensive chemical and biological methods suitable for screening for the presence of PCDDs and PCDFs should be developed and validated.

6. Studies to determine the mechanisms of toxicity of PCDDs and PCDFs are needed to support an evaluation of the differences in effects between species and to support an extrapolation to man.

7. Further investigation of immunotoxicity is important, including cytotoxic T-lymphocyte function. Studies of the effects of perinatal exposure and of the duration of actions on the immune system are important.

8. Long-term toxicity studies should be carried out, including multigeneration reproductive studies in different species with three of the most widespread PCDDs and PCDFs, namely 2,3,4,7,8-pentaCDF, 1,2,3,7,8-pentaCDD, and octaCDD.

9. Because humans are exposed to complex mixtures of PCDDs and PCDFs, test systems, including human cell culture systems, should be developed further and validated for evaluating the toxic potency of these compounds and other mixtures. These systems can be used to study mechanisms of action, structure activity relationships, and interactive effects.

10. Investigations to examine the body burden and to correlate it with clinical effects and laboratory findings are indicated. Follow-up studies of previously exposed groups are important.