ACTIVITIES OF THE WORLD HEALTH ORGANIZATION ON POLYHALOGENATED DIBENZO-p-DIOXINS, DIBENZOFURANS AND BIPHENYLS

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Introduction

The sound management of chemicals is an essential component of environmental health in the framework of sustainable development. Assessment and management of risks from exposure to chemicals, therefore, are among the highest priorities in pursuing the principles of sustainable development, and a pre-requisite to sustaining health. In this context, WHO views its work in chemical safety, conducted in a co-ordinated manner with other international organizations, as a priority. Persistent organic compounds, particularly dioxins and PCBs, pose a particular challenge in this respect. For this reason, a comprehensive programme addressing various aspects related to the assessment and management of these compounds has been introduced and is being jointly implemented by the WHO European Centre for Environment and Health, and the International Programme on Chemical Safety (IPCS). The areas of work cover evaluation of risks from exposure to these chemicals including the derivation of intake guidelines, the development and continuous review of toxic equivalency factors (TEFs), and the comparative assessment of exposure to dioxins in various countries (including inter-laboratory quality assessment studies).

Assessment of Risks from Exposure to Dioxins and PCBs

Environmental Health Criteria (EHC) monographs were prepared on polychlorinated biphenyls and terphenyls (1,2), polychlorinated dibenzo-p-dioxins and dibenzofurans (3), polybrominated biphenyls (4) and polybrominated dibenzo-p-dioxins and dibenzofurans (5). They provide a comprehensive summary of all relevant data available at the time of the review. Also, during the updating process of the WHO Air Quality Guidelines, a working group reviewed available information with respect to setting a guideline for exposure through air. Given the limited contribution of the inhallation route to the overall exposure, no numerical guideline was developed, but it was recommended that emissions should be reduced to the lowest possible level. In 1990, WHO derived a tolerable daily intake for TCDD of 10 pg/kg body weight. In 1998, a consultation was organized to re-evaluate the TDI for dioxins. The participants discussed the health risks for infants, cancer and non-cancer endpoints in humans and animals, mechanistic aspects, kinetic behaviour, modeling, exposure, and the applicability of the toxic equivalency (TEQ) concept. For the health risk assessment of dioxin-like compounds, the WHO Consultation focused on the most sensitive effects that are considered adverse (hormonal, reproductive and developmental effects) seen at low doses in animal studies (rats and monkeys). Human daily

intakes corresponding with body burdens similar to those associated with adverse effects in animals could be estimated to be in the range of 14-37 pg/kg bw/day. To arrive at a TDI expressed as TEQ, a composite uncertainty factor of 10 was recommended. By applying this uncertainty factor a TDI range of 1-4 pg TEQs/kg body weight was established (6).

Toxic Equivalency Factors (TEFs)

The complex nature of PCDD, PCDF and PCB mixtures complicates the risk evaluation for humans, fish and wildlife. For this purpose the concept of toxic equivalency factors (TEFs) has been developed and introduced to facilitate risk assessment and regulatory control of exposure to these mixtures. To apply this TEF concept, a fundamental understanding of the mechanism of action is a prerequisite. At present sufficient evidence is available that there is a common mechanism for these compounds, involving binding to the Ah-receptor as an initial step. When applying the TEF-concept, the toxicity of these compounds relative to that of 2,3,7,8-TCDD is determined on the basis of available *in vivo* and *in vitro* data. However, it should also be understood that the TEF concept is based on a number of assumptions and has limitations. In this respect the most basic assumption is that the combined effects of the different congeners are dose or concentration-additive and results of many studies support this assumption.

WHO started an effort to compile and maintain a database on data of relevance to the deivation of TEFs. In an initial consultation, human health TEFs were derived for coplanar PCBs (7). In 1997, an expert consultation was convened with the aim of deriving consensus toxic equivalency factors (TEFs) for PCDDs, PCDFs and dioxin-like PCBs for both human, fish and wildlife risk assessment. Based on existing literature data TEFs were (re)evaluated, and either revised (mammals) or established (fish and birds). A few mammalian WHO-TEFs were revised, these include 1,2,3,7,8-PeCDD, OCDD, OCDF and PCB 77. These mammalian TEFs are also considered applicable for humans and wild mammalian species. Furthermore it was concluded that there was insufficient *in vivo* evidence to continue the use of TEFs for some *di-ortho* PCBs as suggested earlier (*7*.). In addition, TEFs for fish and birds were determined. The WHO working group attempted to harmonize TEFs across different taxa to the extent possible. However, total synchronization of TEFs was not feasible as there were orders of a magnitude difference in TEFs between taxa for some compounds. In this respect the absent or very low response of fish to mono-*ortho* PCBs compared to mammals and birds is most noticeable. Uncertainties which could compromise the TEF concept were also reviewed, including non additive interactions, differences in shape of the dose response curve and species responsiveness. In spite of these uncertainties is was concluded that the TEF concept is still the most plausible and feasible approach for risk assessment of halogenated aromatic hydrocarbons with dioxin-like properties (8).

Exposure Assessment and Interlaboratory Quality Assessment Studies

WHO has initiated a series of studies to assess exposure to dioxins in various countries by analyzing pooled samples of human milk. The latest round of studies was completed in 1993, and the next round is planned to start this year. The results of the last round (9) show remarkable differences between the levels observed in the different countries. A few regions and countries have been identified where levels of PCDDs, PCDFs and PCBs in human milk are consistently higher or lower than those found in human milk from the other countries. In this regard, the sample from the Hudson Bay region in Canada appears to have relatively high levels of all

compounds investigated, whereas levels were significantly lower in Albania, Hungary and Pakistan. No consistent rankings apply for the other countries with respect to levels of the different compounds analysed. Different regions in several countries can be identified in which higher body burdens of specific compound classes (i.e., PCDDs and PCDFs, dioxin-like PCBs, or indicator PCBs) are found than in other areas and countries. In this regard, higher PCDD and PCDF levels can be observed for Belgium and the Netherlands, and higher non-ortho and mono-ortho PCB levels have been found in Lithuania. Exceptionally high levels of the six indicator PCBs have been found for particular regions in the Czech Republic, Slovak Republic and Canada.
There is now clear evidence of a decrease in PCDD/PCDF levels in human milk over time in almost every region for which suitabel data exist. The WHO study also shows that the highest rates of decrease, nearly 14% per annum, have been in the areas with the highest initial concentrations. These data imply that a substantial reduction in intake of PCDDs and PCDFs has occurred in recent years

Future Research Needs

While providing guidance on risk assessment related issues, the work of WHO also aims at identifying gaps in our knowledge and research needs. Issues requiring attention include the following:

- Precise data on exposure to various mixtures of dioxins and dioxin-like compounds are lacking. This is particularly true for the brominated congeners.
- There is a need to collect information on the composition of various dioxin and PCB mixtures in the environment. This is of particular relevance for risk assessment to be able to judge whether or not information gathered in experimental studies using commercial mixtures is applicable to the assessment of environmental conditions.
- There is a need to conduct comparative exposure studies covering a larger number of regions.
- There is a need to generate more mechanistic data to allow the application of adequate risk assessment models.
- To improve and refine TEFs, it is important that comparative toxicity data on various congeners are generated. This applies in particular to brominated congeners.
- Given the complexity and expense of analysis of biological samples for dioxins, the development and validation of simple (biological?) screening methods would be useful.

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