WHO revises the Tolerable Daily Intake (TDI) for dioxins

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Introduction

During the last years the WHO European Centre for Environment and Health (WHO-ECEH) has been coordinating a comprehensive programme in close collaboration with the International Programme on Chemical Safety (IPCS) on PCDDs, PCDFs and PCBs, aiming at evaluating the exposure and possible health risks of the population to these chemicals, with the ultimate goal of prevention and control of environmental input.
Several WHO meetings in the field of the health risk assessment of dioxins and related compounds have been convened. At a meeting held in Bilthoven, The Netherlands in December 1990, a tolerable daily intake (TDI) of 10 pg/kg b.w. for TCDD was established, based on liver toxicity, reproductive effects and immunotoxicity, and making use of kinetic data in humans and experimental animals (1, 2). Since then new epidemiological and toxicological data have emerged, in particular with respect to neurodevelopmental and endocrinological effects.
Therefore, WHO-ECEH and IPCS jointly organized a consultation on the "Assessment of the health risk of dioxins: re-evaluation of the Tolerable Daily Intake (TDI)". This consultation was held from 25-29 May 1998 at WHO Headquarters, Geneva, Switzerland, and was attended by 40 experts from Australia, Belgium, Canada, Denmark, Finland, Germany, Italy, Japan, The Netherlands, New Zealand, Spain, Sweden, United Kingdom, and USA.
The participants discussed topics such as health risks for infants, cancer and non-cancer endpoints in humans and animals, mechanistic aspects, toxicokinetics, modeling, exposure, and the applicability of the TEQ concept.

Results

Exposure
Human background exposure to PCDDs, PCDFs and PCBs predominantly occurs through the diet, with food from animal origin being the major source. Information from food surveys in industrialized countries indicates a daily intake of PCDDs and PCDFs in the order of 50-200 pg

I-TEQ/person/day, or 1-3 pg I-TEQ/kg bw/day for a 60 kg adult. If dioxin-like PCBs are also included, the daily total TEQ intake can be a factor of 2-3 higher. Recent studies from countries which started to implement measures to reduce dioxin emissions in the late 80s clearly show decreasing PCDD/PCDF and PCB levels in food and consequently a lower dietary intake of these compounds by almost a factor of 2 within the past 7 years.
Compared to adults, the daily intake of PCDDs/PCDFs and PCBs for breast fed babies is 1-2 orders of magnitude higher. The latest WHO field study (3) showed higher mean levels of PCDD/PCDF and PCB in human milk in industrialized areas (10-35 pg I-TEQ/g milk fat) and lower levels in developing countries (< 10 pg I-TEQ/g milk fat). There is clear evidence of a decrease in PCDD/PCDF levels in human milk between 1988 and 1993, with the highest rates of decrease in areas with the highest initial concentrations (3).

Mechanism
Data on TCDD and dioxin-like compounds has shown the importance of the Ah receptor in mediating the biological and toxicological effects of dioxins. Although the precise chain of molecular events is not yet fully understood, alterations in key biochemical and cellular functions are expected to form the basis for dioxin toxicity. The activated receptor exerts two major types of functions: enhancement of transcription of a battery of genes (e.g. encoding drug-metabolizing enzymes), and immediate activation of tyrosine kinases. Alteration of expression of other networks of genes may be directly or indirectly regulated by the Ah receptor. Activation of the Ah receptor can result in endocrine and paracrine disturbances and alterations in cell functions including growth and differentiation. Some of these effects have been observed both in humans and animals, indicating the existence of common mechanisms of action.

Kinetics
The toxicokinetic determinants of dioxin and related chemicals depend on three major properties: lipophilicity, metabolism, and binding to CYP1A2 in the liver. Lipophilicity controls absorption and tissue partitioning, metabolism is the rate-limiting step for elimination and induction of CYP1A2 leads to sequestration of dioxin.
There is a range of apparent half-lives for the various dioxin-like compounds. When background exposures are involved, an average half-life similar to that of TCDD may be used, but will underestimate daily exposure in short half-life chemicals and overestimate exposure for those with longer than average half-lives.
In general, concentration in the target tissue would be the most appropriate dose metric. However, the body burden, which can be readily estimated in humans and animals, is highly correlated with tissue and serum concentration, and integrates the differential half-lives between species. Therefore, the consultation concluded that in order to compare risks between humans and animals, the body burden is the metric of choice.

TEFs
Recognizing that additional compounds can possess "dioxin-like" activity, the consultation concluded that the use of TCDD alone as a measure of exposure to PCDDs, PCDFs and PCBs would severely underestimate the risk to humans from exposure to these compounds.

Therefore, the daily intake (TDI) in humans of PCDDs, PCDFs, *non-ortho* PCBs and *mono-ortho* PCBs will be expressed in units of TCDD equivalents (TEQs) applying the recently established WHO TEFs (4).

Animal data

A variety of effects have been reported in animal studies following exposure to PCDDs, PCDFs and PCBs. Among the most sensitive endpoints are: endometriosis, developmental neurobehavioral (cognitive) effects, developmental reproductive (sperm counts, female urogenital malformations) effects and immunotoxic effects. The lowest doses giving rise to statistically significant effects in these endpoints, have resulted in body burdens in the exposed animals of about 10 to 75 ng TCDD/kg bw.

TCDD has been shown to be carcinogenic in several species at multiple sites. Short-term studies, however, have shown a lack of direct DNA-damaging effects, illustrating that TCDD is not an initiator of carcinogenesis. Tumour promotion studies in various animal species indicated a non-genotoxic mechanism, and the ability of TCDD to enhance proliferation and inhibit apoptotic processes in focal hepatic lesions further supports an indirect mechanism of carcinogenicity. The consultation noted that the no-observed adverse effect level of TCDD for hepatic adenomas of 1 ng/kg/day in the Kociba study (5) corresponds with a body burden of 60 ng/kg bw.

Human data

Epidemiological evidence from the most highly 2,3,7,8-TCDD- exposed cohorts studied produces the strongest evidence of increased risks for all cancers combined, along with less strong evidence of increased risks for cancers of particular sites. It was noted, however, that the general population is exposed to levels of dioxins which are several orders of magnitude lower than those experienced by the industrial populations or the population at Seveso.

Noncancer endpoints were evaluated among groups exposed to dioxins, dioxin-like and non-dioxin-like polychlorinated aromatic compounds in a variety of exposure scenarios. Among children exposed *in utero* to background levels, effects include subtle developmental delays and thyroid hormone alterations. Of the many effects evaluated in exposed adult populations, many were transient effects disappearing after the end of exposure. A few conditions appear to be in excess among the exposed cohorts when compared to unexposed referent groups including alterations in metabolic parameters, as well as mortality from cardiovascular and non-malignant liver disease.

Models

The consultation discussed the applicability of mechanistic and curve-fitting models for risk assessment purposes. It noted that the outcome of the models strongly depends on the assumptions used, and that discrepancies may exist between the prediction of effects and the actual data, leading to caution in the use of models. Therefore, a more traditional approach using body burden calculations and emperical observations was preferred for the curent risk health risk evaluation.

Conclusions

For the purposes of risk assessment of human exposure to dioxin-like compounds, the consultation focused on the most sensitive effects which are considered adverse (hormonal, reproductive and developmental effects) seen at low doses in animal studies. These effects occur at body burdens in rats and monkeys in the range of 10-50 ng/kg bw.
Human daily intakes corresponding with body burdens similar to those associated with adverse effects in animals can be estimated to be in the range of 10-40 pg/kg bw/day.
Since body burdens have been used to scale doses across species, the consultation concluded that the use of an uncertainty factor to account for interspecies differences in toxicokinetics is not required. However, the estimated human intake was based on LOAELs and not on NOAELs. In addition the consultation noted that although for many parameters humans might be less sensitive than animals, still uncertainty remains regarding animal to human susceptibilities. Furthermore, differences exist in the half lives of elimination for the different components of a TEQ mixture. To account for all these uncertainties, a composite uncertainty factor of 10 was recommended.
Based on the range of estimated daily human intakes for the most sensitive responses in animal studies (10- 40 pg/kg bw), and applying this uncertainty factor of 10 a TDI range of 1-4 pg TEQs/kg body weight was established.
The consultation recognized that subtle effects might already be occuring in the general population in developed countries at current background levels of exposure to dioxins and dioxin-like compounds. It therefore recommended that every effort should be made to reduce exposure to the lower end of this range.

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