DIOXINs AND DIET:A REAL RISK?

Corrado Lodovico Galli and Marina Marinovich

Unit of Toxicology, Institute of Pharmacological Sciences, University of Milan, Via Balzaretti, 9 20233 Milan, Italy

Introduction

Different exposure routes can be distinguished for exposure to dioxins and related compounds by the general human population: direct exposure through inhalation of air and ingestion of particulates from air, ingestion of contaminated soil, dermal absorption and indirect exposure through consumption of food.
Polychlorinated dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs) and biphenyls (PCBs) contamination of food is primarily caused by deposition of emission from various sources on farmland. Other sources may include contaminated feed for cow's, chicken and farmed fish, improper application of sewage sludge, flooding of pastures, waste effluents, food processing and migration from chlorine-bleached packaging material (Furst et al, 1992; McLachlan and Riechter, 1998; Rappe et al., 1998.
PCDDs and PCDFs and PCBs constitute a group of environmental chemicals that due to their persistent nature accumulate in the food chain; over 90 percent of human exposure is estimated to occur through the diet, with foods from animals origin being the predominat sources (Gilman et al. 1991; Travis and Hatterner-Frey, 1991).
PCDDs, PCDFs and PCBs exist in environmental and biological samples as complex mixtures of various congeners and the complex nature of these mixtures complicates the risk evaluation for humans. There is sufficient evidence that there is a common mode of action for these compounds, involving binding to the Ah-receptor as an initial step.
To facilitate risk assessment and regulatory control of exposure to these mixtures the concept of toxic equivalency factors (TEFs) has been developed. The TEF values express the toxic potencies of the other congeners (an *order of magnitude* estimate of the toxicity of a compound) relative to that of 2,3,7,8-tetrachloro-dibenzodioxin (2,3,7,8-TCDD).
The TEF values, in combination with chemical residue data, can be used to calculate toxic equivalent (TEQ) concentrations in various environmental samples, food, animal and human tissues.
TEFs for dioxin like compounds apply only to AhR-mediated responses and this concept assumes a model of dose additivity.
During the last decade several different TEF schemes have been developed. The most widely used schemes have been the International TEFs (TEFs) (NATO/CCMS, 1988), the WHO-TEFs (WHO, 1991) and the US EPA-TEFs (US EPA, 1989) for PCDDs and PCDFs, and the WHO-ECEH scheme for PCBs (Ahlborg et, 1994). In 1997, ECEH-WHO and the IPCS resulted in the consensus TEFs for PCDDs, PCDFs and dioxin-like PCBs for both humans, fish and wildlife risk assessment.

RISK ASSESSEMENT

Basically, two different approaches have been used in the risk assessment of PCDDs, PCDFs and dioxin-like PCBs. Most country, except USA have derived Tolerable Daily (or weekly) intakes (TDI) for TCDD or TEQs assuming the existence of a threshold dose, while USEPA and FDA have used probabilistic estimates of cancer potency, treating cancer as a non-threshold effect, in the derivation of a Risk Specific Dose (RsD).

The concept of TDI has been derived from the ADI (Acceptable Daily Intake for humans) which was originally developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and defined as "an estimate of the amount of a food additive, pesticide or veterinary drug residue, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk". The Tolerable Daily (or provisional weekly) Intake (TDI or PTWI) is applied to contaminants in food. The term "tolerable" is used as contaminants do not serve an intended function, and as intake is unavoidable associated with the basic consumption of foods.

In December 1990, a WHO expert meeting reccomended a TDI for TCDD at 10 pg/kg bw and the use of TEFs as an interim approach to evaluate mixtures of dioxin related compounds for risk management purposes (WHO, 1991). The meeting conclude that humans are not more susceptible to TCDD than rats and decided to establish a TDI on the basis of a NOEL of 1 ng/kg bw/day for carcinogenic liver toxicity. It was calculated what daily intake would lead to the same concentration of TCDD in the human liver after 70 years of exposure as the 540 ppt measured in the liver of the rats fed 1 ng/kg bw/day for two years in the Kociba study (Kociba et al., 1978). In assuming steady state conditions, an elimination half-life of 7 years in humans, and a liver to adipose tissue ratio of 0.15 the intake was calculated to be 110 pg TCDD/kg bw/day. Thus the calculation showed that a daily dose for humans of about 1/10 the daily dose for rats would lead to the same liver tissue concentration. This was equal to the safety factor of 10 normally used to extrapolate from rat to humans. An additional safety factor of 10 was applied to account for potential differences in the susceptibility of the target organs and the poor data base on reproductive effects.

The use of probabilistic models, such as the linearized multistage model, assume cancer as a non-threshold effect. The USEPA uses a descriptor that addresses upper bound risk, RsD. In establishing a RsD for cancer it is attempted to describe the lowest possible dose which could be interpreted to result in a specific risk e.g. one in one million. The use of the one in one million probability of cancer is an arbitrary convention which, when used consistently across chemicals, allows for the comparison of relative cancer potency.

In both the US and other countries there is a growing concern over the non-cancer effects of dioxin and dioxin-like compounds. Traditionally EPA has used Reference Dose (RfD) as an aid in making decisions about the acceptability of these kind of effects. The RfD is not in itself an action level, nor does it establishes an acceptable dose. The derivation of the RfD shows similarities to the TDI in that it departs from a NOEL or benchmark dose and takes on board a safety or uncertainty factor.

Since 1991 the WHO European Centre for Environment and Health (WHO-ECEH) has been coordinating a comprehensive programme in collaboration with the International Programme on Chemical Safety (IPCS) on PCDDs, PCDFs and PCBs aiming at evaluating the possible health risk, and prevention and control of environmental exposure of the general population to these chemicals. 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). The consultation considered that the application of traditional approach to set a TDI using NOAEL and uncertainty factors may be inappropriate for persistent, bioaccumulative, chemicals like dioxins and related compounds. Free concentration in the target tissue would be the most appropriate measure. However, the body burden, which is highly correlated with tissue and serum concentration, integrates the different half-life between species. Much higher daily dose are required in rodents to achieve the same body burden, or tissue concentration, as a lower daily dose in people. Body burden is readly estimated in both people and rodents. Therefore, in order to compare risk between humans and animals, the body burden is the metric of choice.
Estimation of TDI for dioxin and related compounds requires that either a reliable No-Adverse-Effect-Level (NOAEL) or a reliable LOAEL be identified for the most sensitive and relevant adverse response. The LOAELs for the most sensitive adverse responses reported in experimental animals were associated with exposure levels that could be trasformed into a range of estimated long-term human daily intakes of 14-37 pg/kg bw/day. In order to arrive at a TDI for TEQs the use of uncertainty factors also has to be addressed to account for the use of a range of sensitive LOAELs instead of a NOAEL, the possible differences between humans and experimental animals in susceptibility to these compounds, the potential differences in susceptibilities within the human population, and differences in half-lives of elimination for the compound of a comple TEQ mixture. Since body burdens have been used to scale doses across species, the use of an uncertainty factor to account for species to species differences in toxicokinetics is no required. With regards to the potential differences in susceptibility to the effects of these compounds, humans are generally regarded as less sensitive than experimental animals, a small uncertainty factor needs to be employed. As the sensitive LOAELs of 14-37 pg/kg bw/day were considered to be within a factor of 2-3 to the NOAELs, it was considered that a composite uncertainty factor of 10 would be adequate. By applying an uncertainty factor of 10 to the range of sensitive LOAELs of 14-37 pg/kg bw/day a TDI, expressed as a range, of 1 - 4 TEQ pg/kg bw was established. The TDI express a tolerable chronic daily intake and that occasional short-term excursion above the TDI would have not health consequences provided that the averaged intake over time is not exceeded.

Human health risk assessment

General Population

Since 90% of human background exposure to PCDDs, PCDFs and PCBs is estimated to occur through the diet, with food from animal origin usually being the predominant source, great attention is posed on the food chain contamination.
The available information derived from numerous studies in industrialized countries indicates a daily intake of PCDDs and PCDFs in the order of 50 - 200 pg TEQ/person/day, or 1 - 3 pg TEQ/kg bw/day for a 60 kg adult. This intake results in average human background levels in the range of 10 - 30 pg TEQ/g lipid, equivalent to a body burden of 2 - 6 ng TEQ/kg bw. If the dioxin-like PCBs are also considered, the daily TEQ intake can be a factor of 2 - 3 higher. The intake of PDDDs, PCDFs and PCBs increases during childhood and stabilizes in adults of about 20 years of age. However the intake on a per kilogram basis decreases in this period to the increaing body weight. (IARC, 1997)

Breast fed babies

Compared to adults, the daily intake of PCDDs, PCDFs and PCBs for breast fed babies is still 1 - 2 orders of magnitude higher. The latest WHO field studies showed differences between the PCDDs/ PCDFs and PCBs contamination, with higher mean levels in industrializes areas (10 - 35 pg I-TEQ/g milk fat) and lower means levels in developing countries (<10 pg I-TEQ/g milk fat). Within one country a variation of a factor of 5 - 10 was observed for most congeners, mainly due to the age of the mother, number of breastfed babies, length of nursing period and consumption habits. (WHO/ECEH, 1996) There is clear evidence of decrease in the PCDDs/ PCDFs levels in human milk over time in almost every region for which suitable data exist. Latest results from Germany revealed a decrease of the PCDDs/ PCDFs levels in human milk of approx. 65% between 1989 and 1997.

Accidental and Occupational exposure

Examples of accidental exposure of population are the incident at Seveso where the serum levels for 2,3,7,8-TCDD ranged up to 56,000 pg/g lipid, with median levels of 500 pg/g lipid for Zone A and 126 pg/g lipid for Zone B.
High exposure may also be caused by fodd items accidentally contaminated. Known examples are the contamination of edible oil, such as the Yusho (Japan) and Yu-Cheng (Taiwan) food poisoning (Kuratsune et al., 1987; Masuda, 1994) . For a group of Yusho patients, average intake by ingestion of the Kanemi rice oil contaminated with PCBs, PCDFs and polychlorinated quarterphenyls (PCQs) was estimated at 154,000 pg/TEQ/kg bw/day, which is 5 order of magnitude higher than the reported average background intake in several countries.
Industrial activities in which 2,3,7,8-TCDD and related compunds are unintentionally produced, such as waste incineration or production of certain pesticides or chemicals may also result in an additional human exposure. Historic median 2,3,7,8-TCDD levels in blood of highly exposed workers, estimated by extrapolation back to the time of the last exposure, ranged from 140 to 2000 pg/g lipid. This estimates are 1 - 3 order of magnitude higher than the blood levels measured in the general population.

Conclusions

The interpretation of the results from cohort studies concernning the effects on reproduction and developing nervous system is complicated by the simultaneous exposure to non-dioxin-like PCBs (and may be other compounds) that might have played a significant role in eliciting these effects that have been demonstrated at TEQ body burden concentrations only slightly higher than that of the average general population. Although the effects were reported to be marginal, it should be recognized that the ubiquitous presence of these compounds in humans complicated the identification of a "normality" with respect to these parameters in the human population, and hence their presence points to the need of continuing efforts in reducing human exposure to these compounds, by controlling their imput to the environment.

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