Risk assessment of Dioxins and Dioxin-like PCBs in Food – Comments by the German Federal Environmental Agency

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Introduction

Potential health effects of dioxins are an important issue of concern to both politicians and the public. As all humans are exposed to measurable levels of dioxins and related substances, the determination of the tolerated daily intake is a very significant decision. Moreover the revision of this value is not only of academic interest but may also directly influence limit values guiding risk reduction measures, target levels such as those for tolerated residues in food. Council Regulation (EC) No 2375/2001 (setting maximum levels for certain contaminants in food)[1] states in 11: "Target levels indicate the levels to be achieved in order to ultimately bring human exposure for the majority of the population down to the TWI set by the Scientific Committee". These target values will be set before 31 December 2004. Thus the level of the TDI may indirectly influence entire sectors of industry in some member countries such as the fish industry of some Nordic States or the feed industry throughout the European Union.

Recommendations of a daily intake should involve a very low likelihood of a risk for humans. In particular some prerequisites have to be fulfilled:

- The proposed TDI has to protect all subpopulations. In the case of dioxin this is of high importance as the exposure of infants through breast feeding may exceed the exposure of adults by one or two orders of magnitude.
- The degree of uncertainty should be indicated at every step of the risk assessment as requested by the Communication from the Commission on the Precautionary Principle *"Where possible, a report should be made which indicates the assessment of the existing knowledge and the available information, providing the views of the scientists on the reliability of the assessment as well as on the remaining uncertainties. If necessary, it should also contain the identification of topics for further scientific research "* Uncertainty of the models applied should be characterised carefully and assumptions made should be checked for their plausibility[2].
- Epidemiological findings should complement the risk assessment based on animal experiments.

Discussion on TDIs for dioxins and related compounds

Nearly all human health risk assessments carried out on dioxins (PCDD/PCDF and dioxin-like PCBs) in the past (with the exception of the one by US-EPA) recommended health based exposure limits within the range of 1-10 pg X/kg bw per day (X = I-TEQ (Nato-CCMS), Nordic-TEQ, BGA-TEQ and finally WHO-TEQ).

As early as 1985 the Federal Environmental Agency in Berlin (UBA) together with the former Federal Health Office[3]evaluated 2,3,7,8-TCDD. A tolerable daily intake of 1-10 pg I-TEQ/kg bw per day was recommended on the basis of a 2 year carcinogenicity study on rats[4] . The lower end of the range (1 pg I-TEQ/kg bw per day) has been used as a precautionary value, the higher end (10 pg I-TEQ/kg bw per day) as a level requiring regulatory action. These values have been derived from a NOAEL of 1ng/kg bw for hepatocellular neoplasms in female SD rats, applying uncertainty factors of 100 – 1000.

Following an expert meeting in Stockholm in 1997, organized by the WHO, where consensus toxic equivalency factors (TEFs) for PCDDs, PCDFs and dioxin-like-PCBs were derived for humans , fish and wildlife[5], an expert consultation under the umbrella of WHO-ECEH and IPCS was organized in May 1998 in Geneva. The objective of this expert meeting was the health risk assessment of dioxins, with a view to establishing an updated TDI for dioxins. The expert consultation ended with a recommendation for a TDI-value of 1-4 pg WHO-TEQ/kg bw per day[6] . The consultation also stressed that "the ultimate goal is to reduce human intake levels below 1 pg TEQ/kg bw per day".

In November 2000 the Scientific Committee on Food of the European Commission published an 'Opinion of the SCF on the Risk Assessment of Dioxins and Dioxin-like PCBs in Food'[7]**.** On the basis of this extensive review of data and experimental results the Committee recommended a temporary tolerable weekly intake (t-TWI). Because of the long half-lives of dioxins in humans (7 years or more) the committee decided to establish a temporary intake on a weekly basis and proposed a tolerable intake of 7 pg WHO-TEQ/kg bw per week.

Only six months later the SCF carried out a re-evaluation of its t-TWI from November 2000[8] . The SCF regarded - in contrast to its evaluation of November 2000 - the long-term feeding studies on rhesus monkeys [9,10] as well as the studies of Gehrs et al.[11] and Gehrs and Smialowicz [12] no longer as 'pivotal studies'. As 'new' pivotal studies it identified a study by Faqi et al.[13] and a study by Ohsako et al.[14] . From these studies LOAELs were derived, maternal steady state body burden estimated - using data from Hurst et al.[15,16] and finally the associated estimated human daily intakes (EHDI) calculated. Applying an overall uncertainty factor of 10 to the LOAEL derived EHDI, the SCF concluded (on the basis of the Faqi-study) "that 14 pg/kg bw per week should be considered as a tolerable intake for 2,3,7,8-TCDD".

Similarly the Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated PCDDs/PCDFs and dioxin-like PCBs at its 57th Meeting in June 2001[17]. In the summary of this meeting, which is in part identical with the SCF re-evaluation from May 2001, JECFA recommended a provisional tolerable monthly intake (PTMI) of 70 pg WHO-TEQ/kg bw per month**,** which is the mean of a calculated range of 40 - 100 pg WHO-TEQ/kg bw per month.

Overview of recently recommended limit values for PCDDs, PCDFs and dioxin-like PCBs using WHO-TEFs:

WHO (1998):	TDI	1 - 4 pg WHO TEQ/kg bw per **day**
SCF (2000) :	t-TWI	7 pg WHO TEQ/kg bw per **week**
SCF (2001) :	TWI	14 pg WHO TEQ/kg bw per **week**
JECFA (2001):	PTMI	70 pg WHO TEQ/kg bw per **month**

This overview of limit values for dioxins and dioxin-like PCBs has the common feature that the values were derived from non carcinogenic endpoints and the confusing feature that they refer to different exposure periods.

Comments on the SCF re-assessment

All 4 studies selected as pivotal studies [13,14,18,19] are studies designed as developmental toxicity studies on male offspring of perinatally exposed pregnant rats. This reconsideration led to the situation that the re-assessment is now based only on rat studies which investigated only reproductive effects only on male offspring and, in addition, three of these studies are single dose studies at gestational day 15 (GD15).

The re-assessment of the SCF is based on a number of assumptions the committee made that involve some uncertainties. The core of the re-evaluation is the transformation of a single dose to a subchronic exposure by comparing the resulting maternal and foetal body burdens at gestational day 16. By choosing this procedure the SCF made the basic assumption that the body burden on GD 16 is the relevant body burden at the time when the effects under study are caused in the foetus. None of the pivotal studies indicate at which time of pre- or postnatal development the alterations are induced.

In calculating the associated estimated daily intake (EHDI), the SFC used 50 % as the fraction of dose absorbed. Studies indicate however a significantly higher absorption rate of 89 percent[20]. It should also be considered that infants and children absorb higher rates and that small doses are more readily and effectively absorbed[21]. In addition, uncertainty is also inherent in the use of a half life of 7.5 years (2,3,7,8-TCDD) for the calculation of the EHDIs, because it does not take into account the real mixture of PCDD/PCDF in the food and in fatty tissue. Ideally an overall TEQ half life should be applied.

The examples given above show, that the application of measured absorption rates – instead of assumed ones - together with an overall TEQ half life, which reflects the real situation better than 2,3,7,8-TCDD alone, will shift the calculated TDI to levels <u>below</u> 1 pg/kg bw per day.

The decision not to apply an ‘uncertainty factor’ for differences in toxicodynamics between experimental animals and humans and for inter-individual variation among humans is not comprehensible. The choice of the ‘uncertainty factor’ to account for the use of the LOAEL instead of

NOAEL should more appropriately be based on the quotient LOAEL/NOAEL determined in the Ohsako study[14], likewise in rats, and this factor would then be at least 4 and not 3 as indicated by SCF. In addition it is questionable whether the chosen LOAELs are really LOAELs.

Studies for immunological and behavioural effects as well as studies with dioxin-like compounds as endocrine disruptors are available and should be included as pivotal studies. Endocrine disrupters in general and dioxin in particular can exhibit non monotonic dose-response curves and can show different effects in different windows of critical exposure. This can be crucial for the extrapolation to low doses as done routinely in the derivation of critical doses such as TDI. Unfortunately this has not been discussed in the SCF documents. Results of epidemiological studies should also be included and this would likely lead to considerably lower TDI.

The SCF re-evaluation did not discuss the carcinogenic properties of dioxins/PCBs. In the SCF's first evaluation of November 2000 carcinogenicity was addressed under Chapter 3.3 'Effects considered as not being critical in the derivation of the tolerable daily intake'. Dioxins have proved to be carcinogenic and tumour-promoting in animal experiments. In particular experimental data show TCDD to be carcinogenic for a number of target organs in different species and both sexes even at doses below the maximum tolerable dose (MTD). Based on epidemiological data it can be assumed that TCDD is responsible for the elevated tumour rates observed in exposed human cohorts. Therefore, Germany has classified TCDD as "substance known to be carcinogenic to man" (Carc. Cat. 1) in accordance with Annex VI to EU Directive 67/548/EEC [22].

A recent risk assessment[23] tried to overcome the controversial discussion over carcinogenicity with respect to the mechanisms of TCDD carcinogenicity (genotoxic/ non genotoxic; threshold versus non threshold). In this 'biologically based risk assessment', early indicators of response for nongenotoxic carcinogens were used. Using CYP1A1 as the sensitive marker, an acceptable daily intake of 5 - 50 fg TCDD/ kg bw per day was estimated. This is similar to the current EPA recommendation. The difference between these estimations of TCDD associated risks and the SCF's proposal is obviously large and needs to be clarified. At least it may be indicative of the difficulty of setting a precise tolerable daily intake for TCDD on the basis of a generally accepted scientific procedure.

The proposed TDI has to protect all relevant subpopulations of the human society. The overall daily intake of dioxins and dioxin-like PCBs has decreased in the last decades. However there are tremendous differences in uptake rates between humans of different ages. As children consume more food than adults in relation to their body weight, and have other consumption habits, children ingest higher doses of dioxin-like compounds than adults. The SCF (2000) stated that on a body weight basis, the intake of breast-fed infants has been estimated to be one to two orders of magnitude higher than the average adult intake. Uncertainties remain about whether the high perinatal exposure of infants leads to a reservoir that is at least partially maintained until puberty. Recent German data suggest that the body burden of formerly breast-fed children aged 9-11 is still 20 percent higher than those of their formula-fed age-mates[24].

In order to protect the whole human population it is essential to include the vulnerable group of children in the risk assessment process. As breast feeding has measurable benefits for neurological and immunological development, formula feeding can not be recommended as a substitute for

breast feeding. The only remaining way to lower the dioxin uptake is to drastically reduce the background exposure of the general population.

The question whether 'related compounds'(dioxin-like compounds) should be included in the risk assessment process for dioxins and dioxin-like PCBs was discussed briefly by the SCF in its first opinion of November 2000. Examples of these dioxin-like substances are hexachlorobenzene, polychlorinated naphthalenes and polybrominated diphenylethers. It is acknowledged that it is difficult at present to include these dioxin-like substances with precise specific TEFs into a TDI, but it is clear that any TDI based only on PCDD/Fs and dioxin-like PCBs underestimates the real overall TEQ intake. Therefore this uncertainty has to be included in the risk assessment process.

In the case of the WHO recommendation for a TDI value of 1-4 pg WHO-TEQ/kg bw per day (WHO, 2000) one would favor at least the lower end of the proposed range, that means 1 pg WHO-TEQ/kg bw per day.

It is acknowledged that any recommendation of a precise number for a TDI is flawed by uncertainties and the possibility of different weight being given to the studies of relevance.

For further risk assessment the following should be taken into account:

- Indication of adequate uncertainties in the risk assessment and use of adequate uncertainty factors,
- Risks for immunological, behavioural and carcinogenic effects from animal experiments and epidemiological data indicating that these effects may occur at lower doses than the developmental effects,
- Epidemiological data on developmental effects and endocrine disrupting effects of dioxins which may exert non monotonic dose response curves,
- Calculation of the EHDIs using a reliable absorption factor and overall TEQ half lives,
- The consideration that any TDI based only on PCDD/Fs and dioxin-like PCBs underestimates the real overall TEQ intake because other dioxin-like compounds can contribute significantly to the daily intake.

The determination of the TDI has influence on all regulatory limit values that are based on the TDI value. A higher TDI lowers the level of protection for humans though breast-fed infants in particular are already exposed to a level that is highly undesirable. Any additional exposure would prevent the achievement of intake levels below 1 pg TEQ/kg bw per day and would persist over decades because of the overall TEQ half life of about 15 years.

We suggest, therefore, that

- the lower end of the WHO TDI range, of 1 pg/kg bw per day, should be used for all standard settings and risk reduction measures.
- the WHO proposal, to set a TDI instead of a TWI, should be followed because a TWI does not adequately reflect the long half lives of the substances under consideration, either.
- the goal set by the WHO, "to reduce human intake levels <u>below</u> 1 pg TEQ/kg bw per day", should be maintained.

Finally it is proposed that the TDI be reassessed in a process transparent to the public and on the basis of all relevant endpoints from animal experiments and human epidemiology, including the assessment of cancer risks.

Detailed comments by the German Environmental Agency on the SCF-Re-assessment is available at the Internet. [25]

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