HEALTH-BASED GUIDANCE VALUES FOR DIOXINS AND DIOXIN-LIKE PCBS

Thatcher N[1] *

[1]European Food Safety Authority, Parma, Italy

Introduction

The European Food Safety Authority (EFSA) undertakes risk assessments on food and feed safety at the European level. As the risk assessor, EFSA produces scientific opinions and advice to provide a sound foundation for European policies and legislation. Thus EFSA supports the European Commission, European Parliament and EU Member States in their risk management decisions. The remit of EFSA covers food and feed safety, nutrition, animal health and welfare, plant protection and plant health.

In the process of developing its scientific opinions, EFSA's Scientific Panels and Committee have crucial roles. The EFSA Panel on Contaminants in the food chain (CONTAM Panel) carries out risk assessments in the area of chemical contaminants in food and feed, namely process contaminants, environmental contaminants, natural toxicants, mycotoxins and residues of unauthorised substances. In order to assess the risk for public and/or animal health and to prepare the related scientific opinions, the CONTAM Panel collects and examines scientific information available in the public domain on the contaminant, the occurrence in food and feed, exposure to humans and animals, toxicokinetics and toxicity including dose-response data. Within this risk assessment process, the CONTAM Panel establishes health-based-guidance-values, compares the estimated exposure levels to the established health-based-guidance-values (humans), or to the identified no-observed-adverse-effect levels (animals). Finally the Panel concludes on the risk to health for humans and/or animals. The CONTAM Panel scientific opinions then advise and help the risk managers such as the European Commission and Member States to determine the need for possible revisions to the current legislation, or other follow-up actions required in relation to contaminants in food and feed.

The European Commission requested that EFSA provides an explanation of the differences in the health-based guidance values for dioxins and dioxin-like PCBs (dl-PCBs) established by different authorities, specifically the Scientific Committee on Food (2001), JECFA (2001) and US-EPA (2012).

The Scientific Committee on Food (SCF) last provided advice on risks to human health from exposure to dioxins and dl-PCBs in food to the European Commission in June 2001, establishing a tolerable weekly intake (TWI) of 14 picogrammes (pg) World Health Organisation toxic equivalent (WHO-TEQ)/kg body weight (b.w.) for dioxins and dl-PCBs[1]. The Joint Expert Committee on Food Additives (JECFA) of the WHO and Food and Agriculture Organisation (FAO) established a provisional tolerable monthly intake (PTMI) of 70 pg/kg b.w. for dioxins and dl-PCBs in June 2001[2]. Converted to a tolerable daily basis, this equates to a dose of 2.3 pg/kg b.w. per day, comparable with the TDI from SCF. In February 2012, the US Environmental Protection Agency (US EPA) published an assessment of the non-cancer endpoints for dioxins in February 2012, establishing an oral reference dose (RfD) of 0.7 pg per kg b.w. per day[3].

Based on the EFSA report[4] of the published risk assessments EFSA will undertake a comprehensive assessment on the risk for animal and public health related to the presence of dioxins and dl-PCBs in feed and food taking into account the more recent occurrence data. This is the first time EFSA will carry out a comprehensive risk assessment on dioxins and dl-PCBs. However, EFSA has previously issued risk assessments on specific risks for public health relating to the presence of high levels of dioxins and dl-PCBs in liver from sheep and deer (2011), on risks for infants and young children related to the presence of dioxins and dl-PCBs in food (2012), and on the risks for public health due to the presence of dioxins in pork from Ireland (2008) (urgent advice of EFSA).

This abstract outlines EFSAs examination of the health-based-guidance-values established by the different authorities and how EFSA will undertake the subsequent comprehensive risk assessment of dioxins and dl-PCBs in feed and food.

Health-based guidance values established by different authorities

The Scientific Committee on Food

In their assessment the SCF calculated the total amount of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the fetus (i.e. the fetal body burden) and the associated maternal body burden in the pivotal studies. A specific issue was the difference in the fetal versus the maternal body burden observed during a single or a repeated dosing

regimen, the latter being considered to be more representative of the average consumer. A factor of 2.6 was derived to correct for this.

Studies of developmental toxicity in rats examining effects upon the reproductive system and the immune system of male offspring were considered by the Committee[5-8], effects in studies of the latter being noted to occur at higher doses and as such not considered pivotal. The SCF discussed human studies noting in particular a recently published follow-up study on the Seveso cohort[9]. These studies were considered as not being critical in the derivation of the tolerable intake.

The SCF used both the no-observed-adverse-effect levels (NOAELs) and the lowest-observed-adverse-effect levels (LOAELs) in deriving a tolerable intake for TCDD, using a body burden approach to calculate the equivalent estimated human daily intakes (EHDIs). Results from the single dose studies were corrected because of the differences in fetal body burdens observed between a single and repeated dose, the timing of administration of the dose being critical.

In deriving an EHDI, differences in kinetics between rats and humans were taken into account, like the much longer half-life of TCDD in humans. As a result, the SCF concluded that no uncertainty factor was needed to account for toxicokinetic differences between experimental animals and humans. They also concluded that there was no need to apply an uncertainty factor for differences in toxicodynamics between experimental animals and humans and for inter-individual variation among humans, as 'humans are less sensitive to TCDD than responsive rodent strains'. The Committee deemed it appropriate to use the WHO (1994) default uncertainty factor of 3.2 to account for inter-individual variations in toxicokinetics in humans, given that the most sensitive effects of TCDD were seen after exposure of female animals, but they had no structured information on the potential variation amongst women regarding the most important determinants in toxicokinetics, i.e. size of body fat stores, CYP1A2 concentrations in liver, and rate of metabolism of TCDD.

Applying this uncertainty factor of 3.2 to the EHDI of 10 pg TCDD/kg b.w., calculated from the NOAEL (of 12.5 ng/kg b.w. single bolus dose by oral gavage) in the Ohsako study[8], indicated a tolerable intake of 3 pg/kg b.w. per day. The Committee found it appropriate to use an additional factor of 3, as the LOAELs were close to the NOAEL, giving an uncertainty factor of 9.6 (i.e. 3 × 3.2). The lowest tolerable intake of 2 pg TCDD/kg b.w. was obtained by applying this uncertainty factor to the EHDI of 20 pg/kg b.w. from the Faqi et al. (1998) study[7]. The SCF considered that the Wistar rats used in this study might be the most sensitive rat strain and therefore this value of 2 pg/kg b.w. should be the tolerable intake for TCDD. As TCDD and related compounds have very long half-lives in the human body, the SCF thought it more appropriate to express this as a tolerable weekly intake (TWI), extended to include other dioxins and dl-PCBs as a group TWI of 14 pg WHO TEQ/kg b.w.

The Joint Expert Committee on Food Additives

The JECFA established a provisional tolerable monthly intake (PTMI) of 70 pg/kg b.w. for dioxins and dl-PCBs in June 2001. Converted to a tolerable daily basis, this equates to a dose of 2.3 pg/kg b.w. per day, comparable with the group TDI of 2.0 pg WHO TEQ/kg b.w. from SCF, and the basis for its derivation is similar.

JECFA calculated the same average maternal and fetal body burdens as those established by SCF after a single dose and repeat doses of TCDD to pregnant Long Evans rats[10,11]. The Committee assessed the same studies as SCF concluding that a tolerable intake could be established for TCDD on the basis of the assumption that there is a threshold for all effects, including cancer. Consideration of the studies determined the lowest no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs), were provided by the studies of Faqi et al. (1998)[7] and Ohsako et al. (2001)[8], respectively. Following toxicokinetic conversion, these studies give maternal body-burden LOAELs and NOAELs for effects on male offspring of 25 ng/kg b.w. and 13 ng/kg b.w., respectively.

JECFA used the same rationale as the SCF in concluding that an uncertainty factor of 9.6 should be applied to the LOAEL or 3.2 to the NOAEL, resulting in a range of PTMIs from 40–100 pg per kg b.w. per month. The Committee chose 'the mid-point of this range' 70 pg per kg b.w. per month as the PTMI.

The US Environmental Protection Agency

The US EPA published an assessment of the non-cancer endpoints for dioxins in February 2012, establishing an oral reference dose (RfD) of 0.7 pg per kg b.w. per day. The US EPA define the oral RfD as 'an estimate (with

uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime'. An oral RfD is derived from a benchmark dose lower confidence limit (BMDL), a NOAEL, a LOAEL, or another suitable point of departure (POD) on the dose response relationship, with uncertainty/variability factors applied to reflect limitations of the data used, and as such an oral RfD is comparable to a TDI.

RfDs were derived from epidemiological studies, which the EPA consider preferentially when deriving an RfD. The key studies were evaluations of the cohort exposed as a result of the explosion in Seveso, Italy in 1976, i.e. they were directly exposed to TCDD[9, 12,13]. These studies were deemed appropriate for use in the RfD derivation as exposures were primarily to TCDD, with exposure to other dioxin-like compounds apparently being minimal in addition to exposure associated with background intake. Though these specific publications were not available to SCF and JECFA at the time of their evaluations, these papers constitute repeated follow-up studies on the Seveso cohort, of which publications were available. From each of these studies a POD was estimated from the NOAEL/LOAEL identified for the critical effect observed in the key studies.

Two studies, Baccarelli et al. (2008)[13] and Mocarelli et al. (2008)[9], were selected to be co-principal studies for the RfD. They described the most sensitive endpoints; increased thyroid-stimulating hormone in neonates and decreased sperm count and motility which were designated as co-critical effects and an adjusted LOAEL of 20 pg/kg b.w. per day was identified as the POD for determination of the RfD.

The US EPA concluded that the assumption of a constant half-life value for the clearance of TCDD from long-term or chronic exposure is not well-supported biologically, given the dose-dependent elimination that is observed in rodents and humans. As such they decided that the dynamic distribution of TCDD between fat, liver and blood as a function of time and dose would be better described using physiology-based models. These models provide estimates for other dose metrics (e.g. serum, whole blood, or tissue levels) that the US EPA describe as more biologically relevant to response than a body burden estimated based on an assumption of first-order accumulation/elimination over time. Thus, a physiologically based pharmacokinetic (PBPK) model was used by the US EPA to simulate the 2,3,7,8-TCDD blood concentrations from these studies.

To establish the RfD, EPA applied an uncertainty UF of 30. The standard factor of 10 (in the absence of information suggesting a lower value) was applied as the RfD was derived from a LOAEL. A factor of 3 was applied to account for human inter-individual variability, i.e. to account for variability from human-to-human because the effects were elicited in sensitive life-stages. The EPA explained that a UF of 1 was not applied because 'the sample sizes in these two epidemiological studies were relatively small, which, combined with uncertainty in exposure estimation, may not fully capture the range of inter-individual variability. In addition, potential chronic effects are not well defined for humans and could possibly be more sensitive'. The resulting calculation gave an RfD for TCDD of 0.7 pg/kg b.w. per day.

Comparison of SCF and JECFA HBGVs with US EPA RfD

- SCF and JECFA concluded that the critical studies for derivation of a HBGV were animal studies whereas the US EPA selected the human data as it is their preferred basis.
- SCF and JECFA applied a body burden one compartment kinetics approach to derive a HBGV from rat data, whereas US EPA applied PBPK modelling of blood levels estimated from epidemiology studies.
- The application of an uncertainty factor of 3 by SCF and JECFA as the LOAEL was close to the NOAEL (observed in another animal study) as opposed to the US EPA applying their default uncertainty factor of 10 for extrapolation from a LOAEL in the absence of a NOAEL results in the RfD being 3-fold lower than the TWI/PMTI.
- In view of the different approaches used in the most recent assessments undertaken by the authorities, it seems appropriate to undertake a comprehensive risk assessment on the risks for animal and human health related to the presence of dioxins and dl-PCBs in feed and food.

Forthcomng Scientific opinion of the EFSA Panel on Contaminants in the Food Chain on the risk for animal and human health related to the presence of dioxins and dl-PCBs in feed and food

In response to a request from the European Commission EFSA will undertake a full risk assessment on the risk for animal and human health related to the presence of dioxins and dl-PCBs in feed and food. This will be the first EFSA risk assessment of dioxins and dl-PCBs in feed. The risk assessment will be published in June 2017. It will be developed applying a structured methodological approach; as such the protocol will be developed a priori to the full risk assessment. Each step of the risk assessment will be performed in line with the protocol and thoroughly documented during the process.

The scientific publications that were available when the risk assessments described above were performed will be considered alongside any new publications. In addition recent occurrence data submitted to EFSA by Member States of the European Union will be used to calculate exposures.

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