Summary of the draft EFSA opinion on dioxins 2025

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20. Following the publication of the new TEFs by JECFA, EFSA was asked by the European Commission (EC) to update its 2018 assessment, considering the potential impact the change in TEFs could have on the exposure assessment and derivation of the TWI. EFSA thereby took into account the updated TEFs for all 29 congeners and as such the sum of PCCD/F and DL-PCB TEQ. The assessment also included an update on exposure of food-producing animals and transfer of PCDD/Fs and DL-PCBs from these animals to animal derived food products.

21. Based on human milk samples from the WHO/UNEP monitoring program and individual milk samples from Germany, the application of the new TEFs resulted in consistently lower total TEQ concentrations, with an average decrease of 40%, compared to the previous (2005) TEFs.

22. EFSA applied a systematic approach to retrieve relevant information since their last (2018) assessment. No new essential data was identified on the toxicokinetics of dioxins, while effects reported in new experimental animal studies were considered not adverse and/or not suitable to derive a reference point (RP).

23. Numerous eligible epidemiological studies were identified, however, the number of studies per endpoint were limited and EFSA noted considerable heterogeneity, with few studies being prospective. Hence, EFSA did not identify any new evidence to change the previous conclusions.

24. EFSA continued to consider a decrease in sperm production in male offspring of rats upon exposure to TCDD (via the dams) as the most sensitive endpoint. Lower sperm concentrations were also observed in the three different human cohort studies, the two Seveso studies (TCDD), and the Russian Children's Study (significant associations between serum levels and TCC, PCDD-TEQ, PCDD/F-TEQ and sperm concentrations, but not for PCDF-97 TEQ, DL-PCB-TEQ or Total-TEQ).

25. As the current assessment was meant to apply all 29 congeners, EFSA concluded that the studies in humans could no longer be used as basis for establishing the TWI. The Russian Children's Study showed no statistically significant association for total TEQ and the two Seveso studies lacked information on exposure to other congeners than TCDD in both the exposed and control group. Thus, EFSA decided to use a study in rats (Faqi et al., 1998a), while the human studies were used as supportive evidence, including decisions on uncertainty factors (UF) to use.

26. In the critical study, dams were exposed to TCDD s.c. with a single dose of 25, 60 or 300 ng/kg bw two weeks prior to mating, followed by weekly injections of 5, 12 and 60 ng/kg bw during mating, pregnancy and lactation. The aim was a stable body burden. Three animals were killed on gestation day 21 (GD21) to confirm the intended body burden and male offspring were killed either postnatal day 70 (PND70) or PND170. Male pups showed reduced sperm production at both, 70 and 170 days.

27. At day 170 a near-maximum response was obtained at the lowest dose, corresponding to a body burden in the dams of 25.1 ng/kg bw. However, EFSA considered it more informative and scientifically robust to derive a RP from a benchmark dose (BMD) lower credible limit (BMDL) than extrapolating from a lowest observed adverse effect level (LOAEL) to a NOAEL. Hence, performing BMD

modelling (EFSA Guidance, 2022) on the daily sperm production data from the Farqi et al. (1998) study, EFSA derived a maternal body burden of 1.7 ng TCDD/kg bw using a benchmark response (BMR) of 15% decreased sperm production. Although the BMDL15 is based on TCDD, EFSA concluded that it should also apply to the sum of PCDD/Fs and DL-PCBs based on the TEQ concept.

28. EFSA did not apply the default UF for interspecies toxicokinetic variability as the starting point for the assessment was body burden. In addition, there is evidence demonstrating that humans are not more sensitive than rats. Therefore, the default UF for inter and intraspecies variability in toxicodynamics were not applied. The default UF of 3.16 for intraspecies variability in kinetics in humans, such as variations in maternal body fat content and amount of milk consumed by infants, however, was considered appropriate, while differences in metabolism likely play a minor role and absorption is almost complete.

29. The RP of 1.7 ng TEQ (2022)/kg bw correspond to a lipid-based level of 6.8 ng TEQ (2022)/kg body fat (based on 25% body fat) and using the concentration and age-dependent toxicokinetic model (concentration- and age-dependent (CADM) model) this lipid-based level would be reached after chronic exposure to 0.29 pg TEQ (2022)/kg bw per day. Applying the default UF of 3.61 for interspecies variability in kinetics, this results in a daily intake of 0.09 pg TEQ (2022)/kg bw per day or 0.63 pg TEQ (2022)/kg bw per week. EFSA rounded this to establish a TWI of 0.6 pg TEQ (2022)/kg bw per week for the sum of PCDD/Fs and DL-PCBs.

30. This TWI is lower than the TWI of 2 pg TEQ/kg bw/week established in 2018 and also lower than the TWI of 14 pg TEQ/kg bw/week that the SCF derived from the same study in 2001.

31. EFSA considered the TWI protective for the general population and all endpoints. Toxicokinetic modelling of chronic exposures at the TWI resulted in body burden in women age 35 years of 2.2 ng TEQ (2022)/kg fat, the highest body burden in women that does not raise a health concern for their sons. The fat-based levels in milk would be similar to the body burden. The TWI prevents woman of childbearing age reaching the body burden that could lead to in utero and lactational exposures associated with health concerns in offspring. EFSA recognised that infants have higher exposure per kg bw during breastfeeding than the TWI, resulting in a higher body burden. However, this was already taken into account when setting the TWI. Therefore, the TWI is not applicable for infants, and it is not appropriate to compare it to the exposure of infants.

32. EFSA noted that the differences in HBGVs (SCF, 2001; JECFA, 2002; EPA, 2012; EFSA 2018) were based on the selection of the critical studies, application of BMD modelling, toxicokinetic modelling and application of a correction factor for dosing regimens.

33. Exposures estimated with the new 2022 TEFs were between 27% and 35% lower than using the 2015 TEFs across all age groups. The non-ortho DL-PCBs showed the highest contribution (41%) to the total 2022-TEQ exposure, followed by PCDFs (27%), PCDDs (24%) and mono-ortho PCBs (9%).

34. When comparing the mean current dietary exposure to the 29 PCDD/Fs and DL-PCBs a 3- to 12-fold exceedance of the TWI was observed (lowest LB-highest UB) in ‘Adolescents’, ‘Adults’, ‘Elderly’ and ‘Very Elderly’. At the P95, exceedances ranged from 6- to 30-fold (lowest LB-highest UB). For ‘Toddlers’ and ‘Other Children’, the mean dietary exposures exceeded the TWI by 6- to 27-fold and at the P95 from 11- to 55-fold. The exceedance for ‘Toddlers’ and ‘Other Children’ raised a concern for developmental effects.

Food producing animals

35. Ratios of 2022-TEQ vs 2005-TEQ concentration estimates for the 29 PCDD/Fs and DL-PCBs ranged from 0.8 to 1.2 for most food-producing animal species and categories considered. The variation in this ratio was largely driven by the congener pattern in the feed material or compound feed. The updated occurrence data and methodological refinements resulted in generally lower or comparable estimated concentrations of the 29 PCDD/Fs and DL-PCBs in the daily diets of food-producing animals compared to the 2018 Opinion based on the 2005 TEFs.

36. EFSA used new studies to update the information and contribute better to the understanding on the transfer of PCDD/Fs and DL-PCBs in dairy cows, laying hens and pigs to milk and eggs and accumulation in liver, fat and meat of food producing animals. The change in TEFs does not affect the transfer rates of individual congeners but EFSA noted that it could impact total TEQ, and the extend of said impact may be evaluated based on a case-by-case basis and ideally using congener-specific toxicokinetic models that are available for some species.

37. EFSA noted a number of uncertainties, including the derivation of the RP from the critical study, the absorption, distribution, metabolism, excretion (ADME) and the toxicokinetic model, the relevance for humans of the new TEFs for DL-

PCBs, the derivation of the TWI including the applicable UF, left-censored occurrence data and occurrence in foods of plant origin. Taking into consideration the uncertainties EFSA concluded with about 95% certainty that the TWI would be equal or higher than the value derived from the available data, if the identified uncertainties were resolved. EFSA considered it 99-100% certain that the mean exposure in adults would be higher than the TWI for all dietary surveys that were considered, if the identified uncertainties affecting the exposure assessment were resolved. Even taking into account the discrepancy between the exceedance of the TWI from dietary exposures and measured milk levels, EFSA considered it likely (80-90% certainty) that mean exposures would raise a health concern based on the new TEFs. For P95 exposures, the certainty was 95-99%. However, when uncertainties related to the new TEFs for DL-PCBs were also taken into account, the probability for health concerns were reduced (mean to 33-6%; P95 to 70-80%).

38. EFSA made a number of recommendations to reduce the uncertainties in the risk assessment, i.e. further development of approaches to compare animal- and human-based data, further data on occurrence levels in plant-derived foods, improvement of toxicokinetic models (including inclusion of other congeners (other than TCDD)), further biomonitoring data, also of other European populations, development of analytical methods, better understanding of the involvement of the AHR in regulation of sperm production and how it is disrupted by dioxins. The latter should contribute to the development of an adverse outcome pathway (AOP) for the AhR in relation to sperm production/effects on reproduction and development.