

National Toxicology Program

National Institute of Environmental Health Sciences

COMMENTS ON EPA'S DRAFT NON-CANCER RISK ASSESSMENT FOR DIOXIN

The USEPA's Draft Non-Cancer Risk Assessment for dioxin is well written and responsive to the comments of the NAS and the Scientific Advisory Board. The studies considered critical for the development of a reference dose for non-cancer effects are well documented and the reasons for choosing these studies are well articulated. The EPA identified numerous studies that examined low dose effects of dioxin in experimental animals and humans. Their rationale for narrowing down the number of studies under consideration was clearly articulated and thoughtful.

One of the biggest challenges was determining the Bench Mark Response level for the POD for specific endpoints. In the 2003 draft, the EPA presented data on the 1% response level for all studies evaluated. This approach was criticized by both the SAB and the NAS. In the present draft, the EPA developed criteria that are more rigorous for BMRs depending on the type of endpoint and available data. This approach is consistent with the NAS comments (p. 72, NAS, 2006). The rationale for the different BMR choices is clearly described in the report.

The previous draft report used body burden as the cross-species dose metric. Due to the large difference in half-life between humans and experimental animals, body burden is a better dose metric than administered dose divided by an uncertainty factor. However, the use of body burden has uncertainties associated with the differences in body fat composition between humans and experimental animals. The present draft uses estimated blood concentrations as the cross-species dose metric. Blood concentrations are estimated using rodent and human PBPK models. This approach is more appropriate than the use of body burden.

The EPA uses several human studies from Seveso in the development of its RfD. One of the challenges in the use of these studies is determining the human exposure. The Seveso population was exposed to a high dose of dioxin for a short period (days to weeks). In order to use this data in the development of an RfD, the EPA must convert measured blood concentrations to an average daily dose to attain either a peak concentration or an average serum concentration for the window of sensitivity. For all of these studies, the exact window of sensitivity is unknown and the EPA has made reasonable assumptions on the individual windows.

The justification of the use of the Baccarelli et al (2008) and the Mocarelli et al (2008) studies for the development of the RfD are well described and appropriate. EPA appropriately used a neonatal TSH level of 5uU/mL based on the WHO recommendation of its use as an indicator of potential thyroid

problems. The EPA chose to describe this point of departure as a LOEL and applied a Uf of 10 for a LOEL to NOEL conversion. Because the WHO describes this value as an indicator of potential thyroid problems, one might consider this a NOEL or perhaps use a factor of 3 instead of 10 for the UF. Unfortunately, the designation of this point of departure as a LOEL or NOEL or the use of a UF of 3 or 10 cannot be clearly defined. The designation of 5uU/mL TSH levels as a LOEL is not unreasonable, given the uncertainty about the quantitative relationship between TSH levels and hypothyroidism. However, it is clear that from the citations provided by EPA that moderate decreases in circulating thyroid hormones during development are cause for concern.

The EPA assessed the Mocarelli study as a LOEL as opposed to a NOEL. The support for this position is not as strong as it is for the Baccarelli study. The EPA suggests that this is a LOEL because in the Seveso accident, individuals 1 standard deviation below the mean had sperm concentrations of 21.8 million/mL and that this concentrations falls at the low end of the range of reduced fertility suggested by Skakkebaek, 2010. It should be noted that for the control group, individuals 1 standard deviation below the mean had sperm concentrations of 31.7 million/mL, which is also within the range of reduced fertility suggested by Skakkebaek, 2010. If the EPA had used the WHO suggestion of 20 million/mL instead of Skakkebaek's suggestion of 15-40 million/mL, it is possible that the bench mark response for sperm concentrations may have been a NOEL and not a LOEL. Given the large proportion of the control population that is within Skakkebaek's recommendations, EPA may wish to reconsider whether this is a NOEL or LOEL.