The Debate About Linear vs. Non-Linear Approaches For Cancer and Different Approaches for Developing Non-Cancer Toxicity Benchmarks: Practical Implications and Why It's Important to Get It Right

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Three sets of analyses were conducted in an effort to describe some of the practical implications of the EPA toxicity values by comparing them to results associated with alternative toxicity values. The objective was to provide the SAB with a better sense of the range of uncertainties and importance of relying on the best available science and overall weight of the evidence rather than simply relying on default precautionary principle-type approaches. These analyses focus on predicting serum concentrations based on doses equivalent to cancer and non-cancer toxicity benchmarks that reflect different derivation approaches, most notably linear vs non-linear approaches for cancer. As the cancer and non-cancer toxicity benchmarks all represent "safe" levels that people can be exposed to on a daily basis throughout their lifetime without risk of adverse health effects, the serum levels associated with these "safe" doses represent "safe" serum levels. The PBPK model developed by Aylward et al (2005) was modified slightly to account for the faster elimination during the childhood years and *in utero* exposures to dioxins and was then used to predict serum concentrations for all three sets of analyses. A number of toxicological benchmarks were applied in these series of analyses, including the EPA's draft proposed RfD (0.7 pg/kg-day) and oral cancer slope factor (OSF) (1,000,000 mg/kg-day^{-1}, risk levels E-4, E-5, and E-6). Other benchmarks that represent the best available science and/or consensus values from international health-based agencies that were applied in these analyses included the JECFA TDI (2.3 pg/kg-day; JECFA 2001), which is protective of both cancer and non-cancer effects, as well as a cancer-based RfD (100 pg/kg-day) developed by Simon et al (2009) based on a non-linear dose-response modeling approach.

The results of these analyses convey the range of uncertertainties associated with the different approaches for deriving cancer and non-cancer toxicity benchmarks for TCDD, with an emphasis on the practical implications of these different approaches. More specifically, the results demonstrate that the draft EPA values equate to serum concentrations that are below background serum levels in the general U.S. population and, in some cases are even below the most sensitive detection limits achieved in the biannual national biomonitoring study conducted by the U.S. government – NHANES. This suggests that the entire U.S. population is essentially at a significant health risk

based on current serum levels – a conclusion that not only seems unlikely but also fails to pass a common-sense test given the overall weight of the evidence demonstrating a receptor-based mode of action and general lack of constitutive expression of very sensitive AHR responses in the general population, such as CYP1A1 activity despite substantially higher background blood dioxin levels in past decades. In contrast, the toxicity values that represent the best available science and/or consensus values from international health-based agencies (JECFA TDI and cancer based RfD) yield very different results. These data suggest that serum levels must exceed background levels as measured in NHANES as well as exceed predicted levels estimated via modeling following exposures to background sources before one would approach levels of concern. As a result, these different toxicity benchmarks lead to very different regulatory decisions than do the EPA cancer and noncancer toxicity benchmarks which in turn have substantial public health and economic impacts.

ANALYSIS #1
Objective: compare serum concentrations associated with cancer benchmarks to serum concentrations measured in the general U.S. population

Approach:

- Use the Aylward et al (2005) PBPK model to predict serum concentrations
- Assume exposures to the OSF (risk levels E-4, E-5, and E-6), JECFA TDI, or cancer-based RfD for 19, 29, 44, 59, or 85 years.
- Compare terminal serum concentrations to the range of concentrations measured in the general U.S. population as reported in the NHANES 03/04 dataset.

Findings (slide 2)

- The proposed EPA OSF values resulted in serum concentrations that were at or below the minimum value in the general U.S. population.
- Serum concentrations associated with exposures to the OSF at risk levels of E-5 and E-6 were below the most sensitive limits of detection as reported in the NHANES 03/04 dataset (i.e., the CDC could not actually measure the serum levels using current analytical techniques).
    - This essentially says that if you believe that the EPA OSF is accurate, then everyone in the general US population is at risk. For reasons already described above, this finding seems implausible.
- In contrast, the JECFA TDI and cancer-based RfD resulted in serum concentrations that were within or above the range observed in NHANES.

ANALYSIS #2
Objective: compare serum concentrations associated with both non-cancer and cancer benchmarks to serum concentrations associated with typical background levels of dioxins in the environment

Approach:

- Use the Aylward et al (2005) PBPK model to predict serum concentrations.
- Assume lifetime (70 years) exposures to doses equivalent to
    a. the EPA RfD, JECFA TDI, OSF (risk levels E-4, E-5, and E-6), or cancer-based RfD, *or*
    b. background sources including diet, air, and soils (based on estimates from Lorber et al, 2009), as well as *in utero* and breast milk exposures
- Compare terminal serum concentrations of (a) and (b) above.

Findings (slides 3 and 4)

- Lifetime exposure to the proposed EPA RfD resulted in a serum concentration that was approximately the same as that associated with exposures to background sources (slide 3). In contrast, exposures to the JECFA TDI resulted in a serum concentration that was approximately double that of the EPA RfD.
- Lifetime exposure to the EPA OSF at all risk levels evaluated resulted in serum concentrations far below those associated with background exposures (Slide 4). Serum concentrations associated with the JECFA TDI or cancer-based RfD were at least an order of magnitude higher.
- These findings indicate that if the EPA RfD and OSF are correct, then everyone is essentially at risk. For reasons already described above, this conclusion seems implausible.

ANALYSIS #3
Objective: compare serum concentrations associated with exposures to doses equivalent to the toxicological benchmarks to serum concentrations resulting from excess exposures to dioxins in soil (i.e., exposures above background levels)

Approach:

- Use a PBPK model to predict serum concentrations.
- Assume lifetime (70 years) exposures to
    a. the EPA RfD, JECFA TDI, OSF (risk levels E-4, E-5, and E-6), or cancer-based RfD, *or*
    b. background sources including diet, air, and soils (based on estimates from Lorber et al 2009), as well as *in utero* and breast milk exposures.

- Compare serum concentrations over time for evaluation of non-cancer and lifetime average serum concentrations for evaluation of cancer (focus on excess cancer risk associated with exposures above background).
- This analysis looks at the impact of the different toxicity benchmarks in guiding potential regulatory decision-making regarding the establishment of an updated soil preliminary remediation goal (PRG).

Findings (slides 5 and 6)

- When the serum forecasts based on the noncancer benchmarks are compared (slide 5), it is clear that serum concentrations associated with exposures to the JECFA TDI are higher than those associated with the EPA RfD. More importantly, both are higher than exposures to background sources + additional exposures to dioxins in soils at a concentration of 72 ppt, thus suggesting that the EPA's draft PRG of 72 ppt based on non-cancer effects is unnecessarily conservative.
- In the evaluation of cancer benchmarks (slide 6), data indicate that the lifetime average serum concentration associated with the EPA OSF were below those associated with exposure to background sources, regardless of the risk level. In contrast, the lifetime average serum concentrations associated with the JECFA TDI and cancer-based RfD were substantially above serum levels associated with background exposures.
    - Based on the JECFA TDI and cancer-based RfD, one would conclude that a soil PRG could be set at 1000-2000 ppt and be more than adequately protective based on serum concentrations (the dose metric that is widely accepted as the best measure of exposure for dioxin-like compounds)
    - This soil PRG is very different from the draft value of 3.7 ppt recently proposed by the EPA.

Conclusion

This debate over linear vs non-linear approaches for cancer and different approaches employed for noncancer effects lead to vastly different toxicity values and these different toxicity values result in vastly different regulatory decisions.

These different regulatory decisions have substantially different societal impacts and costs associated with them.

As a result, the science underlying these different toxicity values needs to be very carefully examined and emphasis should always be placed on the overall weight-of -the-evidence rather than simply relying on default precautionary principle-type approaches.

References

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