Reassessment of TEFs: A Mathematical Approach

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1. Introduction

Current toxicity equivalency factors (TEFs) for dioxin-like chemicals are not derived from the mathematically optimal model, given the assumed mechanism of action and analyses of available data. Theoretical examples suggest that the more mathematically accurate TEFs may differ substantially from the current TEFs under many conditions of practical interest. Furthermore, the conversion factor for dose-additivity is likely to be a function rather than a number, as is presently used by regulatory agencies.

The goal of TEFs is to derive a method by which an exposure or dose of a mixture

of dioxin-like chemicals can be converted (when appropriate based on the toxicological analysis) to an equivalent exposure or dose of 2,3,7,8-TCDD. This concept of dose-additivity, however, makes no a priori assumptions about either the shape of the dose-response curves or the method used for conversion of the doses. Specifically, the concept of dose-additivity does not require that the equivalent doses are the same linear proportion of each other for all response levels, as is assumed with current TEFs. Furthermore, while the functions for dose-additivity can be based on assumed mechanism of action, the method for converting between response-equivalent doses can also be derived empirically based on a best fit of the data. Specifically, the process of dose-conversion need not incorporate assumptions (especially policy-based assumptions) concerning the shape of the dose-response curve of the reference chemical, in this case 2,3,7,8-TCDD, after the conversion has occurred. These analyses demonstrate that dose-additivity based on simple point estimates, i.e., linear ratios of doses, is not to be expected for most conditions.

Logically, the dose-response curves for dioxin-like chemicals are either parallel or they are not parallel. This statement was used as the initial axiom for a mathematical analysis of the current TEFs. The consequences of either assumption *(parallel or non-parallel dose-response curves) for the development of TEFs are* considered below. For the purposes of simplifying the mathematics during this heuristic evaluation, the dose-response curves in these theoretical examples are assumed to be straight lines.

2. Assumption 1: Parallel Dose-response Curves

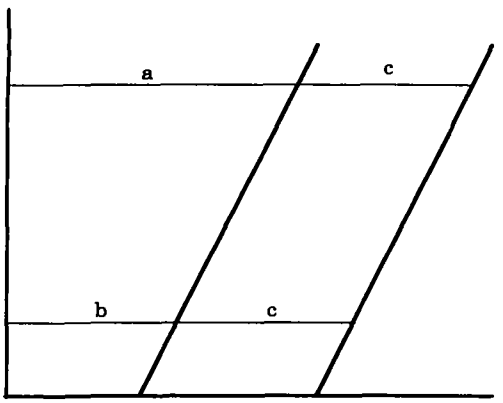

Figure 1. Analysis of linear, parallel dose-response curves

USEPA's recent reassessment[1] of the potential toxicity of dioxin-like chemicals often mentions the observation that the some of the dose-response curves for dioxin-like chemicals are parallel. If the dose-response curves are parallel, then the relative doses of dioxin-like chemicals required to produce the same response can not be the same ratio for all response levels, as is the case for the current TEFs. Figure 1 illustrates that the ratio of the doses required to produce the same response will depend on the dose at which the relative potency of the doses is measured. Depending on the response level (y-axis) on which of the horizontal lines in Figure 1 is selected, the ratio of the doses (x-axis) to produce the selected response (the current definition of a TEF) is defined either as a/(a + c) or b/(b + c) .

The potential consequences of ignoring this change in relative potency of doses at

different response levels may be substantial. If, for example, it is assumed that a = 100, b = 10, and c = 1,000 then the relative doses required to produce the same response, or the TEF, is either

$$TEF = a/(a + c) = 100/1,100 \cong 0.1$$

or

$$TEF = b/(b + c) = 10/1,010 \cong 0.01,$$

about a 10-fold difference in the conversion factor. If the relative potency is estimated at even lower response rate, e.g., b' = 1, then

$$TEF = b'/(b' + c) = 1/1,001 \cong 0.001,$$

about a 100-fold difference from the dose ratio measured at the highest response level calculated in this example.

Thus, for parallel dose-response curves, the ratio of the doses of two chemicals that would produce the same response can differ by orders of magnitude, depending on the level at which the ratio is measured. Since, by definition, the TEF is the factor necessary to convert the dose of one dioxin-like chemical to the dose of 2,3,7,8-TCDD that would produce the same response, the TEF for this example can not be a single number but must vary with the level at which the relative potency of the doses is to be determined. Furthermore, the current TEFs would be expected to

become more inaccurate as the response level differs substantially from the level at which the TEF was estimated. This finding has direct implications for the use of current TEFs at doses substantially lower than those that can be observed in the laboratory.

The comparative accuracy of dioxin-like chemicals with various relative potencies can also be examined. Using the same initial assumptions as above, i.e., a = 100, b = 10, and c = 1,000, the difference of the ratios at the two response levels remains approximately 10-fold. If the ratio of the doses is estimated for a chemical with even lower potency, e.g., c' = 10,000, then

$$TEF = a/(a + c') = 100/10{,}100 \cong 0.01$$

and

$$TEF = b/(b + c') = 10/10{,}010 \cong 0.001,$$

and the difference of the ratios at the two response levels is again approximately 10-fold. If the difference between the two potencies is much smaller, e.g., c is within an order of magnitude of a or b, the results differ. For example, if c" = 10, then

$$TEF = a/(a + c") = 100/110 \cong 1$$

and

$$TEF = b/(b + c") = 10/20 \cong 0.5,$$

about a 2-fold difference. In the general case, as c becomes very large with

respect to a and b, it will dominate the result of the ratios. In particular for such cases, the value of c may set the approximate order of magnitude of the ratio. For chemicals that are much less potent than TCDD, this fact may account, in part, for the observation that current TEFs have been reported to predict experimental results within an order of magnitude. Of greater importance, however, is that the current definition of a TEF may be more inaccurate (under these assumptions) when the chemicals of interest have potencies closer to that of 2,3,7,8-TCDD, especially for those chemicals whose potencies are within an order of magnitude of that of 2,3,7,8-TCDD.

3. Assumption 2: Dose-response Curves that Intersect

If dose-response curves are not parallel, they must intersect at some point. Two cases were considered: when the intersection is at the origin and when the intersection is not at the origin. If dose-response curves intersect at the origin and the dose-response curves are straight lines, then the relative doses required to produce a response will be linearly proportional, i.e., as with the current TEFs. If these conditions occur, then

$$Response_{other\ dioxin} = (k_{other\ dioxin})\ (Dose_{other\ dioxin})$$

and

$$Response_{2,3,7,8\text{-}TCDD} = (k_{2,3,7,8\text{-}TCDD})\ (Dose_{2,3,7,8\text{-}TCDD}).$$

For all response levels that are the same for the two chemicals, i.e., $Response_{other\ dioxin} = Response_{2,3,7,8\text{-}TCDD}$ and

$$(k_{other\ dioxin})\ (Dose_{other\ dioxin}) = (k_{2,3,7,8\text{-}TCDD})\ (Dose_{2,3,7,8\text{-}TCDD}).$$

Solving for $Dose_{2,3,7,8\text{-}TCDD}$ and substituting $TEF = (k_{other\ dioxin})/(k_{2,3,7,8\text{-}TCDD})$ produces the equation currently used, i.e.,

$$(Dose_{2,3,7,8\text{-}TCDD}) = TEF\ (Dose_{other\ dioxin}).$$

Because this is a condition for which the current TEFs are mathematically accurate, some implications of the assumptions are warranted. The majority of the data used for deriving TEFs are based on non-cancer endpoints. For these effects, the dose-response curves are usually not assumed to be straight lines that intersect the origin, the conditions under which the current form for TEFs was observed to be valid.

If the dose-response curves intersect, but not at the origin then: (1) the TEFs can not be simple linear ratios and (2) the rank order of the potencies may change with response level. If the dose-response curves intersect, the dose-response equations are

$$Response_{other\ dioxin} = (m_{other\ dioxin})\ (Dose_{other\ dioxin}) + B_{other\ dioxin}$$

and

$$Response_{2,3,7,8\text{-}TCDD} = (m_{2,3,7,8\text{-}TCDD})\ (Dose_{2,3,7,8\text{-}TCDD}) + B_{2,3,7,8\text{-}TCDD}$$

where m and B are the respective slopes and intercepts. For any response level that is the same for the two chemicals, then $Response_{other\ dioxin} = Response_{2,3,7,8\text{-}TCDD}$ and

$$(m_{other\ dioxin})\ (Dose_{other\ dioxin}) + B_{other\ dioxin} = (m_{2,3,7,8\text{-}TCDD})\ (Dose_{2,3,7,8\text{-}TCDD}) + B_{2,3,7,8\text{-}TCDD}.$$

Solving for $Dose_{2,3,7,8\text{-}TCDD}$ produces the equation

$$Dose_{2,3,7,8\text{-}TCDD} = \{(m_{other\ dioxin})\ (Dose_{other\ dioxin}) + B_{other\ dioxin} - B_{2,3,7,8\text{-}TCDD}\}/(m_{2,3,7,8\text{-}TCDD}).$$

Use of the equation above, while more complex than the current TEFs, is straightforward. If the dose-response curves were straight lines (as is assumed in this example), sufficient data should exist to determine the constants and solve the equation accurately for the 2,3,7,8-TCDD equivalent dose for all doses of most dioxin-like chemicals for any dose. As the dose-response curves are not straight lines, the equations will be more complex, but the analyses will be similar.

Finally, if the dose-response curves are not parallel and cross in the positive quadrant of the graph, another issue must be considered: the rank order of the two chemicals will reverse at the point of intersection. Therefore, the chemical which is more potent will be less potent after the dose-response curves cross. The issue of change in rank order is considered elsewhere.[2] Currently, the same TEFs are used for all toxic endpoints. The relative potencies of some of the isomers appear to change depending on endpoint. Two possible explanations for this observation

are that either the TEFs should not be the same for each endpoint and/or that the dose-response curves cross between the two response levels at which the different endpoints were measured.

4. Non-linear Dose-response Curves

The analyses above assume linear dose-response curves; the dose-response curves for dioxin-like chemicals are not expected to be straight lines. The procedures for analyzing non-linear dose-response curves is similar but mathematically more complex. Some concepts, however, can be inferred directly. If the dose-response curves are parallel, dose-additivity can not be a linear proportion of dose. If the dose-response curves are not parallel, they must cross. If they cross in the positive quadrant, the rank order of the potencies will invert at that point.

More mathematically accurate representations of the concept of dose-additivity are possible using available data. They are currently being developed. Preliminary analysis suggest that these toxicity equivalencies will not be point estimates, i.e., factors, but rather will be mathematical functions. Therefore, TEF may come to represent toxicity equivalency functions rather than toxicity equivalency factors.

5. Conclusions

Current TEFs may be significantly inaccurate under many conditions where they are used in risk assessments. The estimates would be expected to be least accurate for

those conditions where most of the calculated risk of a mixture is dependent on dioxin-like chemicals rather than 2,3,7,8-TCDD. Calculated risks would also be less accurate when the risk results from a sum of a relatively large number of small exposures, each of which is small compared with the dose at which the original TEF was estimated.

6. Acknowledgements

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7. References

1) USEPA (1994) : Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds. USEPA, Office of Research and Development, External Review Draft, June. EPA/600/BP-92/001a - c.

2) Putzrath, R. M. (1995) : Comparing Apples and Oranges: Combining Data on Value Judgments, Handbook of Environmental Risk Decision Making, (C. Richard Cothern, ed.), Lewis Publishers, Boca Raton, FL.