Analysis of Potential Confounding in Methylmercury Studies

Alan H. Stern, Dr.P.H., D.A.B.T.

Independent Consultant;

Adjunct Assoc. Prof., Rutgers. Univ. School of Public Health

The Particular Challenge in Deriving a MeHg RfD

- RfDs have traditionally (and to my knowledge) without exception been derived without explicit consideration of co-exposures
  - This is the case for the current RfD for MeHg
- This is a reasonable approach when:
  - exposure is not characteristically or consistently linked with a co-exposure

and/or

  - such a co-exposure does not confound the assessment of the chemical in quesiton

- For MeHg, these conditions are not met
  - In the U.S., essentially all exposures of concern result from fish consumption
  - All fish contain PUFAs (omega-3 fatty acids)
  - PUFAs from fish have beneficial DNT effects on the same endpoints the experience adverse effects from MeHg – negative confounding
- This is illustrated in the following figure (Stern and Korn, (2011)

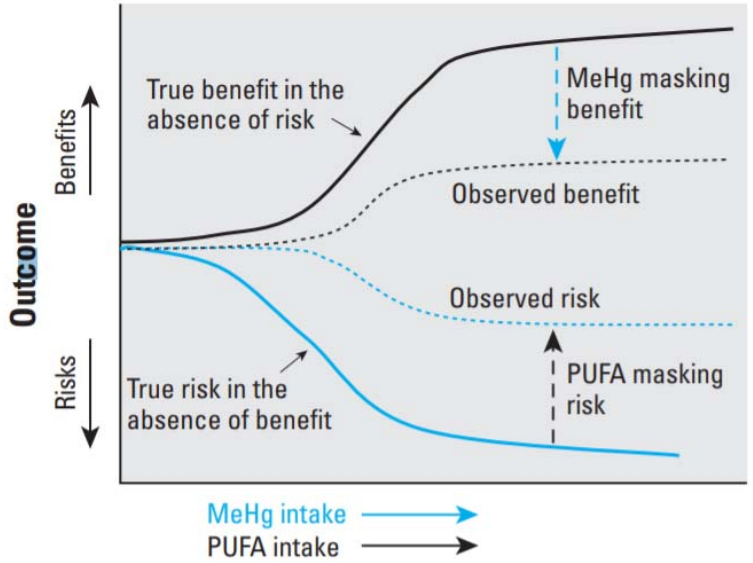

Figure 1. Negative confounding of MeHg risks and PUFA benefits.

The Problem in Deriving an RfD for MeHg

- As discussed in detail in Stern and Korn (2011), because of the almost universal occurrence of MeHg and PUFA co-exposures, it does not appear possible to obtain DNT effect data for MeHg that are not confounded by PUFA effects
  - With respect to the figure, the underlying adverse effect of MeHg will be masked by the beneficial effect of PUFA co-exposure
  - Only MeHg exposure from non-fish sources can provide “naked” (i.e., unconfounded) MeHg toxicity data
  - With one possible exception (see below) I am unaware of any useful data that can support such data
    - The Iraq poisoning data from grain are too imprecise (see NRC, 2000) to be useful

- The only possible exception to this is MeHg from rice exposure
  - This does not appear to be a significant source of MeHg exposure in the U.S.
  - This may, however, be a significant source of MeHg in some parts of China
  - However, the only MeHg DNT study in a rice-consumption population that I am aware of is Rothenberg et al. (2016)
  - However, this study has limitations for derivation of an RfD
    - The population size (n = 270 mother-child pairs) was modest
      - This is especially the case when considering those who did not also consume fish
    - The BSID assessment was conducted at 12 mos.
      - This did not permit assessment of cognitive endpoints previously found to be most sensitive to MeHg – language, attention
    - It is (to my knowledge) the only DNT study of a population with MeHg exposure from rice
      - Its accuracy and precision are difficult to assess

The Problem in Application of a MeHg-only RfD

- Even if an RfD could be derived that correctly addresses the DNT toxicity resulting from “naked” MeHg exposure, it is hard to see how it could be appropriately applied
- Since MeHg exposure in the U.S. is essentially from fish consumption, any useful application of a MeHg RfD would have to take co-exposure to PUFAs into account
  - Co-exposure to PUFAs will vary depending on the nature of an **individual’s** fish consumption
    - With respect to both frequency and type of fish consumed
  - Even for a given rate of MeHg intake, PUFA co-exposure will vary from one individual to another

- An RfD based on “naked” MeHg DNT effects if used for fish consumption advisories could result in uneccesarily limiting fish consumption
  - Because the beneficial masking of adverse MeHg effects by PUFA co-exposure would not be taken into account
  - Current fish advisories, based on the current RfD for MeHg, are derived from studies that reflect an unknown balance of MeHg and PUFA effects
    - That RfD was derived without knowledge of PUFA negative confounding
  - It is hoped that a new RfD could reflect the current state of knowledge about MeHg-PUFA balancing in U.S. fish consumers
  - This may involve re-thinking the nature and use of an RfD for the unique case of MeHg