TALKING POINTS FOR EPA IRIS WORKSHOP

SESSION ON "Advancing Dose-Response Analysis—Uncertainty (and Variability)"

Adam M. Finkel, Sc.D.

October 16, 2014

I plan to discuss six major themes; the outline below includes topics and examples for each theme.

1. ***IRIS Must Not Abandon its Primary Purpose as it Seeks to Evolve a Secondary Purpose.***

<u>If EPA is determined to create a repository for "gold-plated" potency values—a worthy goal that I support with one major caveat (see ** below)—it must *bifurcate* IRIS into two pieces, one that will contain the new values and one that maintains and **expands** the existing repository of "bronze-plated" values that are crucial for many regulatory, right-to-know, risk-risk, and other social purposes.</u>

- I agree almost completely with this observation by George Gray and Josh Cohen (*Nature,* 9/6/2012, pp. 27-28): "The slow pace of IRIS threatens public health… Rough-and-ready estimates are often sufficient for policy-making, and are better than nothing. IRIS should include information from private groups and other governments, and apply available techniques for calculating the risks of chemicals for which there are little data."

- My only quibble with their statement is with the last two words: EPA has <u>also</u> failed to add to IRIS potency estimates for many chemicals for which there are *ample* data! I will describe in some detail the case of 1-bromopropane, a rapidly-expanding substitute for (generally safer) chlorinated compounds. Various studies were completed more than 10 years ago showing frank human neurological effects at approx. 1 ppm, and a positive cancer bioassay was completed circa 2009 showing an eight-fold tumor excess at 62 ppm—and yet EPA has no IRIS entry for 1-BP, while occupational exposures above 50-100 ppm persist.

- ** I urge that EPA, along with the OMB Office of Information and Regulatory Affairs (and perhaps relevant Congressional committees), advocate for a clear "quid pro quo" that is needed to justify the resources and time spent on a new "gold IRIS": *if EPA is going to exhaustively consider every bell and whistle to arrive at a fully comprehensive and maximally participatory risk assessment, that assessment must be usable "off the shelf" by* ***any other federal and state agency conducting rulemaking.*** OIRA should issue guidance making clear that other agencies can use "gold IRIS" assessments without duplicating EPA's work, and Congress should make clear that, although plaintiffs should certainly remain free to challenge the details of a regulatory analysis in court, the fact that one agency used a "gold IRIS" assessment as its own should not be judicially reviewable *per se.*

2. ***EPA Must Not Ignore the Central Methodologic Recommendation of the NAS "Silver Book"—Move Away from Bright Line Reference Values (RfC/RfD) for Non-Carcinogens, in Favor of Estimating Dose-Response Functions.***

- The techniques and models for "unified" cancer/noncancer risk assessment recommended in the "Silver Book" 5 years ago were already 10-20 years old when the Committee recommended them. Reference values are of very limited use in risk assessment and regulation (they can provide no information about the benefits of reducing exposures that start and end on the same side of the "bright line"), and EPA's reliance on them (see theme #6 below) has popularized a false sense of security—exposures at the RfC/RfD are NOT "safe," but may represent roughly a 1-in-10 risk to substantial portions of the human population.

- If "gold IRIS" values are going to take years to develop, I see no excuse for not using the time to make them useful, by presenting probabilistic potency estimates for non-carcinogens, as well as dose-response functions (as opposed to scalar cancer potency factors) for carcinogens. I recommend presenting the 95th percentile upper bound and the expected value (NOT the median or some other bogus "best estimate") for the dose-response function for each substance.

3. ***EPA Can and Should Expeditiously Develop Common-Sense Procedures for Estimating and Communicating the <u>Parameter Uncertainty</u> in IRIS Potency Values.***

- Many long-time students of uncertainty recommend a conceptual separation between parameter and model uncertainty. Doing a good job on the former is helpful for communication and regulation, even though it is true that model uncertainty is "larger" and may remain difficult to quantify.

- For cancer risk assessment, quantifying parameter uncertainty now requires a *trivial* amount of thought and computation, and could have become routine at EPA roughly 30 years ago: Monte Carlo methods can easily propagate the uncertainty due to imprecision in curve-fitting to data, combining it with uncertainty due to animal:human adjustments and comparisons and other well-understood sources of parameter uncertainty.

- For non-carcinogens, the techniques recommended in the "Silver Book" easily lend themselves to quantitative analysis of parameter uncertainty (the population dose-response curves are basically *defined* by the imprecision in animal:human and interindividual differences.

- Even if EPA persists in using reference values, the raw material for reporting the central and upper tendencies of each *adjustment factor* already exists. I emphasize that the factors of 3 and 10 used in "old-style" non-cancer risk assessment are NOT "uncertainty factors" (nor, needless to say, are they "safety factors")—they are adjustment factors that *map* the high risk at the NOAEL onto an equivalent (high) risk for the typical or the susceptible human—but they CAN be *surrounded* with the uncertainty inherent to each adjustment!

4. ***EPA Can and Should Adopt the NAS "Silver Book" Recommendations to (Finally!) Take Account of Interindividual Variability in Susceptibility to Carcinogenesis.***

    - Non-cancer risk assessment *may* adequately account for most of the outbred and highly variable human population via the intraspecies factor of 10. For decades, evidence has accrued that with respect to susceptibility to cancer, the human population is substantially *more* heterogeneous than a factor of 10 above the median, but EPA persists in taking NO account of this in cancer risk assessment. The NAS Committee recommended that EPA adjust its individual-risk estimates for cancer upwards by a factor of from 10- to 50-fold to make these estimates appropriate for reasonably more susceptible individuals. It also recommended that EPA adjust its *population* risk estimates (not currently applicable to IRIS) upwards by roughly 7-fold, to account for a mathematical property of the interindividual distribution of susceptibility (the expected value exceeds the

median value by roughly this amount). I will briefly summarize the history of EPA's "explanations" for avoiding this crucial issue.

5. ***The Problem of <u>Model Uncertainty</u> is More Perilous—EPA Should Publish Multiple Potency Estimates when Two or More Fundamentally Irreconcilable Models are Sufficiently Plausible—but should not Abandon its Evidence-Based Default Models while it Awaits Sufficient Evidence to the Contrary.***

- EPA's recent statements about the need to "reduce reliance on defaults" and "replace defaults with data" are inappropriate (the former) and nonsensical (the latter). Chapter 6 of **Science and Decisions** explains the Committee's views about why a system of defaults, and a clear process for overturning them WHEN sufficient and reliable evidence to the contrary accrues in a particular case, remains important despite EPA's confusion. It also contains a long footnote dissecting the illogic of pitting defaults against "data"—in a nutshell, the defaults are *based* on substantial theory and evidence already, and any new data must be evaluated for whether it *supports a model or assumption* that conflicts with the default.

- A responsible science and public-health agency would never seek to "reduce reliance on defaults" as a goal in itself, but would seek to reduce reliance on *those* defaults that are deemed incorrect or inappropriate, either in general (calling for a revised default) or in specific cases (calling for, e.g., a case-specific mode of action to supplant the generic default). The NAS "Blue Book" (20 years ago), as well as the "Silver Book," called on EPA to develop clear evidentiary criteria to judge the plausibility of alternative assumptions for the 3-5 recurring controversies in risk assessment (relevance of animal effects to humans, interspecies dose adjustment, MOAs leading to non-linearities, etc.)—to date, the Agency has not made much progress here.

- Indeed, IRIS has always been built around an unstated, and *"anti-conservative"* default—that the potency value for a sentinel effect can be used for standard-setting. This is a perfectly sensible short-cut, but we must understand that IRIS values are *by definition* not useful for risk estimation, because here [potency times exposure] does not equal risk, but *the risk of a single effect out of many.* So I see no reason why these default-based values cannot also be constructed from sensible default assumptions about the models and mechanisms usually appropriate to make such estimates.

- If EPA wants to communicate something about model uncertainty, it should by all means do so—but NOT by averaging irreconcilable models together into some happy-faced hybrid. If there is real controversy about whether the potency values under default assumptions are incorrect, in light of a well-constructed alternative theory, EPA should certainly present multiple potency estimates, and could even use expert judgment techniques (carefully!) to give some sense for the relative weights that experts place on the competing theories.

- Model averaging techniques are, however, less inappropriate and subject to mischief when functional forms are being compared and objective criteria (e.g., the AIC or entropy) are used to inform the weighting process.

6. ***The Workshop Question About the Problem of Estimates being "Overly Conservative" Reveals Inappropriate Bias—Current IRIS Estimates are in Some Important Respects not "Conservative" AT ALL.***

Proper uncertainty analysis will reveal to what extent current point estimates of potency are in fact "conservative" at all. But if EPA persists in using point estimates, why assume that we must keep vigilant lest they be "overly conservative"?

- Current IRIS values for carcinogens *may* indeed be conservative for the typical person, but they cannot (except by accident) be conservative for the millions of humans whose susceptibility exceeds the typical value;

- As mentioned above, the risk of the most sensitive effect is by definition greater than the risk of all other effects—but by the same token, the risk *posed by the substance* is by definition SMALLER than the risk of its sentinel effect only;

- The RfCs are not necessarily "safe" or conservative. They are derived off of the NOAELs (or adjusted LOAELs), which are clearly not "safe" levels. Extensive comparison with a large suite of Benchmark Dose values (see, e.g., Wignall et al. *Environmental Health Perspectives*, 122(5): 499-505, May 2014) now confirms what theory always dictated anyway—the risk at the NOAEL is approximately 5-10%. So even a factor of 10x10 below the NOAEL, in real situations where the average human is indeed 10x more sensitive than the average rodent, may pose a 5-10% risk for real humans who are 10x more sensitive than the average

> human. The "adjusted NOAEL" (the RfC) may be an exposure posing unacceptably high risk.

Again, I agree with Gray and Cohen on this most fundamental point: "The EPA's definitive values are illusions: they conceal uncertainty that cannot be resolved scientifically." The first step is to draw back the curtain on uncertainty, and not to draw back only the parts of it that would support the preconception that the illusory values are overestimates, rather than underestimates of risk.