Even though the NAS, in its 2006 report, *Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment*, stated that “the current weight of evidence on TCDD, other dioxins, and DLCs carcinogenicity favors the use of nonlinear methods for extrapolation below the point of departure (POD) of mathematically modeled human or animal data,” EPA has chosen to use linear extrapolation methods in its latest external review draft. There is disagreement between EPA and the rest of the scientific community on the use of linear (no threshold) vs. threshold models and the following comments are provided in support of the NAS assertion that dioxin is a threshold carcinogen.

The effects of all chemical, biological and physical agents (and combinations of these) have two things in common. First: all of the effects that they produce are the result of an interaction between the agent and a target and we define this interaction as the exposure. We can define each agent by the effects it is capable of producing and the target by its susceptibility to these effects. It is evident that if any of these (agent, target or exposure) is missing, there will be no effect. It is also evident that even if the agent is capable of producing an effect to which the target is susceptible, the exposure must be sufficient to produce the effect. When the exposure is just sufficient to produce a specific effect in the target, we have defined a threshold for the effect even if we can’t measure it. The bottom line here is that we should focus on the measurement problem which requires dose response data rather than arguing about whether or not biological agents have thresholds.

The second thing that these agents have in common is that all of their effects result from an action of the agent on the target (dynamics) or from the action of the target on the agent (kinetics). Thus the key or rate limiting events that we use to define the mode of action must occur in the dynamic or kinetic pathways. We focus on injury and recovery for events in the dynamic pathway (effects) and on uptake and elimination for those in the kinetic pathway (exposure). Distinguishing the key events that occur in the dynamic pathway from those occurring in the kinetic pathway is a critical first step for defining the exposure and effects thresholds and the mode of action of the biological effect.

These observations are applications of general biologic principles but extending them to the “real world” situation can be complicated. For example, the main factors of exposure are dose and time but there are other factors such as the route and the presence of other ingredients (vehicles, adjuvants etc.). Dose can be a simple variable such as mass or surface area (nanotechnology) but time includes not only the exposure duration and frequency but also the persistence of the agent (kinetics) and its effects (dynamics). Agents may be mixtures not only of chemicals but also of pathogens, radiation etc. Targets can range from genes to cells to organs and systems and from individuals to populations. Most agents exhibit multiple effects with increasing exposure (therapeutic versus toxic doses, hormesis) and targets may exhibit adaptation or altered susceptibility with repeated exposure (allergens). For most chemical agents, recovery is slower (and therefore rate limiting) than injury in the dynamic pathway and elimination is slower than absorption (and therefore rate limiting) in the kinetic pathway. In the dynamic pathway injury can be reduced by adaptation and recovery is modulated by repair, reversibility and adaptation. Distribution, biotransformation and excretion are the major factors in the kinetic elimination pathway of chemicals. With pathogens, the rate of multiplication and the host defenses of the target can influence both the dynamic and kinetic pathways. Exposure to physical agents (radiation, heat,
vibration, noise etc.) introduce new exposure units. Emotional stress can also produce adverse effects and there is growing pressure to recognize behavior, dietary, life style and other environmental factors as adverse effect agents. Since all such biological actions are chemically mediated the basic principles would still apply despite exposure and mechanism of action differences.

With this approach, it is evident that there is no effect if the agent, target or exposure is missing and it is equally evident there are exposure and effect thresholds for each combination of agent(s) and target(s) when the homeostatic capability of the system is exceeded. A log probit plot or a log normal plot plus the Gaussian distribution can be used to identify the individual thresholds and estimate the relative risks in a population or an individual. Risk assessors recognize that the exposure factors of dose and time are inversely related (Haber’s rule) and that under conditions of continuous exposure, plotting equivalent combinations of these factors yields a line with a slope of -1. The ends of this line are defined when further increases in either factor no longer reduces the amount of the other factor required to produce the response. This defines both the dose and time thresholds for the biological effect. Biological effects do not occur with less than one molecule of agent and they all require finite times so there are absolute none zero dose and time thresholds. Thus any risk assessment model which extrapolates either the dose or the time to zero is flawed.

Two things that would help us address the current challenges in risk assessment are first; updating our definition of adversity and second; developing methods for quantifying benefits to the same level of sophistication as currently exists for risk. This would enhance the utility of the benefit/risk ratio as a regulatory approach.

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We would like to offer the following three questions to the EPA Panel which is evaluating the EPA’s Reanalysis of Key Issues Related to Dioxin Toxicity and Response to the NAS comments.

1. Did the EPA document respond adequately to the NAS panel 2006 recommendation to use a threshold basis for the cancer risk assessment of dioxin?
2. Did the EPA document use the best available data to establish the reference dose for dioxin?
3. What specific recommendations would you make to help the agency resolve the controversial issues associated with the risk assessment of dioxin?

Sincerely;

William Waddell, MD

John Doull MD, PhD