Comments of Michael L. Dourson, Ph.D., DABT, ATS to the Science Advisory Board of EPA Regarding the IRIS Assessment of Acrylamide

Good morning. I am Michael Dourson, a board certified toxicologist that has studied the human risk from chemical exposure for 28 years, more than half of this time with EPA.

I speak on behalf of Toxicology Excellence for Risk Assessment (*TERA*), a Cincinnati-based nonprofit corporation with a mission to protect public health. *TERA*'s comments and effort at this meeting are self-supported, but the research described has been sponsored by a number of food industries. Our organization also does work with EPA. I am more than happy to disclose more information about any of this work afterwards.

We recently developed a detailed dose response assessment on thyroid tumors for acrylamide. This text has been submitted to Regulatory Toxicology and Pharmacology, who gave us permission to share it as part of our written comments. We are continuing our research on mammary tumors and TVMs and will share this also.

We agree with EPA that acrylamide shows an increase in both DNA synthesis and DNA damage, indicating that DNA reactivity and cell proliferation may both contribute to acrylamide's carcinogenicity. In fact, EPA's statement should be enhanced by a more thorough consideration of alternative MOAs rather than the simplistic and overly broad categories of "genotoxicity" and "hormone-related." We have done such analyses for thyroid, TVM and mammary tumors. Our conclusions are that multiple modes of action (MOA) are occurring with these tumors and that for the thyroid, these MOAs can be "decoupled" (an EPA word) to support a more accurate dose response assessment.

We agree with EPA that attempts to quantify mutagenic dose response are clearly in the right direction. Our paper shows such a quantification---which does <u>not</u> support dose response concordance among thyroid tumors and 10 *in vivo* surrogates of possible mutagenicity. This same conclusion would apply to TVM and mammary tumors.

We find EPA's non-cancer dose response to be nicely done, and mostly agree with EPA's selection of critical effect, BMD modeling and selection of point of departure, choice of uncertainty factors and description of confidence. We encourage EPA to more closely study whether the default 10-fold uncertainty factor for human variability is sufficient, especially if acrylamide is the likely toxic moiety for noncancer effects, because kids will likely have more acrylamide available than adults at administered dose.

We find EPA's combination of mammary tumors for hazard identification inconsistent with its prior decisions (e.g., EPA's hazard identification for atrazine). In addition, certain statements on statistical significance need to be rechecked with the studies.

We do not understand EPA's statement that brain tumor incidence rates should have been more fully documented in the Friedman et al. (1995) study. All brains were evaluated in females and in control and high dose males. As EPA knows, it is a standard operating

procedure to analyze intermediate doses if the high dose shows an increased incidence (it did not in Friedman et al., 1995). We agree with EPA that Friedman et al. (1995) could have done a better job in the reporting of spinal cord tumors, but do not see a higher incidence of tumors in this latter organ with the available data.

We disagree with EPA's combination of thyroid and TVM tumors for dose response assessment based on two observations. First, the MOAs of these tumors are clearly different as shown in our written public comments. Second, a screening level comparison of TVM incidence in humans, and quantitative linear extrapolation of these tumors from rats using human exposures, is disparate by several orders of magnitude. Since human and rat TVMs are biologically comparable and since both are exposed to acrylamide, this rat quantitative comparison is not appropriate for humans.

We disagree with EPA's mortality adjustment for thyroid tumors in the Friedman et al. (1995) study, since our analysis of raw data does not show any consistently lower or higher tumor incidence in rats dying more than one month prior to, or at, terminal kill.

Contrary to a statement in EPA's acrylamide text that only two approaches for calculating the risks with multiple tumor sites exist, EPA's cancer guidelines actually provide 6 ways to combine tumor incidences. Combining data from different studies in a joint analysis (one of these ways) allows a quantitatively extrapolation that includes more biology. A dose response assessment curve with 19 data points is possible, which enables the MOA "decoupling" concept of EPA to be further investigated. Support for this decoupled MOA and joint analysis is shown in our written comments.

The rat chow in both Johnson et al. (1986) and Friedman et al. (1995) very likely contained acrylamide. We estimated control "doses" using FDA data. This gives 6 additional low doses for modeling, which allows a Benchmark Response Rate (BMR) that is lower than the default 10% BMR EPA chose. In fact, EPA (2005) guidelines suggest using the lowest BMR, that is consistent with the data. EPA's choice of a 10% BMR is not consistent with the available data.

Lastly, we were perplexed with EPA's early life stage risk adjustment. A reasonable conclusion from its analysis is that neonates are less sensitive than adults to developing cancer, because they make less glycidamide, the known genotoxic metabolite. Several studies in humans that show CYP2E1 levels to be absent or minimal during gestation, followed by a rapid increase immediately following birth, and then a gradual increase. In addition, EPA (2005) guidelines states that "…metabolic capacity with respect to P450 enzymes in newborn children is extremely limited compared to that in adults, so that a carcinogenic metabolite formed through P450 activity will have limited effect in the young. Thus, an adjustment to the cancer slope factor for early life exposure is specifically <u>not</u> needed.

On behalf of *TERA*, we appreciate EPA's draft and thank you for the opportunity to help.

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