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Dr. Thomas Armitage, DFO
EPA Science Advisory Board Staff Office

Dear Sir:

As a former member of the 2006 NAS panel, *Committee on EPA's Exposure and Human Health Reassessment of TCDD and Related Compounds*, I agree with the opinion expressed by another former panel member, Joshua Cohen, during the June 24 Science Advisory Board (SAB) public teleconference. EPA's latest revisions to the draft dioxin reassessment ignore key recommendations of the NAS panel.

In its 2003 draft reassessment, the EPA chose to use a linear model to estimate risk at low doses of dioxin exposure. In the 2006 NAS report, *Health Risks from Dioxin and Related Compounds Evaluation of the EPA Reassessment*, we clearly 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. However, in its latest external review draft, *Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments*, EPA once again chooses to adhere to its favored linear extrapolation approach.

EPA states that the 2005 Cancer Guidelines "recommend that the method used to characterize and quantify cancer risk from a chemical be determined by what is known about the mode of action of the compound and the shape of the cancer dose-response curve," and that "the linear approach is used if there is sufficient evidence supporting linearity or if the mode of action is not understood." EPA then defends its decision to use a linear method by arguing that "the mode of action of TCDD induced carcinogenesis beyond potential AhR activation is unknown," and that, therefore, "in the absence of sufficient evidence to the contrary or evidence to support nonlinearity, to estimate human carcinogenic risk associated with TCDD exposure EPA assumed a linear low-dose extrapolation approach."

In arriving at this position, EPA is ignoring considerable information on mode of action (MoA) provided in the NAS report (p113-118). These include the findings of liver oxidative stress, liver toxicity and increased liver cell proliferation at doses of TCDD associated with liver tumor increases in rats. Such effects are established to have liver tumor enhancing effects in rodents. Importantly, these effects do not occur at low doses in rodents and certainly would not occur at the even lower

exposures of humans or else there would be clear evidence of liver injury in exposed populations.

In conclusion, EPA is continuing to pursue, without adequate justification, a risk assessment approach which has been widely challenged by knowledgeable scientists.

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