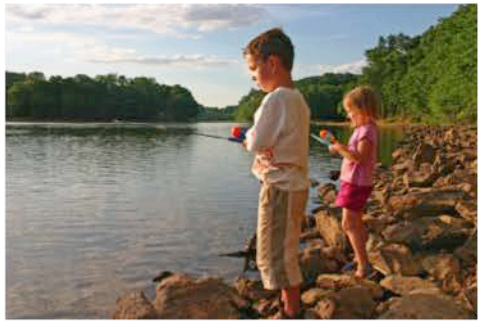



Comments on NTP Technical Report on the Toxicology Studies of TBBPA

Dr. Daniele Wikoff
ToxStrategies
October 29, 2013

ToxStrategies

Overview of comments

1. **Liver tumors observed in the 2-year study**
2. **Uterine tumors (and gene mutations) observed in the 2-year study**
3. **Impact of the selection of dose levels in both the 90-day and 2-year study**

Oral presentation covers both sets of written comments submitted on behalf of the American Chemistry Council's North American Flame Retardant Alliance(NAFRA)

Hepatoblastomas in male mice

"The level of evidence of carcinogenic activity for male mice receiving Tetrabromobisphenol A should be "Equivocal evidence" and not "Some evidence" as indicated in the draft Technical Report released for Peer Review on October 29, 2013" - Dr. James Popp, D.V.M., PhD

Key findings related to hepatoblastomas

1. **Hepatoblastomas should not be considered as a separate tumor type**
2. **Hepatoblastoma incidence should not be used as an independent or sole basis for determination of level of evidence of carcinogenicity**
3. **The evolving increase in incidence of spontaneous hepatoblastomas make comparison of incidence in the treated groups in the current study of questionable relevance**
4. **Data from all groups should be considered in the evaluation of a carcinogenic response**

Historical incidence of uterine tumors in female Wistar Han rats

Shortcomings in the comparison of the uterine tumor incidence to historical controls

Comments

1. No comparable (same route of administration) NTP historical control data for Wistar Han rats used in the 2-year study
2. No historical control data for the longitudinal review used to characterize uterine tumors

Clarifications requested:

- Clear indication that meaningful comparisons to historical control data cannot be made
- Clarify which specific data are used as the basis for historical control comparisons
  - Provide all historical control data in the report or make such data publicly available

Limitations in the evaluation and interpretation of the Tp53 mutation data

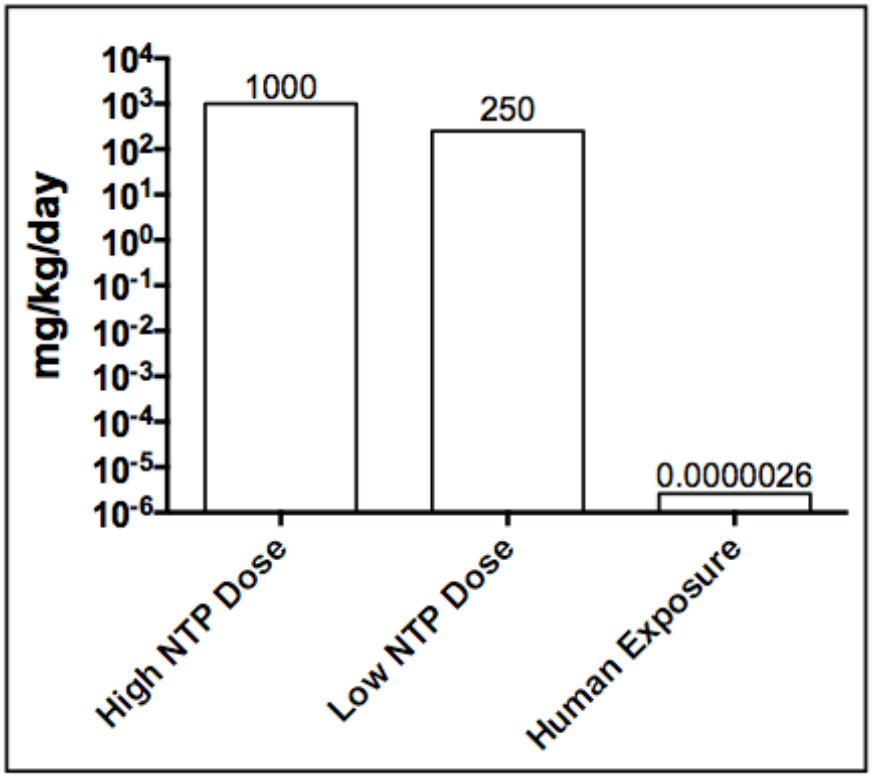
Overall conclusion: the shortcomings with the methods and data handling need to be addressed before the data can in fact be used to support the conclusions purported for the mutation analysis.

1. **The findings from *Tp*53 mutation assay are all not statistically significant when the dose groups are evaluated separately**
2. **An independent *post hoc* analysis that accounted for Type 1 errors (the NTP analysis did not) indicated that the mutation incidence was not statistically significant**
3. **An independent analysis in which all mutation types were accounted for (NTP did not account for all mutation types) resulted in an increased incidence of background mutations**

Limited relevance and unclear impact of NTP study dose levels

Even the lowest doses tested were substantially higher than is human exposure and therefore it is difficult to accurately extrapolate the findings in this study to humans, particularly considering the uncertainties as to how the high doses where adverse effects were observed in the NTP study may have perturbed normal physiological functions and protective mechanisms.

- Historically, the NTP has avoided discussions related to risk assessment in the technical reports; however, in the case of TBBPA, there is a fair bit of speculation related to human risk.
- It is requested that the points in our written comments regarding the lack of relevance and unclear impact of the NTP dose levels be addressed in the report if such discussion remains.



ToxStrategies