

**Comments on  
NTP-CERHR Expert Panel Report (June 2004) on the  
Reproductive and Developmental Toxicity of Acrylamide**

*Submitted to*  
Center for Evaluation of Human Risk to Reproduction (CERHR)  
National Toxicology Program  
ATTN: Dr. Michael Shelby

*by*  
*The Sapphire Group, Inc.*<sup>1</sup>  
Bethesda, Maryland

*On behalf of*  
Snack Food Association  
Alexandria, Virginia

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<sup>1</sup>These comments are attributed to Robert G. Tardiff, Ph.D., ATS, and Christopher Kirman, M.S., 3 Bethesda Metro Center, Suite 830, Bethesda, MD 20814.

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The National Toxicology Program (NTP) is commended for having prepared a thorough, thoughtful, and sound report of the data on reproductive and developmental toxicity of acrylamide. Furthermore, the process by which this report was prepared, including the public meeting, is a tribute to NTP's commitment to be fair and open in considering the views of many types.

For the final report entitled, "*NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Acrylamide*," we ask NTP to consider some additional modifications that, in our view, would be particularly important to those who use the document's contents, particularly for the estimation of risk to the reproductive health of those exposed to acrylamide in the workplace as well as in other walks of life.

Specifically, we recommend some changes to the text in the box found on page 145 of the subject report.

The text of the sentence of lines 15-16 in question states:

*"Such effects [genetic alterations to male germ cells] can lead to genetic disorders and infertility in subsequent generations."*

First, the verb "can lead" should be changed to "may lead" since such an outcome has not been shown to occur. Furthermore, should such a consequence indeed be manifest, it would likely be dose-dependent, and it may not be operational at all dose rates below those that produced genetic alterations under laboratory conditions. The verb "may lead" conveys a stronger sense that certain conditions would need to be met for the event to occur, and that sense is most fully consistent with not only the data on acrylamide but with the broader understanding the ways in which genotoxic chemicals can be harmful at high doses but be of little or no threat to health at considerably lower doses.

Second, the words "and infertility" should be deleted since the impact of a theoretical heritable change will depend upon which part of the genome is affected, and that this would involve the parts of the genome that are important for fertility is pure speculation at this point.

Third, some further clarification of the sentence noted above should be provided to the reader to convey the full range of understanding. Notably, the issue of acrylamide's potential to produce reproductive effects in subsequent generations and the concept of "genetic risk" needs to consider the mode of action, of which there are at least three: (1) epigenetic (protamine binding & neurotoxicity) which is described in detail by Tyl *et al.* (2003); (2) genetic (*i.e.*, mutations); and (3) genetic (*i.e.*, reciprocal translocations). Each of these modes shares sources of nonlinear kinetics associated with acrylamide metabolism (*e.g.*, saturable

metabolism, sulfhydryl depletion) that while complicating low-dose extrapolation, are also consistent with the presence of biological thresholds.

With respect to these modes of action, agents can be classified into three categories: (1) N-alkylating agents, like glycidamide, that are readily repaired (nonlinear dynamics consistent with biological thresholds); (2) O-alkylating agents, that are repaired slowly, and are, therefore, more potent (not known to be applicable to acrylamide/glycidamide); and (3) agents producing structural changes (which relate to the protamine binding mechanism as described for acrylamide) that generally exhibit a small dose range, only producing effects at toxic or near-toxic dose levels which are also consistent with biological thresholds (Vogel *et al.*, 1998).

The dose-response relationship for heritable translocations induced by acrylamide in mouse spermatids is nonlinear (Adler *et al.*, 1994). By analogy to acrylamide (via glycidamide formation), ethylene oxide produces reciprocal translocations, which by its nature is nonlinear with dose, and risk is likely to diminish by the square of the dose as suggested by the work of Preston *et al.* (1995). Thus, this mode of action, when applied to acrylamide would support a greatly diminished likelihood of producing trans-generational adverse effects via alteration of sperm.

A threshold for heritable translocations likely exists, below which the genetic risk is negligible. A NOAEL for dominant lethal mutations was reported by Tyl $\acute{a}$  *et al.*, 2000; this event would likely occur by the same mechanism that would theoretically produce heritable changes, and, therefore, is consistent with a biological threshold for heritable changes.

This information should be incorporated into the subject text to provide the reader with a realization that trans-generational toxicity will not necessarily result at the relatively doses encountered by humans in the general environment.

Furthermore, the sentence on lines 19-21 of this text box on page 145 should be clarified. Presently, the sentence reads:

*“However, considering the incidence in treated and control animals of the response detected for heritable translocation at the lowest level tested (40 mg/kg bw/day  $\times$  5 days), it is likely that such effects would occur at lower dose levels.”*

As stated the sentence may be interpreted to mean that these adverse effects will be manifest 20 mg/kg bw/day as well as 20 ng/kg bw/day. While the former may be correct, the latter is not supported by the broader data demonstrating the presence of assorted defense and repair

mechanisms that would reduce considerably the likelihood of any injurious genetic alterations in the first place and of dissemination of unrepaired genetic damage from one generation to the next at a dose rate six orders of magnitude below the observation range.

Further down, the text states,

*“Such risks were not considered by the Expert Panel in their evaluation of LOAELs because of the lack of testing at low dose levels where reproductive and developmental effects are observed.”*

This sentence is internally inconsistent in citing a “lack of testing” where “effects are observed”, which at a minimum should be revised to state where “effects may be observed”. More importantly, the statement is inconsistent with the one stated on page 33 of the report where the Dearfield *et al.* assessment is described,

*“The Expert Panel chose to place very little weight on the estimated risks due to the uncertainties associated with the assumptions employed”*

This statement indicates that such risks were considered by the Panel, but were considered to be too uncertain. This concluding section should be revised to be consistent with the earlier statement.

We hope that these suggested modifications will be of value as NTP completes this important document.

## *References*

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