

TENTATIVE TALKING POINTS for NATIONAL TOXICOLOGY PROGRAM'S  
PEER REVIEW OF THE CARCINOGENICITY OF 1-BROMOPROPANE

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**1. Personal Background:**

- In 1999, when I was the Director of Health Standards Programs for OSHA (during the five years that I was the Department of Labor's voting representative on the NTP Executive Committee), I nominated 1-BP for short- and long-term testing. Nearly fourteen years later, the carcinogenicity bioassay and other tests have been completed, analyzed, and vetted through several groups. During this time, worker and general-public exposures to 1-BP have increased dramatically.
- I have more than 25 years experience pioneering methods of quantitative risk assessment currently in use, especially for dose-response assessment and quantifying the uncertainty and interindividual variability therein. I am one of three individuals chosen to serve on both the National Academy of Science's "Blue Book" (1994) and "Silver Book" (2009) reviews of risk assessment methods and policy.

**2. Summary:**

- Today's proceeding is first and foremost a *hazard identification* determination: is the agent capable of causing neoplasms in humans? Questions of risk, potency, and exposure are secondary to this determination and should not be invoked to divert NTP from the task at hand. However, if others bring up risk and exposure I would hasten to point out that NTP has in effect conducted a "low-dose bioassay," in the sense that many workers are currently exposed to airborne levels of 1-BP comparable to, and in some cases *exceeding*, the 62.5 ppm exposure that caused an eight-fold excess of lung tumors in female mice as compared to control animals. (See part 3 of these talking points.)
- In my expert opinion, 1-BP has clearly been shown by NTP to be an animal carcinogen, and therefore should *at least* be classified as "reasonably anticipated." The NTP listing criteria require this outcome: 1-BP produced neoplasms in multiple species of test animal, at multiple sites (the criteria only require multiple sites "*or*" species—this is an "*and*" finding). The seriousness of the current occupational risks (exposures in relation to frank-effect levels in the bioassay) does make it important for NTP to conclude this lengthy process expeditiously.

- I say “at least” because the listing criteria for “known” anticipate that some substances will be so classified absent traditional epidemiologic findings, but in the presence of compelling *in vitro* evidence in humans. I am not recommending NTP consider upgrading to “known” at this time; I simply observe that the NTP bioassay (and other experiments; see e.g. Anderson et al. 2010) establishes that 1-BP causes immunosuppression in rodents. Human *in vitro* studies of immunosuppression, and improved bioassays that do not bias against the development of lymphomas (Strauss and Heiger-Bernays 2012), may provide the kind of mode of action (MOA) support needed to classify 1-BP as “known” while we await the statistical power and latency needed for traditional epidemiology to be useful in cases such as these.

### ***3. Irrelevant and/or Incorrect Arguments Against Classification:***

As of March 20, only two written comments have been posted for this substance: both are without merit and should be ignored. I am aware of other arguments that may be raised again in this forum, so I will rebut those as well.

Most generally, I’m confident that the Panel understands well the role of ancillary data, particularly purported MOA data, in an NTP classification proceeding: the listing criteria make clear that it is permissible to ignore sufficient and positive bioassay data **only** if there exist “compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.” Note especially the word “compelling” and the qualitative nature of the words “do not operate.” Any theories and “findings” presented in an attempt to cast doubt on the bioassay results must be “compelling” and must be sweeping—no “weaker in humans than in animals,” or “may be safe at very low doses,” or “may not operate in some human subpopulations” will do.

*But in this case, nothing even vaguely resembling a “compelling” or qualitative argument has been offered, so your decision to classify is an uncomplicated one:*

- Dr. Smith (Albemarle Corp.) writes that 1-BP is not mutagenic, and therefore has a threshold. This is incorrect, misleading, and irrelevant: (1) as the NTP monograph makes clear, 1-BP is mutagenic in various tests that were not made invalid by poor experimental conditions; (2) there are, of course, “reasonably anticipated” and known human carcinogens that have not been demonstrated as mutagenic in standard assays; (3) there is no logical connection between non-mutagenicity and the existence of a threshold—either can apply without the other; (4) the presence of an individual threshold for an adverse effect does not imply that there is a population threshold, or that the latter won’t be far below the former (see Chapter 5 of the NAS “Silver Book”); and (5) the listing criteria are oblivious to the possibility of a threshold—again, you are engaged in a hazard identification determination, not a quantitative risk assessment.

- Most importantly, I find it offensive to posit a threshold, and to strongly imply that the “very low levels” of worker exposure are below such a (purported) threshold, in light of the *actual* levels of current and recent worker exposures, which are known to EXCEED the level (**62.5 ppm**) shown to cause an 18 percent incidence of lung neoplasms in female mice (as against a 2% control incidence). From Dr. Smith’s letter, one might think 1-BP might possibly be “non-carcinogenic” because the bioassay doses were so far above actual workplace conditions, unless one bothered to look at the actual human exposure data. For example, Blando et al. (2010) measured 8-hour personal 1-BP exposures (N=14) at three dry cleaners, and found concentrations ranging from non-detect to 55 ppm. Nine of the 14 measurements were within an order of magnitude of the bioassay dose (that is, above 6.25 ppm). An earlier study (Majersik et al. 2007) found an *average* 1-BP concentration of 130 ppm. *Statements from the 1-BP manufacturers themselves indicate that workplace exposures can be higher still than these worrisome levels.* A report prepared for Enviro Tech International (Stelljes 2010) states that “the ‘high end’ of human occupational exposure, based on the above information, is in excess of 100 ppm” (page 7 of report).<sup>1</sup> And Albemarle Corp. itself has submitted data to EPA, indicating that of 34 measurements made at customers of theirs, 1-BP concentrations ranged from 5 to 108 ppm. Referring to the Smith comment, I urge the panel to ignore any such brazen discussion of a threshold for this substance, in light of the lack of evidence for it and the fact that exposures are often so high with respect to bioassay doses that human risk assessment will involve *interpolation* from the bioassay NTP conducted, not extrapolation at all!
- There may be arguments raised about rodent:human site concordance (purported lack thereof). Again, such arguments will be far from “compelling,” and will in my experience ignore the large literature on this complex issue.

Thank you for the opportunity to present my views on this matter. I am presenting them on my own behalf and on my own time: any mention of my academic affiliations is for purposes of identification only.

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<sup>1</sup> Indeed, Stelljes claims in that report that Majersik et al. *underestimated* actual workplace exposures: “Concentrations estimated in the Utah study four days later, after air exchange was implemented by installing large fans, averaged about 130 ppm, with some concentrations as high as 176 ppm. Therefore, it is likely that actual exposure concentrations during the time the affected workers were engaged in their activities were substantially higher than these estimates.” (p. 4 of Stelljes 2010).

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