# UPDATE ON A SAFE OCCUPATIONAL EXPOSURE LEVEL FOR 1-BROMOPROPANE

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## Executive Summary

This paper re-evaluates EnviroTech Europe's (ETE's) current occupational exposure level recommendation of 100 ppm for 1-bromopropane (1-BP) [106-94-5] in the vapor degreasing industry in light of the recent lowering of the ACGIH Toxicity Threshold Value (TLV) from 10 ppm to 0.1 ppm. The 0.1 ppm value is based on a study of 86 workers exposed to 1-BP during its manufacturing in China in four different facilities. The authors reported significant effects at all 1-BP exposure levels down to 1.28 ppm. The 1-BP in these facilities had concentrations of the isomer 2-bromopropane [75-26-3] (2-BP) present as a contaminant at about 10-20 times the level sold for vapor degreasing.

There are several factors that undermine the conclusions reached in the paper that a concentration of 1.28 ppm resulted in toxicity in exposed workers. These factors were related to:

(1) Exposure measurements – passive rather than active samplers were used, and concentrations varied by more than tenfold for the same activity.

(2) Exposure via other routes in addition to inhalation – described worker activities indicate substantial dermal exposure, which increases the overall dose of the chemical relative to just inhalation exposure.

(3) Exposure to other chemicals – at least 20% of the workers were previously exposed to 2-bromopropane (2-BP), and no testing was done for other chemical exposure.

(4) Statistical methods and interpretations – instead of using paired patient-exposure data, authors categorized exposure into groups (e.g., high, low); this resulted in apparent statistical relationships that may not be biologically relevant.

(5) Lack of robust dose-response relationships – when evaluating typical dose-response relationships, only a single parameter (vibration sense in the toes, a subjective parameter) was shown to be significantly different across all dose levels.

(6) The outcome of the subjective vibration sense test was in part dependent on the testing doctor – this dependency should remove the test and its results from consideration in the paper as a scientifically defensible endpoint.

When all of this information is considered as a whole, it is unlikely that the 1.28 ppm lowest effect concentration reported in the paper is accurate. The interpretations in the Li et al. study are inconsistent with expectations based on the ways in which 1-BP acts in rodents relative to humans. Studies on how 1-BP acts in the body of rats and mice and studies on metabolism of the chemical in humans indicate that humans should be no more sensitive to 1-BP than either of these rodents.

Based on the weight of evidence available for the toxicity of 1-BP in humans and rodents, there is no credible scientific reason to target an occupational concentration as low as 10 ppm or 0.1 ppm. ETE's current recommendation of 100 ppm should be maintained, and employers together with vapor degreasing personnel should not be concerned about the much lower levels recommended by the ACGIH.

## Introduction

In 2011, the American College of Government Industrial Hygiene (ACGIH) lowered their threshold limit value (TLV) for occupation exposure to 1-bromopropane [106-94-5] (1-BP) from 10 parts per million (ppm) to a recommended 0.1 ppm, and added the phrase "A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans". This recommendation was then adopted in 2014.

EPA developed a recommended occupational exposure level for vapor degreasing of 25 ppm in 2004; this value has not been revised since originally published. However, a recent animal cancer study was completed by the National Toxicology Program (NTP). Agencies have not yet incorporated the results of this study into any target levels or regulations.

This paper discusses the relevance and protectiveness of EnviroTech Europe's (ETE) recommendation to self-regulate target indoor air concentrations associated with the use of 1-BP in vapor degreasing at 100 ppm given that the TLV has dropped 100-fold since that recommendation was made.

Since there are now multiple target concentrations of 100 ppm, 25 ppm, and 0.1 ppm, it is important to understand the level of safety associated with these concentrations. While 0.1 ppm is undoubtedly below a level of concern for occupational exposure, a more relevant question is whether 15-24 ppm is also below a level of concern for occupational exposure, since that is the typical upper range of exposure concentrations seen in 1-BP use in the vapor degreasing industry.

### Summary of ACGIH Revised TLV

The current ACGIH TLV of 0.1 parts per million (ppm) is equal to 0.5 milligrams per cubic meter ($mg/m^3$). One of the key statements made in the TLV documentation is that the TLV is applicable to commercial grade 1-BP, which is contaminated with 2-bromopropane (2-BP; aka isopropylbromide) at levels between 0.1 and 0.2% (i.e., 1000 to 2000 ppm in the product). However, ETE uses only analytical grade 1-BP manufactured by ICL. Batches purchased by ETE from ICL since mid-2009 have certificate of analyses showing the maximum amount of 2-BP to be 0.0096% (i.e., 96 ppm), and an average of 0.0046% (46 ppm). This is 10-20 times lower than the 2-BP levels confirmed in the 1-BP solvent tested by ACGIH that were used as the basis for their TLV. Given that 2-BP is known to be more toxic than 1-BP, and less 2-BP is present in the solvent sold by ETE than in the product evaluated by ACGIH, the TLV recommendation is likely lower than necessary for the ETE product.

The current proposed TLV is based primarily on a study of worker exposure to 1-BP (and the 2-BP contaminant at 1000-2000 ppm) during its manufacturing (Li et al., 2010). In this study, the authors listed a lowest-observed-adverse-effect-level (LOAEL) of 1.28 ppm for both neurological (e.g., nerve conduction speed) and hematological effects (e.g., red blood cell count). Dividing this by an uncertainty factor of 10 (not presented in the ACGIH document but assumed to have been used) results in a value of 0.128 ppm, which ACGIH rounded down to 0.1 ppm.

However, there are several technical concerns regarding the information provided in Li et al. (2010) and not recognized in the updated ACGIH TLV that compromise the confidence in their 0.1 ppm recommendation. These are discussed below. Also, a Letter to the Editor was published in July 2011 by a group of six PhDs and one MD from both

industry and medicine that provided critical comments on the Li et al. (2010) paper (Smith et al., 2011). This provides supporting evidence that the conclusions reached by Li et al. (2010) may not be appropriate given the inadequacies of the study. This would imply that the ACGIH should not have used this study as the basis for developing a TLV.

**Comments on the Li et al. (2010) Article**

This study presents information on 60 female and 26 male workers exposed to 1-BP during its production. The article lists four different facilities where these workers produced 1-BP, and the exposure duration across all workers averaged around 3 years. Prior to producing 1-BP, 20% of these workers were also exposed to 2-BP for some time, which causes similar neurological effects as 1-BP, but at lower levels. This confounding factor reduces confidence in the conclusions reached by the authors that the effects seen are directly due to 1-BP exposure.

The ambient 1-BP concentrations at these four locations were measured using detection tubes that quantify all brominated hydrocarbons, including 1-BP and 2-BP. These detection tubes do not appear to be particularly accurate based on the information presented in the article. Average concentrations across these four locations ranged between 3.3 ppm and 58.3 ppm, despite sampling the same relative locations in each facility (i.e., above a “mixing pot”). This wide variability reduces confidence in the reported average concentrations used as the basis for the evaluation.

Based on description of activities conducted by the workers, it is likely they also received a substantial exposure through direct contact with 1-BP liquid. Both human and rodent data suggest that 1-BP is readily absorbed through the skin. This dose was not incorporated into the exposure estimates. Therefore, actual exposures received by the workers were likely substantially higher than the concentrations measured in ambient air.

Another technical issue is the personal exposure monitoring conducted on these 86 workers. The monitoring was done using passive samplers, which includes a patch on the worker’s clothing worn during their 8- or 12-hour shift. The Occupational Safety and Health Association (OSHA) requires active sampling for personal exposure monitoring; otherwise the amount of material passing through the sampler over a workday, which is needed to determine a concentration, is not known and has to be estimated.

Finally, after the shift ended the personal samplers were stored in individual sealed bags at 4 degrees Celsius until analysis. Storing volatile chemical samples in a bag will not eliminate volatilization, and it was not reported how long the samples were stored before extraction. This likely resulted in underreporting the actual exposure concentrations.

These technical issues in estimating concentrations reduce confidence that the exposure concentrations accurately reflect actual exposure. Based on these issues, it is likely that actual air concentrations were higher than those reported by the authors, and that exposure via other routes (e.g., skin) could have been substantial.

With regard to the results and interpretations provided by the authors, most of the significant effects (which included neurological function and sensation, blood parameters, and some circulating enzymes and hormones) were seen only in females. The authors said this was due to the small sample size for males relative to females. In male workers, the only reported dose-dependent effect was on blood urea nitrogen (BUN), which was not significantly affected in female workers. This complete lack of

concordance between reported effects in male and female workers is surprising, particularly since the toxicity of 1-BP is not sex-specific.

The reported significant dose-dependent effects in females were further examined. The significant effects were identified primarily through the use of statistical comparisons across all dose groups, rather than specifically based on a clear dose-response relationship. Dose-response is one of the basic concepts of toxicology, and demonstrates that, as the dose increases above a "threshold" level, the degree of response also increases. The steepness of this dose-response relationship (i.e., how quickly the response increases relative to a unit change in dose) defines the potency of a chemical. The steeper the dose-response curve, the more potent a chemical is considered to be with regard to toxicity.

Evaluating the statistical tests provided by the authors that focused solely on comparing doses with each other (instead of all doses evaluated together) presents a different picture. These so-called "pairwise tests" indicate that typical dose-dependent responses are not evident for almost all of the reported significant endpoints. As an example, hematocrit levels were identical in controls and the medium dose level test groups, but significantly different from controls in both low and high dose level groups. If a true dose-response relationship existed, then the medium dose level group should have had more response than the control group, which was not exposed to 1-BP.

It is generally accepted that neurological and reproductive systems are the most sensitive targets of 1-BP toxicity in rodents; only neurological effects have been reported in humans. However, the only neurological endpoint with significant differences from controls at all three dose levels reported in the study was loss of vibration sense in the toes. This endpoint is subjective as it involved placing a tuning fork on a toe and measuring the amount of elapsed time until the subject can no longer feel the fork vibrating, at which time the tuning fork is placed on the same toe of the examining doctor, who served as the "control" and measured the additional length of time before the doctor could not sense the vibrations. More than one doctor administered these tests, and the results were significantly affected by which doctor conducted the exam. Therefore, results for this endpoint are of questionable validity.

In summary, the measured 1-BP exposure concentrations vary by more than 10-fold for the same activity, the reported effects do not follow classic dose-dependent response patterns, and a portion of the sample population had exposure to at least one other, more toxic, solvent during their work history. When all of this information is considered as a whole, it is unlikely that the 1.28 ppm lowest effect concentration reported in the paper is accurate. Given these flaws, along with the small sample population, it is not surprising that clear relationships were not seen, particularly given the relatively low exposure concentrations (whether 1.28 or 58.3 ppm).

**Comments on the ACGIH Revised TLV**

Animal studies, including neurological and reproductive studies, have not shown significant effects in any parameter at concentrations below 100 ppm. If the Li et al. (2010) article accurately reports workplace conditions, it indicates that human impacts can occur from relatively short durations (4% of a lifetime) at 100 times lower concentrations than seen in animals exposed throughout their lifetime.

There have been a few human case studies where neurological damage has been reported, but these have been isolated cases in the spray adhesive industry where

exposure included both deposition onto skin and inhalation of high concentrations (likely above 200 ppm). There are no occupational exposures to 1-BP at concentrations below 100 ppm that have resulted in toxicity, based on evaluations by credible agencies (e.g., OSHA) or groups (NIOSH).

The interpretations in the Li et al. study are inconsistent with expectations based on the ways in which 1-BP acts in rodents relative to humans. Studies on how 1-BP acts in the body of rats and mice (conducted by the NTP), and studies on metabolism of the chemical in humans (occupational metabolism studies) indicate that humans should be no more sensitive to 1-BP than either of these rodents. This is supported by analogy of comparative toxicology studies with other solvents that are similarly metabolized, including 1,3-butadiene and naphthalene.

**Conclusions and Recommendations**

The EPA and SLR both conducted an extensive review of the toxicity literature on 1-BP in the early 2000s, and both independently identified the same endpoint (sperm motility) in the same study (a 2-generation reproduction study on rats and mice) as the most sensitive endpoint for 1-BP toxicity. The calculated concentrations in these two studies were 159 ppm and 168 ppm, or almost identical. ETE used the average of this 159 ppm concentration from SLR and the results of the human volunteer study published by Doull and Rozman to develop their internal recommendation of 100 ppm for occupational exposure. EPA took their 168 ppm concentration and divided it by an uncertainty factor of 9, then rounded to 25 ppm as their occupational exposure concentration. Both of these recommendations were specific to the vapor degreasing industry.

Since then, the NTP kinetics and metabolism study of 1-BP in rodents supported these values and provided no evidence that humans should be considered more sensitive to the toxicity of 1-BP than rodents.

Around this same time, the ACGIH put forth their recommendation of 10 ppm as a TLV, based on identifying a body weight effect in offspring at 100 ppm and dividing that value by a safety factor of 10. This was done despite the fact that the “effect” was actually not test-related but was rather an artifact of how the body weights were measured in the study. The authors of the study agreed, and stated that this result should not be considered test-related because the effect was due to changing when they weighed the baby rodents each day, and not due to exposure to 1-BP. So the initial 10 ppm value published by ACGIH is not based on a relevant endpoint.

It is not particularly surprising, therefore, that the ACGIH has again identified a study that is flawed and purportedly shows a lower effect level than in controlled studies, and used that study to further lower an already insupportably low TLV.

Based on the weight of evidence available for the toxicity of 1-BP in humans and rodents, there should be no reason to target an occupational concentration as low as 10 ppm or 0.1 ppm. The current management practice of ETE should be maintained, and employers along with vapor degreasing personnel should not be concerned about the much lower levels recommended by the ACGIH.

## References

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### About the Author

Mark Stelljes is the Director of Risk Assessment and Toxicology for SLR International Corporation, an environmental consulting firm based in the United Kingdom. Dr. Stelljes has a Ph.D. in Environmental Toxicology and Pharmacology from the University of California-Davis, and has over 24 years of experience as a consultant. Dr. Stelljes published a recommended occupational exposure level in a peer reviewed journal in 2003, and has been active in the toxicology of 1-BP since 2001. He served on the California Occupational Safety and Health Administration Health Effects Assessments Committee, which focused on updating permissible exposure limits (PELs) used as occupational exposure limits for regulated chemicals in California. He has expertise in public outreach and education, and has published a primer book for non-scientists, *Toxicology for NonToxicologists*, which printed its second edition in 2008.