# Scientific Review of 1-Bromopropane Occupational Exposure Limit Derivations – Preliminary Thoughts and Areas for Further Analysis

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## Abstract

Current OELs for 1-bromopropane (1-BP) are diverse in both the selection of critical effects and judgments of remaining uncertainties. The resulting values differ by ~16-fold. We critically evaluated the underlying basis of existing OELs through the use of concepts such as critical effect, benchmark dose and uncertainty factor. We conclude that the critical effect is decreased live litter size with a BMDL of 190 ppm. Using an uncertainty factor of 10-fold, 3 for extrapolation from an animal study and 3 for human variability results in an OEL of 20 ppm.


## Introduction

The development of Occupational Exposure Limits (OELs) for various chemicals found in our workspace is an important endeavor for risk assessment scientists and managers. 1-Bromopropane (1-BP) is used as a solvent for fats, waxes, or resins, as an intermediate in the synthesis of numerous products, including pharmaceuticals, insecticides, flavors and fragrances, and as a solvent in spray adhesives and as a degreaser. Current OEL derivations for 1-BP include a number of organizations or investigators, presented in Table 1.

As shown in Table 1, current OELs for 1-BP are diverse in both the selection of critical effects and judgments of remaining uncertainties. The resulting OELs differ by ~16-fold. Some of these differences reflect the year of evaluation and lack of recently published studies. The purpose of this paper is to critically evaluate the underlying basis of existing OELs and bring some common understanding through the use of concepts such as critical effect, benchmark dose and uncertainty factor. We conclude that the most appropriate OEL for 1-BP takes from elements of each of these current OELs.

Table 1. OELs Derived for Various Groups and Their Basis.

| Group | **OEL (ppm)** | Critical Effect | Uncertainty | Reference |
|---|---|---|---|---|
| ACGIH TLV (2004) | **10** | LOAEL of 100 ppm for decreased fetal weight | An apparent factor of 10 was used, no specific factor or rationale was provided | Huntingdon, 2001 |
| Stelljes and Wood (2004) | **156** | BMDL of 156 ppm for decreased sperm motility in $F_1$ generation | 1-fold, no uncertainty remains | WIL Research, 2001 |
| Rozman and | **60 - 90** | NOAEL of 170 ppm for | 2-3-fold for | NIOSH, 2000 |

| | | | | |
|---|---|---|---|---|
| Doull (2002) | | mild CNS effects (headache) in workers | within human variability | |
| U.S. EPA (2002) | **25** | BMDL (adjusted) of 177 ppm for decreased sperm motility in $F_1$ generation | 10-fold for within human and animal to human variability | WIL Research, 2001 |
| ICF (1998) | **100** | NOAEL (adjusted) of 300 ppm for mild liver histopathology and NOAEL of 280 ppm for decreased sperm motility | 3-fold for animal to human variability | ClinTrials BioResearch, 1997 |

## Methods

The methods used in this review are those as published by Haber et al. (2001). In brief, we use the concept of critical effect, benchmark dose (BMD) and uncertainty factor as described by these authors because we feel that such concepts can be useful in the determination of OELs in general, and specifically can be used to harmonize seemingly disparate judgments for 1-BP.

The critical effect is defined as the first adverse effect, or its known precursor, that occurs as dose rate or concentration increases. One or more effects may be critical for any particular chemical. This concept is used world wide for both environmental and occupational risk assessments.

Uncertainty factors are considered a necessary reduction in the exposure level, based on scientific judgments of available toxicity, toxicokinetics or toxicodynamics and inherent uncertainty. Although default values of 10-fold are commonly used for different areas of uncertainty, especially in environmental risk assessment, such defaults are seldom used in occupational risk assessment. However, the environmental area of assessment is now emphasizing the use of specific data and better judgment in the development of uncertainty factors, rather than the usual default values of 10-fold (Dourson et al., 1996; IPCS, 2001). The occupational area of assessment is now emphasizing a more structured approach to uncertainty judgments (Naumann and Weidman, 1995; Haber and Maier, 2002). Thus, we feel that the two lines of judgment are not as far apart as some scientists might think.

The benchmark dose (BMD) approach was also used in conjunction with the more standard NOAEL/LOAEL technique to analyze the data for 1-BP. The use of both approaches necessitates expert judgment and adds value to the overall assessment. U.S. EPA's BMD software, version 1.3.2 (U.S. EPA, 2001) was used to reproduce each critical benchmark dose (BMD) and lower bound benchmark dose (BMDL) for 1-BP calculated by Stelljes and Wood (2004) and to expand the analysis to additional endpoints of interest for the 2-generation study (WIL Research, 2001). Benchmark responses (BMRs) of 1.0 control standard deviation were used by *TERA* for all

continuous data and BMRs of 10% were used for all dichotomous data. These choices reflect standard operating procedure. All the available models in the BMDS software were run for each data set, and BMDs and BMDLs from the best fitting model were selected.

## Results and Discussion

### Issues related to Critical Effect with Existing OEL Estimates

Neurotoxicity. Neurotoxicity is a common effect from exposure to 1-BP. However, its selection as a critical effect is made difficult because of inconsistencies in the overall database. For example, an argument is presented by Stelljes and Wood (2004) that CNS vacuolization found in the Ichihara et al. (2000a) study should not serve as the critical effect. This argument needs to be sharpened, particularly with regard to the absence of the finding in longer-term studies and the possibility that the effect resulted from methods used for tissue preparation. However, this argument is consistent with the fact that none of the longer-term studies, including preliminary data from the 13-week NTP study (NTP, 2003), identified CNS histopathology changes.

The finding of reduced hind-limb grip strength from the Ichihara et al. (2000a) study would generally be an appropriate endpoint for risk assessment with a BMDL calculated by Stelljes and Wood (2004) of 214 ppm (Table 2). However, documented concerns with the conduct of the study reporting this finding (O'Malley, 1999), the inability of GLP 90-day study (ClinTrials BioResearch, 1997) to duplicate this finding, the absence of CNS histopathology in the NTP 13-week study (NTP, 2003), and inconclusive evidence of psychomotor performance effects in an investigation of workers (NIOSH, 2002) weaken the argument that the BMDL of 214 ppm for reduced hind-limb strength is an appropriate choice for the critical effect level.

Neurological effects remain of interest based on recent neurotoxicity studies that suggest spontaneous locomotor activity was raised in rats at exposure of 50 ppm and higher; other clinical signs were also noted as statistically significant at exposures of 200 or 1000 ppm (Wang et al., 2003). Biochemical changes in the brain of rats occurred at exposures of 200 ppm and higher (Honma et al., 2003). Subjective symptoms were also reported in human case studies at average exposures of about 60 to 70 ppm, but the effects were not definitively attributable to 1-BP (NIOSH, 2002), or an increased incidence of headaches at average concentrations between 190 and 200 ppm (NIOSH, 2000). This latter effect was the basis of the OEL proposed by Rozman and Doull (2002).

For the neurotoxicity findings the bottom line appears to be that some animal and human studies suggest effects in the range of 100 to 200 ppm or higher, but results across the overall database are not consistent. Furthermore, definitive effect levels in these studies generally fall in the same range as for reproductive toxicity endpoints (which are of greater severity as shown below). The human data are limited by co-exposure to other solvents, small populations examined, and limitations in the exposure estimates. Due to these uncertainties, the human data appear inadequate to serve as the primary basis for

the critical effect as suggested by Rozman and Doull (2002), although they are quite useful in serving as a comparison to any derived OEL.

Liver Toxicity. Most risk assessors would consider the increased incidence of mild liver cytoplasmic vacuolization, such as that seen by ClinTrials BioResearch (1997), as a minimal adverse effect, even though other measures of liver damage (e.g., serum levels of liver enzymes) were not affected in this study. In fact, the lack of additional liver effects further supports the mild cytoplasmic vacuolization as an effect of minimal severity. The BMDL of 226 ppm determined by Stelljes and Wood (2004)[1] for this endpoint corresponds well with the effect level for other endpoints, although the severity is minimal (Table 2). Furthermore, no severe treatment related liver findings (histopathology or clinical chemistry changes) were reported in preliminary data from the 13-week NTP study (NTP, 2003). These data suggest that liver toxicity is not the critical target for 1-BP toxicity, and the older ICF (1998) OEL should be discounted.

Reproductive and Fetal Effects. The ACGIH (2004) use of a LOAEL of 100 ppm for decreased fetal weight in the Huntingdon Study (2001) as the critical basis for its OEL derivation is difficult to justify. As a first consideration, BMDL estimates for this endpoint are greater than for other effects. For example, both the NTP expert panel (NTP, 2002) and *TERA* (shown later in this text and in Table 2) identified a BMDL of approximately 300 ppm. Furthermore, questions about the conduct of the Huntingdon (2001) study, including the change in procedure with control animals that lead to higher body weights, lack of related findings of developmental delays in pups in multi-generation studies at similar concentrations (see WIL Research, 2001), minimal severity of the effect (a maximum of 7% change from control), and potential relatedness to maternal effects (although BMDL for pup fetal weight is lower than for maternal weight) decreases the selection of this endpoint as the most relevant for deriving the OEL.

Stelljes and Wood (2004) argue that the effect level for sperm parameters in the WIL Research (2001) study should be based on the $F_0$ generation results and not those for $F_1$ or $F_2$ animals, because the goal of an OEL is to develop a safe exposure level for workers and the exposure patterns for the parental animals more closely resemble occupational exposure scenarios. A counter to this argument is that *in utero* exposure may cause effects manifested as these exposed animals become adult males. However, it is not clear what mechanisms would generate changes in sperm parameters based on the normal turnover in sperm through the cycle of spermatogenesis, in the absence of findings on male reproductive organ histopathology. The BMDL calculated by Stelljes and Wood (2004) for sperm motility in $F_0$ animals was 263 ppm. *TERA* identified a BMDL of 270 ppm (see later in this text). Based on data from Ichihara et al. (2000b), Stelljes and Wood (2004) calculated a BMDL of 232 ppm for sperm count in $F_0$ adult males. Taken together, the effects of 1-BP on male sperm parameters suggests that the male reproductive effect in parental animals occur in the same general range, but are not more sensitive than other relevant effects.

Benchmark dose modeling for several measures of male and female reproductive parameters from the two-generation study correspond well with each other and provide a

[1] *TERA* identified a BMDL of 200 ppm for this endpoint.

consistent story indicating that 1-BP can affect reproductive parameters in males (decreased sperm motility and prostate weight), females (increased estrous cycle length, no estrous cycle incidence, and maternal body weight at gestation day 20), and functional reproductive performance (litter viability index, pup weight gain at post natal days 21 to 29, and live litter size). The BMDL values for these latter effects are in the same range, but slightly lower, than for the liver effects, and represent a more serious outcome (Table 2). The BMDL value of 188 ppm from Stelljes and Wood (2004) or of 190 ppm from *TERA* for decreased live $F_1$ litter size is the most appropriate basis for deriving the OEL, since this is the lowest measure related to exposure to $F_0$ animals that is clearly adverse.

**Issues related to Critical Effect with New Studies**

A 90-day inhalation study (NTP, 2003) was conducted in rats and mice. Male and female B6C3F1 mice were exposed to 0, 62.5, 125, 250, and 500 ppm 1-BP for 90 days. Male and female Fischer 344 rats were similarly exposed to 0, 62.5, 125, 250, 500, and 1000 ppm for 90 days.[2]

Body weight gain and terminal body weights of female and male mice and female rats were comparable to controls. In rats given 1000 ppm, there was reduction in body weight gain and terminal body weight, which became significant beginning at week 9. No mortality was observed in rats. In mice, no mortality was observed in animals given 250 ppm or below but 3/10 female and 2/10 male animals died from natural causes and 2 females and 2 males found moribund were killed. The only clinical signs of toxicity observed included abnormal breathing and lethargy in 2 male and 2 female mice. No significant signs of clinical toxicity were observed in the rats. It further appeared that 1-BP did not cause any adverse effects on clinical chemistry parameters. There were some slight, dose-dependent but insignificant changes in some of the parameters but these changes are not likely to be of toxicological significance. Hematological parameters were also not adversely affected in mice or rats.

Microscopic evaluation revealed no significant abnormality at 250 ppm or below. At 500 ppm, mice that died or were killed in extremis or survived to the end of the study period had mild, chronic inflammation, marked necrosis, and mild cytoplasmic vacuolization in the centrilobular hepatocytes, moderate to marked necrosis of the adrenal cortex, mild to moderate necrosis and moderate cytoplasmic vacuolization of the bronchioles and trachea, and minimal to moderate necrosis and cytoplasmic vacuolization of the trachea. Similar observations were noted in female and male rats at 500 ppm and 1000 ppm. Minimal cytoplasmic vacuolization of the centrilobular hepatocytes were observed at 250 ppm, the severity of which increased at higher doses. Based on these results, it appears that the body weight changes observed in male rats at 1000 ppm were accompanied by microscopic abnormalities, indicating a possible LOAEL of 1000 ppm and a NOAEL of 500 ppm. In mice, the frank toxicity at 500 ppm was also accompanied by microscopic abnormalities, indicating a possible LOAEL of 500 ppm and a NOAEL of 250 ppm.

[2] Note, this study is not yet published nor peer-reviewed by NTP. The raw animal data are posted on the NTP website, and *TERA* developed these conclusions from the available data.

Wang et al. (2003) reported decreased creatinine kinase activities in central nervous system tissues following 12-week exposures to concentrations beginning at 200 ppm in rats. This is the same group that published the Ichihara et al. (2000a) study, and reports a fairly obscure endpoint for risk assessment purposes.

Honma et al. (2003) reported decreased body weight at 1000 ppm (consistent with the NTP (2003) study), effects on locomotor activity at 50 and 200 ppm (although this was measured as latency in recovery of activity), changes in ambulation and rearing at 200 ppm (but not 1000 ppm), and changes in performance in a traction test (at 200 and 1000 ppm). *TERA* has not had sufficient time to closely analyze this study, and would welcome ACGIH thoughts.

In summary, NOAEL/LOAEL and BMD and BMDL boundaries for experimental animal male and female nervous system, liver toxicity and reproductive and fetal effects are in the same range, suggesting that regardless of endpoint selected the critical effect levels will not vary greatly. These boundaries are generally similar to that seen in humans. This increases confidence the overall OEL value derived will provide adequate coverage for the range of potential endpoints.

**Benchmark Dose Modeling for 1-BP**

The results of Benchmark Dose (BMD) modeling are summarized in Table 2. *TERA's* calculations were generally consistent with those reported by Stelljes and Wood (2004). For example, the BMDL of 263 ppm for $F_0$ sperm motility from Stelljes and Wood (2004) was similar to that of *TERA* of 270 ppm. The BMD and BMDL computed by Stelljes and Wood (2004) for centrilobular vacuolization of 345 and 226 ppm are consistent with the results of using a multistage model of order 4. However, the simpler multistage model of order 2, which is commonly used in BMD modeling, was used to recalculate a BMDL because the $2^{nd}$ order model has a slightly lower Akaike's Information Criterion (AIC) (38 versus 39) indicating a superior data fit ($p = 0.9$) with fewer parameters.

Additional reproductive and developmental effects not considered by Stelljes and Wood (2004) were also evaluated by *TERA*. These endpoints include $F_0$ prostate weights, $F_0$ and $F_1$ estrous cycle lengths, number of $F_0$ and $F_1$ rats not having estrous cycles, maternal body weight at gestation day 20, $F_1$ litter viability index, $F_1$ pup weight gain data from WIL Research (2001) as well as fetal weight data from Huntingdon Life Sciences (2001), and $F_1$ and $F_2$ live litter size. BMDs and BMDLs are shown for all of these endpoints except for the litter viability index, which exhibited no clear dose-response. The number of rats not having estrous cycles was analyzed because the cycle length data analysis necessarily omitted these animals that were experiencing a more severe cycle delay that could not be quantified in terms of days.

A BMDL for fetal weight reduction was computed using the data collected by Huntingdon Life Sciences (2001). Following the NTP-CERHR expert panel on reproductive and developmental toxicity of 1-BP (NTP, 2002), one litter in the 100 ppm dose group was excluded because the average fetal weight was more than 3 standard

deviations from the dose group mean. A BMDL of 310 ppm was estimated using a BMR of 1.0 control standard deviation from the control mean (Huntingdon Life Sciences, 2001). This estimate is similar to the BMDL of 305 ppm estimated by the NTP-CERHR expert panel (NTP, 2002), and they are higher than the BMDLs for reproductive endpoints; therefore, fetal weight reduction is unlikely to be the most sensitive effect. This conclusion is consistent with the findings of the NTP expert panel.

To further evaluate whether developmental effects were the most sensitive basis for deriving an OEL, a BMDL for maternal weight change was also computed by *TERA* using the data collected by Huntingdon Life Sciences (2001). Note that the maternal body weight was calculated as maternal weight on GD20 subtracted by the litter weight at birth. A BMDL of 690 ppm was estimated using a BMR of 1.0 control standard deviation from the control mean. This estimate is higher than the BMDL of 310 ppm estimated by *TERA* for fetal weight reduction, indicating that the change of fetal weight might be due to direct fetal toxicity from exposure to the compound rather than only a secondary effect from maternal toxicity. On the other hand, no consistent dose-related effect on pup weights was observed in the two-generation study, decreasing concern related to the decreased fetal weight finding. Furthermore, since the BMDL for decreased fetal weight was greater than for other reproductive parameters from the two-generation study, this effect should be adequately addressed by an OEL that protects against reproductive effects.

Finally, $F_1$ and $F_2$ live litter size was assessed. BMD and BMDL values of 280 and 188 for the $F_1$ generation, were determined by Stelljes and Wood (2004). These values were confirmed by *TERA* where values of 280 and 190 are shown (Table 2). Stelljes and Wood (2004) and *TERA* also found similar BMD and BMDL values for the $F_2$ generation, although these values were lower than that for the $F_1$. This effect, decrease in live litter size, is of sufficient severity to warrant its choice as the critical effect. Although other effects might occur at the same, or slightly lower exposures, they are not as toxicologically significant. The choice of the BMD and BMDL values of 280 and 190 for the $F_1$ generation, rather than lower values from the $F_2$ generation reflects the desire to replicate the likely exposure in a worker population. Specifically, it is not anticipated that any human will have the exposure pattern of an $F_2$ animal. In contrast, the occupational exposure pattern of an $F_1$ animal might occur in humans.

**Table 2**
**BMD and BMDL Estimates***

| Endpoint | Stelljes and Wood BMD (ppm) | Stelljes and Wood BMDL (ppm) | BMR | TERA BMD (ppm) | TERA BMDL (ppm) | Model | Variance |
|---|---|---|---|---|---|---|---|
| Hindlimb strength | 286 | 214 | 1 sd | 290 | 210 | Linear | Homogeneous |
| Minimal centrilobular vacuolization males | 345 | 226 | 10% | 290 | 200 | Multistage-2 | |
| Fetal body weight | | | 1 sd | 510 | 310 | Poly-2 | Non-homogeneous |
| $F_0$ sperm motility | 343 | 263 | 1 sd | 380 | 270 | Linear | Homogeneous |
| $F_1$ sperm motility | 261 | 156 | 1 sd | 260 | 150 | Power | Non-homogeneous |
| $F_0$ prostate weight | | | 1 sd | 740 | 190 | Power | Homogeneous |
| $F_0$ Estrous Cycle Length | | | 1 sd | 290 | 210 | Power | Non-homogeneous |
| $F_1$ Estrous Cycle Length | | | 1 sd | 810 | 400 | Linear | Non-homogeneous |
| $F_0$ No Estrous Cycle Incidence | | | 10% | 670 | 480 | Multistage-2 | |
| $F_1$ No Estrous Cycle Incidence | | | 10% | 360 | 180 | Quantal Linear | |
| Maternal GD20 body weight | | | 1 sd | 1000 | 690 | Linear | Homogeneous |
| $F_1$ litter viability index | | | No dose-response | | | | |
| $F_1$ pup weight gain PND 21 to 28 | | | 1 sd | 240 | 180 | Linear | Homogeneous |
| **$F_1$ decreased live litter size** | **280** | **188** | **1 sd** | **280** | **190** | **Linear** | **Non-homogeneous** |
| $F_2$ decreased live litter size | 238 | 169 | 1 sd | 240 | 170 | Linear | Non-homogeneous |

*See text for additional details.

**Areas of Uncertainty**

Most organizations that establish OEL's do not have documented approaches for addressing areas of uncertainty, rather a professional judgment approach is used (Haber and Maier, 2002). In order to evaluate potential OELs for 1-BP, we structure a discussion around the U.S. EPA's approach that describes five areas of uncertainty. However, in keeping with the existing OEL approach, we were not constrained to using EPA's defaults.

Interspecies Variability ($UF_A$). This area accounts for the differences that occur between experimental animals and humans and is composed of subfactors for toxicokinetics (how the body distributes and metabolizes the chemical) and toxicodynamics (how the body responds to the chemical). The use of these two considerations is standard practice in the context of environmental risk assessment (Dourson et al., 1996), and is gaining acceptance for assessing occupational risk (Naumann and Weidman, 1995).

Ideally, a quantitative comparison of the toxicant concentrations (e.g. AUC or Cmax) in the target organ between animal species and humans would allow interspecies variability in toxicokinetics to be calculated. However, for 1-BP the information available is not adequate to allow such estimation. An alternative is to calculate the human equivalent concentrations (HEC) from the animal data based on the chemical's properties and

physiological differences between the tested animal species and humans. This dosimetric adjustment generally provides a better estimate of the target organ doses following inhalation exposure than simply dividing the exposure assessment exposure by a default uncertainty factor of 10-fold. If the HEC is used, a toxicokinetic subfactor for interspecies variability is generally not needed because the expected toxicokinetic difference has been considered to some extent in the HEC calculation. If no information is available on the quantitative differences in the organ response to the toxicant of interest between animals and humans, then a default value of 3 for this toxicodynamic difference is used in environmental assessments. If data are available to adequately describe this variability, then actual data may be used to replace this default value as well (IPCS, 2001).

For 1-BP, dosimetric adjustment to the HEC per EPA's methods (see for example ICF, 1998) support using a factor of 1 to account for species differences in toxicokinetics. Toxicodynamic differences, however, also need to be addressed. There appears to be general consistency in effect levels among species for various toxic endpoints. For example, mild CNS effects in humans, as summarized by Rozman and Doull (2002), were observed in a range generally similar to the BMDL for hindlimb grip strength in rats (see Table 2) and several of the clinical findings of Wang et al. (2003). Nevertheless, because there is residual concern about relative sensitivity to reproductive effects, and humans might be expected to be more sensitive to reproductive parameters (based on less excess reproductive capacity) a factor to account for toxicodymanic differences appears appropriate. For example, the *in vivo* dose-response information in humans is scant, and therefore comparative sensitivities of humans and animals are hard to define from the available data. Furthermore, *in vitro* bioassays are available for both human and animal cell cultures, including human hepatocytes, mouse lymphoma and bone marrow cells, but no data were obtained from experiments on reproductive system tissues. Moreover, since the critical effect is decreased live litter size, identifying a suite of relevant *in vitro* studies that could be used to compare animal and human responsive sensitivities would be difficult to obtain without a better understanding of the underlying mechanism of this effect. Since the available data do not provide sufficient information for a quantitative estimation of toxicodynamic variation, a default subfactor of 3 is appropriate for this area of uncertainty. Additional studies investigating relative sensitivities to reproductive effects of 1-BP would be helpful to address this area of uncertainty.

Intraspecies Variability ($UF_H$). This factor accounts for the natural differences that occur among human subpopulations and for the fact that some individuals are more sensitive than the average population. This factor is also composed of two subfactors – one to account for toxicokinetic differences and one to account for toxicodynamic differences. If no information is available on human variability, then a default value of 10 is generally used in the context of environmental exposures to the general population. If adequate information is available on either toxicokinetic of toxicodynamics variability, then this information is used to develop estimates of variability from the data (IPCS, 2001; Meek et al., 2001). Unfortunately for 1-BP, no quantitative information regarding human variability in terms of toxicokinetics and toxicodynamics was identified, and therefore, data-derived estimates of human variability cannot be calculated.

However, for worker populations the degree of variability in toxicokinetic or toxicodynamic variability is expected to be lower than for the general population. Since some degree of variability in response would be expected even among the worker population, a reduced factor of about 3-fold is generally judged to be reasonable. This is similar to what Rozman and Doull (2002) suggest.

Extrapolation from an Effect Level ($UF_L$). A BMDL was used with the critical effect. Generally no additional factor is considered needed in these situations.

Extrapolation from Less than Lifetime to Lifetime Exposure ($UF_S$). This factor is not generally used by groups that establish OELs (Haber and Maier, 2002). The database for 1-BP lacks a completed chronic study,[3] and therefore the likelihood that effects would progress with longer duration exposures needs further evaluation. However, the critical effect appears to be on a reproduction parameter and the critical study evaluated the period of interest. Moreover, workers have been exposed to 1-BP for more than short term exposures and their results are considered in all of these OEL estimations. Thus, it does not appear to us that a factor is needed for this area.

Adequacy of the Database ($UF_D$). This factor is not overtly used by groups that establish OELs (Haber and Maier, 2002). However, OEL decisions routinely consider whether the overall body of literature determines that the most sensitive effects have been evaluated. For 1-BP in particular, reproductive toxicity and possibly neurotoxicity and liver toxicity appear to be the most sensitive effects. A decrease in live litter size appears to be the critical effect. We do not see the need for a factor for this area of uncertainty.

## Determination of OEL

We conclude that the critical effect for the purpose of developing an OEL is decreased live litter size in the $F_1$ generation, with a BMDL of 190 ppm as shown in Table 2. Dividing this BMDL with an uncertainty factor of 10-fold, which is composed of 3-fold for extrapolation from an experimental animal study to humans for expected toxicodynamic differences and 3-fold for expected human variability in toxicokinetics and toxicodynamics within the worker population, results in an OEL of 20 ppm. This OEL could be potentially lower if results in workers show definitive reproductive or other toxicity at levels lower than about 100 ppm. This OEL could be potentially higher if the expected reproductive response in experimental animals is shown to be similar to humans and at similar levels.

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[3]NTP's two-year bioassay is currently in progress.

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