# FINAL STATEMENT OF REASONS
# TITLE 27, CALIFORNIA CODE OF REGULATIONS

## SECTION 25805. SPECIFIC REGULATORY LEVELS: CHEMICALS CAUSING REPRODUCTIVE TOXICITY

## MAXIMUM ALLOWABLE DOSE LEVEL: BUTYL BENZYL PHTHALATE (ORAL EXPOSURE)

This is the Final Statement of Reasons for the adoption of an oral Maximum Allowable Dose Level (MADL) for butyl benzyl phthalate (BBP), a chemical known to the State of California to cause reproductive toxicity (developmental endpoint) under Proposition 65[1]. On June 1, 2012, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to adopt the proposed level of 1,200 micrograms per day by the oral route for BBP in Title 27, California Code of Regulations, section 25805(b)[2]. The Initial Statement of Reasons set forth the grounds for the amendment to the regulation. A public comment period was provided from June 1, 2012 to July 16, 2012. The Notice stated that a public hearing would be held only on request. No request for a public hearing was received. One written public comment was received by OEHHA.

**Peer Review:** On June 1, 2012, OEHHA provided the notice of proposed rulemaking and the Initial Statement of Reasons for the proposed MADL for BBP to the members of the Developmental and Reproductive Toxicant Identification Committee for their review and comment as required by Section 25801(f). No comments were received from any committee members.

SUMMARY AND RESPONSE TO COMMENTS

On July 16, 2012, OEHHA received written comment from William K. Rawson and Ann Claassen of Latham & Watkins LLP, on behalf of Ferro Corporation (hereinafter referred to as “Ferro”).

In the Initial Statement of Reasons released on June 1, 2012, OEHHA proposed an oral MADL of 1,200 micrograms per day for BBP, based on a No Observable Effect Level

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986 (Health and Safety Code, section 25249.5 et seq.)
[2] All further references are to sections of Title 27 of the California Code of Regulations, unless otherwise noted.

(NOEL) of 20 milligrams of BBP per kilogram of body weight per day (mg/kg-day) observed in the study by Nagao et al. (2000)[3]. In its comments submitted to OEHHA on July 16, 2012, Ferro requested that OEHHA use a NOEL of 50 mg/kg-day as observed in the study by Tyl et al. (2004)[4], which would result in a MADL of 2,900 micrograms per day. Comments from Ferro are summarized or quoted below, followed by OEHHA's responses.

**Comment 1**

The commenter appreciated OEHHA's effort to develop a MADL for BBP and stated a MADL would help members of the business community determine whether a Proposition 65 warning is required for their products.

**Response 1**

OEHHA acknowledges the comment.

**Comment 2**

The commenter considers the studies by Nagao et al. (2000) and Tyl et al. (2004) to be robust and well-conducted. However, the commenter recommended using the NOEL of 50 mg/kg-day as observed in the study by Tyl et al. (2004) as the basis for the MADL calculation, instead of 20 mg/kg-day as observed in the study by Nagao et al. (2000). Further, the commenter stated, "For the Nagao study, the NOAEL [No Observed Adverse Effect Level] arguably was 100 mg/kg/day, because the effect at that level was reversible and was plausibly due to litter size rather than BBP." Similarly, for the study by Tyl et al. (2004), the commenter argued that "the NOAEL arguably was 250 mg/kg/day, because the effect observed at that level had no adverse consequences for the reproductive function of the animals."

[3] Nagao, T., R. Ohta, H. Marumo, T. Shindo, S. Yoshimura and H. Ono (2000). Effect of butyl benzyl phthalate in Sprague-Dawley rats after gavage administration: a two-generation reproductive study. Reprod Toxicol 14(6): 513-532.

[4] Tyl RW, Myers CB, Marr MC, Fail PA, Seely JC, Brine DR, Barter RA, Butala JH. (2004). Reproductive toxicity evaluation of dietary butyl benzyl phthalate (BBP) in rats. Reprod Toxicol. 18(2):241-64.

**Response 2**

Proposition 65 regulations specify that "the NOEL shall be based on the most sensitive study deemed to be of sufficient quality" (Section 25803(a)(5)).

In the study report by Nagao et al. (2000), the authors identified 100 mg/kg-day as the Lowest Observed Effect Level (LOEL), based on the statistically significant reduction in the birth weight of F1 pups. As acknowledged by the commenter, the study authors concluded that 20 mg/kg-day was a NOAEL for developmental effects. Similarly, Tyl et al. (2004) identified 50 mg/kg-day as a NOEL, and 250 mg/kg-day as a LOEL, based on the presence of reduced anogenital distance (AGD) in F1 and F2 male pups at birth. The European Chemicals Bureau (2007) also identified 20 and 50 mg/kg-day in these two studies, respectively, as NOELs[5]. Therefore, identification by OEHHA of 20 mg/kg-day as a NOEL in the Nagao et al. (2000) study is consistent with the conclusions by the study authors, as well as with conclusions made by the European Union.

On the issue of reversibility, OEHHA notes the generally accepted principle that effects on growth are evidence of developmental toxicity, even if reversible. For example, the U.S. Environmental Protection Agency (U.S. EPA) Guidelines for Developmental Toxicity Risk Assessment (1991)[6] state that:

> "The major manifestations of developmental toxicity include: (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency."

and further clarify that altered growth

> "can be induced at any stage of development**, may be reversible**, or may result in a permanent change." (emphasis added).

There is a well-documented inverse correlation between litter size and mean pup weight. Although the commenter suggests that it was plausible that the effect In the Nagao et al. (2000) study was due to litter size, there was no statistically significant difference in litter size between the control group and the groups treated with 100 or 500 mg/kg-day BBP. Significant reduction in birth weights in F1 pups was observed in the

[5] European Chemicals Bureau. (ECB, 2007). European Union Risk Assessment Report on Benzyl Butyl Phthalate (BBP). Luxembourg, Office of Official Publications of the European Communities. Available on line at: http://publications.jrc.ec.europa.eu/repository/bitstream/111111111/10948/1/benzylbutylphthalatereport318.pdf

[6] U.S. Environmental Protection Agency (U.S. EPA, 1991). Guidelines for Developmental Toxicity Risk Assessment. 56 Fed. Reg. 63798.

groups treated with 100 or 500 mg/kg-day BBP. Thus, identification of 100 mg/kg-day as the LOEL by OEHHA is consistent with the conclusions made by the study authors.

With regard to the study by Tyl et al., the effect observed at 250 mg/kg-day was reduced anogenital distance (AGD) in both F1 and F2 male pups at birth. AGD is widely used in toxicological studies as one of the most sensitive endpoints for developmental effects on the male reproductive system. There is also clear evidence supporting the use of AGD as an indicator of potential effects on testicular function[7].

Therefore, there is no convincing evidence that the NOELs for the Nagao et al. and Tyl et al. studies should be 100 mg/kg-day and 250 mg/kg-day, respectively. Since both studies are of sufficient quality, selection of the most sensitive study also requires consideration of other data that indicate the levels of exposure at which developmental effects may occur. In a study by Sumner et al. (2009)[8] discussed below, adverse developmental effects were observed at an exposure level of 25 mg/kg-day, a level lower than the apparent NOEL of 50 mg/kg-day in the study by Tyl et al. (2004). On that basis, the study by Nagao et al. (2000) was identified as the most sensitive study.

**Comment 3**

The commenter stated that the study by Sumner et al. (2009) "appears to have been well-conducted." However, the commenter disagreed with OEHHA on identifying 25 mg/kg-day as a LOEL, and stated four reasons against "using the study in a risk assessment context."

- The study was a hypothesis-testing study rather than a study designed to characterize risk for risk management purposes.
- It used a small number of animals and a non-orthodox (for a risk assessment study) dose range.
- The unit of statistical analysis should be the litter, not individual pups.
- The effects at 25 mg/kg-day should not be considered adverse since the effects observed were reversible.

[7] Eisenberg M., L., Jensen, T.K., Walters R. C., Skakkebaek N. E., and Lipshultz L. I. (2012). The relationship between anogenital distance and reproductive hormone levels in adult men. J. Urolog 187:594-598.

[8] Sumner, S., R. Snyder, J. Burgess, C. Myers, R. Tyl, C. Sloan and T. Fennell (2009). Metabolomics in the assessment of chemical-induced reproductive and developmental outcomes using non-invasive biological fluids: application to the study of butylbenzyl phthalate. J Appl Toxicol 29(8): 703-714.

**Response 3**

Proposition 65 regulations specify that:

> "The determination of whether a level of exposure to a chemical known to the state to cause reproductive toxicity has no observable effect for purposes of Section 25249.10(c) of the Act shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of a chemical as known to the state to cause reproductive toxicity. Nothing in this article shall preclude a person from using evidence, standards, assessment methodologies, principles, assumptions or levels not described in this article to establish that a level of exposure has no observable effect at one thousand (1,000) times the level in question". (Section 25801(a))

In compliance with these regulations, OEHHA conducted literature searches to identify relevant studies and review reports on the developmental toxicity of BBP, and reviewed all of them. The regulations do not require OEHHA to determine if a study is for hypothesis-testing or characterizing risk for risk management purposes. All scientific studies can be considered as hypothesis-testing, since the sole purpose of statistical analysis is to accept or reject a hypothesis the study is designed to test.

As summarized in the Initial Statement of Reasons, the study by Sumner et al. aimed to determine if metabolomic changes in urinary samples (i.e., changes in the pattern of endogenous small molecules excreted in the urine; these small molecules are products of the metabolic processes that occur in biological systems) from BBP-exposed offspring were associated with conventional endpoints indicative of developmental effects on the male reproductive system. The authors reported that three dams per group produced 17 male/13 female, 16 male/15 female, and 6 male/9 female pups in the control, low dose (25 mg/kg-day), and high dose (750 mg/kg-day) groups, respectively. The distribution of pups across the three litters per treatment group was not reported.

None of the pups in the control group or female pups in the BBP-treated groups showed signs of alterations in the reproductive system. In the low dose (25 mg/kg-day) group, a total of 9 males in the three litters had reproductive findings, including 7 males with retained aerolae on postnatal day (PND) 11, and 2 males with reduced AGD on PND 21 (but not on PND 0). None of the males in the low dose group had reduced AGD or retained aerolae on PND 26. Gestational treatment with 750 mg/kg-day of BBP in the high dose group caused damage to the reproductive system of the male pups, including retained aerolae, reduced AGD, partial or complete absence of the epididymis and seminal vesicles in all six male pups and missing or abnormal testis in four male pups.

With regard to the metabolomic measurements, the authors found significant differences in the concentrations of endogenous metabolites in the urinary samples of PND 26 pups between the control and BBP-treated groups at both dose levels. The authors suggested that metabolomics changes may reflect an onset of the development of adverse development outcome, or an initiation of increased response to enable the offspring to adapt to the toxic effects of BBP.

OEHHA recognized in the Initial Statement of Reasons that the study by Sumner et al. (2009) used a small number of animals per group but noted that the effects on development of the male reproductive system were obvious and statistically significant.

With regard to the unit of statistical analysis, OEHHA is aware of the recommendation that litters, rather than individual pups, in developmental toxicity studies should generally be used as the unit in statistical analysis. For example, the U.S. EPA Guidelines for Developmental Toxicity Risk Assessment (1991) state:

> "Because the maternal animal, and not the conceptus, is the individual treated during gestation, data generally are calculated as incidence per litter or as number and percent of litters with particular endpoints."

However, those same guidelines also state:

"An increase in the incidence of malformed offspring may be indicated by a change in one or more of the following endpoints: the incidence of malformed offspring per litter, the number and percent of litters with malformed offspring, or the **number of offspring or litters** with a particular malformation that appears to increase with dose (as indicated by the incidence of individual types of malformations)." (emphasis added)

Pup-based statistical analysis is still frequently used and accepted by the scientific community. For example, the commenter considered the studies by Nagao et al. (2000) and Tyl et al. (2004) as "robust reproductive toxicity studies." In the study by Nagao et al., the unit for statistical analysis on anogenital distance at birth in F1 pups appears to be based on individual pups, not litters (Table 6, page 522, of the publication).[2]

Similar to BBP, developmental exposure to di-n-butyl phthalate (DBP) also causes reduced AGD and increased incidence of retained nipples in male pups. Whether the data on the incidence of retained nipples was analyzed on pup or litter-based units, the level of exposure that caused statistically-significant changes was the same. In other words, even though it would be desirable to use the litter as the unit for statistical analysis, the NOEL and LOEL for the developmental male reproductive effects of DBP

were the same, regardless of the unit utilized.[9] OEHHA notes that the commenter estimated the number of individual pups with or without retained areolae or nipples from these three studies (i.e., Sumner et al., 2009; Tyl et al., 2004, and Nagao et al., 2000). In arguing for excluding the data by Sumner et al. (2009) from consideration, the commenter calculated the incidence of reproductive effects (based on individual pups, not the litters) and made a comparison among these three studies (see page 7 and Table 1 on page 10 of the comments). This practice by the commenter, together with the examples given above, demonstrates that while it is generally preferable to use the litter as the statistical unit when analyzing certain developmental toxicity data, pup-based statistical analysis is acceptable in the field of toxicological sciences.

Regarding reversibility of effects in the study by Sumner *et al.,* OEHHA has addressed that issue in the response to Comment 2, and further notes the generally accepted principle that

> "Developmental effects that are induced by exogenous agents are not limited to death, structural abnormalities, and altered growth. Rather, it has been demonstrated in a number of instances that alterations in the functional competence of an organ or a variety of organ systems may result from exposure during critical developmental periods that may occur between conception and sexual maturation. Sometimes, these functional defects are observed at dose levels below those at which other indicators of developmental toxicity are evident. **Such effects may be transient or reversible in nature, but generally are considered adverse**." (U.S. EPA Guidelines for Developmental Toxicity Risk Assessment (1991)) (emphasis added)

The study by Sumner et al. (2009) identified developmental effects that are consistent with the findings from other studies, and is part of the body of data that was considered in identifying the study by Nagao et al. (2000) as the most sensitive study deemed to be of sufficient quality for BBP MADL calculation. The effects in the Sumner et al. study occurred at a lower level of exposure than that at which there were no observed effects in the study by Tyl et al. (2004).

**Comment 4**

The commenter concluded that "a conservative NOEL for BBP is 50 mg/kg/day," and should be used as the basis for the MADL calculation, using "a weight of evidence"

[9] Mylchreest E., Wallace D.G., Cattley R.C. and Foster P.M.D. (2000). Dose-Dependent Alterations in Androgen-Regulated Male Reproductive Development in Rats Exposed to Di(*n*-butyl) Phthalate during Late Gestation. Tox Sci. 55. 143-151.

approach. The commenter's key argument is that "the observations at the low dose in Sumner [sic] were a statistical anomaly, rather than an indication of treatment-related effects." To support this argument, the commenter compared the findings on two endpoints, retained nipples and reduced AGD in male pups, among the three studies (Nagao et al., 2000; Tyl et al., 2004; and Sumner et al., 2009).

The commenter estimated the total number of male pups with or without retained nipples or areolae from the study by Tyl et al. (2004) and concluded that "at 50 mg/kg/day, the incidence of retained areolae was lower than that of controls, and the incidence at 250 mg/kg/day was not statistically greater than controls."

Regarding the reduced AGD, the commenter noted that "there was no statistical difference in AGD between controls and about 374 male pups (F1 and F2) at 50 mg/kg/day in Tyl [sic]." "In Nagao [sic], there was no statistical difference in AGD between controls and 125 male pups at 20 mg/kg [sic] and 181 male pups at 100 mg/kg/day."

The commenter concluded that "Ferro believes the weight of the evidence clearly is that 50 mg/kg/day is a conservative NOEL for the developmental toxicity of BBP."

**Response 4**

OEHHA agrees with the commenter that the study by Sumner et al. (2009) is critical for determining if the NOEL of 20 mg/kg-day as observed by Nagao et al. (2000) or the NOEL of 50 mg/kg-day as observed by Tyl et al. (2004) should be identified as the basis for the MADL calculation. The key argument by the commenter is that the reproductive effects in male pups from timed-pregnant Sprague-Dawley rats exposed to 25 mg/kg-day BBP as observed by Sumner et al. (2009) were not supported by the findings from the other two studies that examined many more male pups.

A summary of the findings from the study by Sumner et al. (2009) was presented in the Initial Statement of Reasons.[10] Evaluation of developmental landmarks (e.g., retained areolae and reduced AGD) and gross examination of the reproductive tract of male pups were included as endpoints for phenotypic changes in support of metabolomic changes that may be more sensitive to BBP-induced developmental toxicity than traditionally-used phenotypic changes. As reported by the authors, developmental exposure to 25 mg/kg-day of BBP caused both phenotypic (increased incidence of retained areolae) and metabolomic changes. With regard to phenotypic changes, the authors reported 7 out of 16 male pups from 3 litters had retained areolae on PND 11

[10] Available at http://oehha.ca.gov/prop65/law/pdf_zip/060112bbpISOR.pdf

(an incidence of 43.75% vs. none in 17 male pups of the control group). The authors did not report any case of retained nipples in male pups at this dose level. Two male pups in this group had reduced AGD on PND 21, but not on PND 0 or 26. The authors did not report the measured values (i.e., actual AGD in millimeters), neither did the authors provided their definition of "reduced AGD." Therefore, for the phenotypic data, OEHHA relied on the data on retained areolae. OEHHA also found that the difference in the incidence of retained areolae between the control and the 25-mg/kg-day group was statistically significant, using Fisher's Exact probability test. Therefore, it is clear that developmental exposure to 25 mg/kg-day of BBP caused both phenotypic and metabolomics changes in the male pups. The rationale to identify 25 mg/kg-day as the LOEL and the limitations of the study were included in the discussion of the study in the Initial Statement of Reasons.

With regard to the data on retained nipple or areolae from the study of Tyl et al. (2004), the commenter used estimated numbers of male pups from the study report. The commenter's assumption of 5 male pups per group seems to be reasonable. However, the commenter made an apparent error regarding the incidences of retained areola. The commenter stated that "none of about 173 F1 male pups and none of about 201 F2 male pups exhibited retained areolae at PND 11-13" at the dose of 50 mg/kg-day. According to Table 3 of the Tyl et al. study report (page 253), none of the F1 male pups had retained nipples or areolae at the lowest dose (50 mg/kg-day). In fact, there were 5.07% of F2 male pups with retained areolae, compared to 2.13% in F2 controls, an increase of more than two-fold, though the increase was not statistically significant as reported by the authors. In the high-dose group (750 mg/kg-day), the authors found 32.3% male pups remaining in the F1 group at PND 11-13 (after culling on PND 4) had retained areolae, vs. 2.63% in control F1 male pups (the difference is statistically significant). Similarly, 72.15% of F2 male pups had retained areolae, vs. 2.13% in F2 controls. Proportions of male pups with ≥ 1 retained nipple in F1 and F2 male pups (respectively) in the high dose group were also significantly higher than the corresponding controls (none in the controls).

At 750 mg/kg-day, Sumner et al. (2009) reported retained areolae in all male pups (100%, vs. 72.15% in the study by Tyl et al., 2004) and retained nipples in 3 pups (50%, vs. 19.23% in F1 and 16.46% in F2 male pups in the study by Tyl et al. 2004). Therefore, the findings on the retained areolae and retained nipple from the study by Sumner et al. are largely in agreement with those by Tyl et al. (2004).

In conclusion, there is no evidence to support the contention that the findings in the low dose group from the study by Sumner et al. (2009) are invalid Accordingly, since effects in the Sumner et al. (2009) were reported at a level of exposure lower than the

apparent NOEL in the study by Tyl et al. (2004), the highest level of effect that causes no observable effect (in other words, the highest NOEL that is lower than the lowest LOEL for the developmental effects of BBP), is 20 mg/kg-day as reported in the study by Nagao et al. (2000).

**Comment 5**

Relying on some findings from three recent studies that compared the testicular effects of di-*n*-butyl phthalate (DBP) among mouse, rat, and human, the commenter concluded that developmental effects in rats treated with BBP "are specific to the rat and not relevant to humans." The three studies are:

- Heger et al. (2012). Human fetal testis xenografts are resistant to phthalate-induced endocrine disruption. Environ Health Perspect 120(8):1137-43.[11]
- van den Driesche et al. (2012). Proposed role for COUP-TFII in regulating fetal Leydig cell steroidogenesis, perturbation of which leads to masculinization disorders in rodents. PLoS One 7(5):e37064.[12]
- Johnson et al. (2012). Of mice and men (and rats): phthalate-induced fetal testis endocrine disruption is species-dependent. Toxicol Sci. 2012 Oct;129(2):235-48.[13]

**Response 5**

All three studies cited by the commenter investigated male reproductive effects of DBP, not BBP, and thus were not included in OEHHA's initial review. In response to the comments, OEHHA reviewed these three studies and found that the studies by Heger et al. (2012) and van den Driesche et al. (2012) are original research studies and the report by Johnson et al. (2012) is a review focusing on potential modes of actions, especially inter-species differences in response to DBP-induced anti-androgenic effects among mice, rats, and humans.

The studies found that the rat is more sensitive than the mouse to DBP-induced alterations in genes that regulate fetal testosterone biosynthesis. However, there was no difference in formation of multi-nucleated giant gonocytes, an abnormal change in the morphology of stem germ cells. All the authors pointed out that there remains a need to better understand the molecular mechanisms responsible for the differences in

[11] Heger, N.E., Hall, S.J., Sandrof , M.A., McDonnell, E.V., Hensley, J.B., McDowell, E.N., Martin, K.A., Gaido, K.W., Johnson, K.J., and K. Boekelheide (2012). Human fetal testis xenografts are resistant to phthalate-induced endocrine disruption. Environ Health Perspect 120(8):1137-43.
[12] van den Driesche, S, Walker, M., McKinnell, C., Scott, H.M., Eddie, S.L., Mitchell, R.T., Seckl, J.R., Drake, A.J., Smith, L.B., Anderson, R.A., and R.M. Sharpe (2012). Proposed role for COUP-TFII in regulating fetal Leydig cell steroidogenesis, perturbation of which leads to masculinization disorders in rodents. PLoS One 7(5):e37064.
[13] Johnson, K.J., Heger, N.E. and K. Boekelheide (2012). Of mice and men (and rats): phthalate-induced fetal testis endocrine disruption is species-dependent. Toxicol Sci. 2012 Oct;129(2):235-48.

sensitivity (rats) or resistance (mice) to developmental phthalate exposure. None of the authors found or stated that the data observed in rats are not relevant to humans. In fact, van den Driesche et al. concluded that "[this] mechanism may also be functional in humans, and its susceptibility to disruption by environmental chemicals, stress and pregnancy hormones could explain the origin of some human male reproductive disorders."

All the species comparison data observed or cited in these three reports were based on experiments using DBP as a model chemical. BBP and DBP share one common active metabolite, mono-butyl phthalate (MBP). Therefore, data on DBP-induced developmental toxicity or reproductive toxicity resulting from prenatal exposure is relevant for risk assessment of BBP. However, BBP has another active metabolite, mono-benzyl phthalate (MBzP), that DBP does not have. In this regard, without a clear understanding of the role of MBzP in inducing developmental or reproductive toxicity, it is inappropriate to draw any conclusion on the toxicity of BBP solely on DBP data. Furthermore, human data available so far find associations between increased maternal exposure to MBP-producing phthalates and shortened AGD in newborn boys.

In conclusion, OEHHA has carefully considered the comments submitted by Ferro, reviewed all the relevant evidence that is available to OEHHA, and concluded that the study of Nagao et al. (2000) is of sufficient quality and the NOEL of 20 mg/kg-day as reported in this study is the highest NOEL that is lower than the lowest LOEL for the developmental effects of BBP.

## ALTERNATIVES DETERMINATION

In accordance with Government Code section 11346.9(a)(4), OEHHA has, throughout the adoption process of this regulation, considered available alternatives to determine whether any alternative would be more cost effective in carrying out the purpose for which the regulation was proposed, or would be as cost effective and less burdensome to affected private persons than the proposed action. OEHHA has determined that no reasonable alternative considered by OEHHA or that has otherwise been identified or brought to the attention of OEHHA would either be more effective in carrying out the purpose for which the action is proposed, or would be as effective and less burdensome to affected private persons, or would be more cost-effective to affected private persons and equally effective in implementing the statutory policy or other provision of law than the proposed regulation.

For chemicals known to the state to cause reproductive toxicity, an exemption from the warning requirement is provided by the Act when a person in the course of doing

business is able to demonstrate that an exposure for which the person is responsible will have no observable reproductive effect, assuming exposure at 1,000 times the level in question (Health and Safety Code sections 25249.9, 25249.10 and 25249.11). The maximum dose level at which a chemical has no observable reproductive effect is referred to as the No Observable Effect Level (NOEL). The Act also provides an exemption from the prohibition against discharging a listed chemical into sources of drinking water if the amount discharged does not constitute a "significant amount," as defined, and the discharge is in conformity with all other laws and regulatory requirements (Health and Safety Code sections 25249.9 and 25249.11). Thus, these exemptions apply when the exposure or discharge in question is at a level that does not exceed the NOEL, divided by 1,000.

Regulations previously adopted by OEHHA provide guidance for determining whether an exposure to, or a discharge of, a chemical known to cause reproductive toxicity meets the statutory exemption (Sections 25801-25821). These regulations provide three ways by which a person in the course of doing business may make such a determination: (1) by conducting a risk assessment in accordance with the principles described in Section 25803 to derive a NOEL, and dividing the NOEL by 1,000; or (2) by application of the specific regulatory level adopted for the chemical in Section 25805; or (3) in the absence of such a level, by using a risk assessment conducted by a state or federal agency, provided that such assessment substantially complies with Section 25803(a). The specific regulatory levels in Section 25805 represent one one-thousandth of the NOEL.

## LOCAL MANDATE DETERMINATION

OEHHA has determined this regulatory action will not pose a mandate on local agencies or school districts nor does it require reimbursement by the State pursuant to Part 7 (commencing with Section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, these regulations do not impose any mandate on local agencies or school districts.