

**FINAL STATEMENT OF REASONS
TITLE 22, CALIFORNIA CODE OF REGULATIONS**

**SECTION 12805. SPECIFIC REGULATORY LEVELS: CHEMICALS
CAUSING REPRODUCTIVE TOXICITY**

This is the Final Statement of Reasons for a specific regulatory level for di(n-butyl)phthalate (DBP). DBP is listed as known to the State to cause reproductive toxicity under the Safe Drinking Water and Toxic Enforcement Act of 1986 (hereinafter “the Act” or Proposition 65, codified at Health and Safety Code, section 25249.5 *et seq.*). On June 29, 2007, the Office of Environmental Health Hazard Assessment (OEHHA) published a Notice of Proposed Rulemaking (California Regulatory Notice Register, 2007; Notice File No. Z-07-0619-02) to adopt Maximum Allowable Dose Level (MADL) for DBP into Title 22, California Code of Regulations, section 12805¹. The Initial Statement of Reasons set forth the grounds for the proposed regulation. Pursuant to the Notice of Proposed Rulemaking, a public comment period of 45 days was provided from the publication of the Notice until August 13, 2006. A total of three sets of written comments, listed in Table 1 (page 2), were received.

On December 7, 2007, pursuant to the requirements of Government Code, sections 11346.8(d), 11346.9(a)(1), and 11347.1, OEHHA provided a Notice of Addition of Documents and Information to the rulemaking file (Notice File No. Z-07-0619-02). This notice identified relevant documents that had not been previously included in the rulemaking file (OAL Notice File No. Z-07-0619-02). These additional documents include those that were cited in the comments submitted to OEHHA or that became available to OEHHA after the draft MADL document was completed. None of these documents contributed directly to the development of the MADL and were thus not cited in the main text of the document supporting the MADL (OEHHA, 2007). However, these papers have now been reviewed by OEHHA and are sources of relevant information. OEHHA reviewed these papers and determined that no revisions to the MADL document were necessitated by information contained in these papers. All the documents identified in the notice of December 7, 2007, were made available for public inspection and comment between December 7, 2007 and January 7, 2008. No comments were received in response to the Notice of December 7, 2007.

This regulatory action hereby adopts a MADL for DBP.

SUMMARY AND RESPONSE TO COMMENTS

Table 1 below provides the names of those commenting on the July 29, 2007, Notice of Proposed Rulemaking. Comments below are summarized and responses are provided for each of those commenting, in the order given in the table. A number of summarized comments and responses cite journal papers in the scientific literature. At the end of this section, references to these scientific articles are provided.

¹ All further references are to sections of Title 22 of the California Code of Regulations, unless otherwise noted.

Table 1. List of Comments on the Notice of Proposed Rulemaking (OAL Notice File No. Z-07-0619-02)

Commenter/Affiliation	Representing	Date Received
Natural Resources Defense Council (NRDC)	NRDC and 13 other organizations	Aug. 13, 2007
Lisa L. Halko Greenberg Traurig LLP	Nail Manufacturers Council of the Professional Beauty Association (NMC)	Aug. 13, 2007
Marian Stanley American Chemistry Council Phthalate Esters Panel	American Chemistry Council (ACC)	Aug. 13, 2007

Summary of and Responses to Comments from the Natural Resources Defense Council (NRDC)

Comment 1

OEHHA has done a commendable job in carefully evaluating the complicated and challenging science around DBP to produce a thoughtful, well-written, and well-referenced document proposing a regulatory level for DBP.

Response

OEHHA acknowledges the agreement with its approach to establishing a MADL for DBP.

Comment 2

OEHHA’s proposed MADL is more protective of human health than the reference dose (RfD) proposed by the U.S. Environmental Protection Agency (U.S. EPA).

Response

Procedures for the development of Proposition 65 MADLs are provided in Sections 12801 and 12803. OEHHA follows these procedures in developing MADLs for DBP.

Comment 3

Based on major findings from a number of epidemiological studies, the commentor agreed “with OEHHA’s conclusion that “these human studies provide strong evidence that exposure to phthalates at certain levels is associated with developmental, male, or female reproductive effects in humans...” In addition, the commentor agreed with OEHHA that “quantitative relationships for individual phthalates cannot be determined from these studies.” However, the commentor expressed concerns “that human epidemiologic studies appear to show effects at levels just 6 times higher than OEHHA’s proposed MADL, leaving a small margin of safety.” In addition, the commentor

suggested OEHHA take into account cumulative effects resulting from exposure to multiple phthalates.

Response

OEHHA acknowledges the agreement with its analyses and conclusions regarding human epidemiological data on the developmental and reproductive effects of DBP. Scientific evidence that is available at this time is not sufficient to establish a clearly defined quantitative relationship between exposure to DBP and developmental or reproductive effects in humans. Therefore, OEHHA believes that the human data do not provide an adequate basis to establish a MADL for DBP. It should be emphasized that OEHHA follows the procedures for development of Proposition 65 MADLs contained in Sections 12801 and 12803. Should adequate human data become available OEHHA would revise the MADL. With regard to the “margin of safety,” OEHHA acknowledges that the MADL is within a factor of 10 of some levels reported in humans.

Improvements in approaches for assessing phthalates, including approaches for addressing cumulative effects resulting from exposure to multiple phthalates, is currently a subject of review by the National Research Council. OEHHA will consider new methods and approaches as they evolve. The DBP document followed current approaches for MADL development in regulation. OEHHA recognizes that cumulative exposure to phthalates is a matter of considerable public health concern and will continue to monitor the field and be alert for newly established methods and data.

Comment 4

Compared to the draft U.S. EPA assessment, OEHHA has used a more scientifically defensible methodology and has more consistently implemented U.S. EPA’s own guidelines for reproductive toxicity risk assessment.

Response

OEHHA acknowledges the comments.

Comment 5

With regard to the application of proposed MADLs, OEHHA proposed that “for the purpose of Proposition 65, exposure by dermal contact or inhalation or via multiple routes that leads to absorbed doses equivalent to the MADL proposed above should be the maximum allowable dose level.”

The commentor stated that “We agree and support this interpretation of the literature and commend OEHHA for setting a MADL that incorporates multiple routes of exposure.”

Response

OEHHA acknowledges the comments.

Summary of and Response to Comments from the Nail Manufacturers Council (NMC)

The commentor “applauds OEHHA’s decision to investigate and adopt a MADL for DBP.” However, the commentor opposes the specific MADL proposed, based on two arguments: that “The proposed MADL fails to comply with sections 12801 and 12803,” and that “OEHHA lacks authority to adopt a MADL based on the Lee study.” In addition, the commentor suggested a “more scientifically appropriate MADL of 2900 mcg/day [sic], based upon the study by Mylchreest et al. (2000).” Details of these comments and OEHHA’s responses are provided below.

Comment 6

To support the conclusion that “the proposed MADL fails to comply with Sections 12801 and 12803,” because the study did not meet generally accepted scientific principles, the commentor stated that “the offspring, not the mother, was considered to be the statistical unit. That is incorrect. Since the effects were due to prenatal exposure, the dam or litter should have been considered the statistical unit.”

Response

For clarification, Section 12801(a) states 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 12803(a)(5) states that “the NOEL [No Observable Effect Level] shall be based on the most sensitive study deemed to be of sufficient quality.”

Following the provisions specified in Sections 12801 and 12803, OEHHA carefully reviewed the study by Lee et al. (2004) and selected it as the basis for the MADL calculation. Both male and female reproductive effects were observed at the lowest dose (20 ppm) used in this study. The NOEL that was relied upon for calculation of the MADL was for male and female reproductive toxicity.

The litter is generally the experimental unit for statistical analysis for studies designed to evaluate developmental effects of chemicals following gestational exposure. However, individual pups are also commonly used, especially when the pups are examined after they have been weaned on postnatal day (PND) 21 or 22. Laboratory rats begin independent ingestion of diets around PND15-18. In the study by Lee et al. (2004),

offspring received DBP in feed until PND 21. Therefore, rats used in the Lee et al. study were exposed to DBP both via dams' milk and through independent ingestion of DBP-containing feed between PND 15 and 21. Individual pups in this study are therefore considered as individual units for analysis.

The main male reproductive effects of DBP observed by Lee et al. were testicular effects and abnormal structural changes in the mammary gland (retained nipples and histopathological changes). Mylchreest et al. (1998, 2000) also reported testicular effects or nipple retention following DBP exposure. The dose response relationships for these effects were similar when the litter or individual pups were used as experimental units.

While use of the litter as the unit for statistical analysis is generally preferable, use of individual pups as the statistical unit in the study by Lee et al. (2004) is not a basis for considering this study to be of insufficient quality. It is also noteworthy that the statistical unit was not considered to be an issue for this study by either the U.S. EPA or the European Union (U.S. EPA, 2006; EFSA, 2005).

Comment 7

The second basis for the commentor's conclusion that "the proposed MADL fails to comply with Sections 12801 and 12803" is that "the changes noted in spermatogenesis and alveolar buds were minimal, and were transient." The U.S. EPA "did not consider either of these effects to be adverse effects. The biological significance of the changes observed in the alveolar bud of males is unclear and they are not regarded as adverse effects in this study."

Response

Lee et al. (2004) was included for review in the U.S. EPA draft report, "Toxicological Review of Dibutyl Phthalate" (U.S. EPA, 2006).

The U.S. EPA recognized the effects of DBP at 20 ppm on the testis and mammary gland in males and on the mammary gland in females, but did not consider these effects as "adverse" since they were reversible (germ cell loss in males and morphological changes in the females) or had unclear biological significance.

As discussed in detail in the MADL supporting document (OEHHA, 2007), morphological changes in the mammary gland in both male and female pups following perinatal exposure to DBP are indicative of hormonal perturbations caused by DBP (e.g., as discussed by Lucas et al. (2007).

With regard to histopathological changes in the reproductive organs, the U.S. EPA 1996 Guidelines for Reproductive Toxicity Risk Assessment state that "significant and biologically meaningful histopathologic damage in excess of the level seen in control tissue of any of the male reproductive organs should be considered an adverse reproductive effect." With regard to reversibility, the same U.S. EPA document states

that “the reversibility of an adverse effect on the reproductive system can be affected by the degree and duration of exposure.” Treatment with DBP in the study of Lee et al. (2004) stopped on PND 21. The histopathological changes in the testis in males and in the mammary glands of both males and females appeared to be reversible at low doses in Week 20 (17 weeks after the exposure ended). As stated in the MADL supporting document (OEHHA, 2007), “available data do not permit a determination of whether this effect would still be reversible if the exposure continued after PND 21.” Therefore, OEHHA’s evaluation of this study is consistent with the U.S. EPA Guidelines for Reproductive Toxicity Risk Assessment, which represent generally accepted scientific principles in this area.

Comment 8

The commentor stated that “The European Union (EU) also discounted the Lee study’s conclusions. An EU Scientific Panel considered the low dose (20 ppm) in this study to be a LOAEL of 2 mg/kg/day, but applied a reduced uncertainty factor.”

Response

As recognized by the commentor, the EU identified an adverse effect level at the lowest dose tested in the Lee et al. study, the same study used by OEHHA as the basis for the MADL, and relied on this study in establishing a Tolerable Daily Intake for DBP. OEHHA’s identification of 20 ppm as a LOEL is therefore entirely consistent with the EU identification (EFSA, 2005).

Comment 9

The commentor challenges OEHHA’s interpretation of the findings in the Lee et al. (2004) study, arguing that the effects relied upon by OEHHA are not “reproductive” effects, citing the Final Statement of Reasons for Section 12830: “In males, the effects include impotence, semen quality changes, genetic damage, or adverse effects of the gonadal function.” Specifically, the commentor states that “the Lee study identified transient, minor changes in immature rats. There is no evidence that those changes caused impotence, semen quality changes, or adverse effects on gonadal function. They can’t have caused them, because the changes went away before the rats were reproductive mature. Therefore, the changes are reproductive effects, and cannot be used to identify a NOEL under section 12801 or 12803.” In addition, the commentor stated that Lee study cannot be used to identify a NOEL based on developmental effects, because the exposure to DBP in this study was both pre- and post-natal, and Proposition 65 does not regulate developmental effect from postnatal exposure.

Response

The commentor’s interpretation of the scope of reproductive toxicity is erroneous in that the manifestations of male reproductive effects listed in the Final Statement of Reasons for Section 12830 are unequivocally examples of such effects, and not an exhaustive list.

Effects seen in the study by Lee et al. (2004) such as a significantly increased number of animals with a reduced number of spermatocytes at the lowest dose tested is a clear indication of the adverse effect of DBP on testicular development.

As discussed in the Response to Comment 7, even though the effects of perinatal exposure to DBP on the testis and mammary gland appear to be reversible when the pups reached adulthood (20 weeks old), these effects can be identified as adverse effects under the 1996 U.S. EPA Guidelines for Reproductive Toxicity Risk Assessment. They have also been identified as adverse effects in the risk assessment document by the EU. It should be pointed out that the study did not evaluate if the observed effects in immature rats could affect the reproductive functions in the adult and therefore the period of time subsequent to discontinuation of phthalate exposure for which the effect may persist is unknown. Human exposure to phthalates is a continuing exposure and for that reason the study may under-represent the effect of continued exposure to phthalates. Clearly, effects on the reproductive system were observed in this study. Therefore, it is both scientifically and legally appropriate to rely on the reproductive effects observed in the study by Lee et al. (2004) for calculation of the MADL.

Comment 10

The commentor concluded that the authors of the Lee et al. study determined a NOEL based on changes with no reproductive effect. Therefore, OEHHA lacks authority to adopt a MADL based on the Lee study.

Response

Consistent with generally accepted principles of reproductive toxicology and the 1996 U.S. EPA Guidelines for Reproductive Toxicity Risk Assessment, the effects of DBP on the testis in males and on the mammary glands in both males and females are reproductive effects. These effects were observed in the Lee et al. study and the findings were totally consistent with findings from numerous other studies and were supported by the generally accepted modes of actions for this chemical. Therefore, OEHHA has the authority to propose and adopt a MADL based on the findings from the study by Lee et al. (2004).

Comment 11

The commentor believed the study by Mylchreest et al. (2000) or the study by Zhang et al. (2004) are “more scientifically appropriate,” and therefore the MADL should be based on a NOEL of 50 mg/kg-day as observed in these two studies.

Response

The studies by Mylchreest et al. (2000) and Zhang et al. (2004), respectively, had been reviewed by OEHHA and were discussed in the MADL supporting document (OEHHA, 2007) and hence the Initial Statement of Reasons. OEHHA agrees with the commentor

that these studies are of sufficient quality. However, compared to other studies that are also of sufficient quality, these two studies are not “the most sensitive study that are deemed to be of sufficient quality,” that is the study to be used for establishing a NOEL pursuant to Sections 12801 and 12803. Therefore, the NOEL (50 mg/kg-day) observed in these two studies was not used as basis for MADL calculation.

SUMMARY OF AND RESPONSE TO COMMENTS FROM THE AMERICAN CHEMISTRY COUNCIL (ACC)

Comments from the ACC argued against use of the study by Lee et al. (2004) as the basis for MADL calculation, proposed that marmosets and mice are less sensitive to DBP than are rats and thus questioned the validity of using effects observed in rats for MADL development. In addition, ACC concluded that the NOEL is 30 mg/kg-day, from the study by Lehman et al. (2004). ACC proposed a MADL based on this NOEL. Details of the ACC’s comments and OEHHA’s responses are provided below.

Comment 12

ACC concluded that the effects reported at the low dose in Lee et al. (2004) are transient, show no clear pattern of response, have no known biological significance, and therefore are not properly considered adverse. Under this argument, the ACC discussed the effects of DBP on the pituitary, mammary gland, and the testis and concluded that all the effects are “transient” and thus should not be considered adverse.

Response

This comment is similar to that raised by the Nail Manufacturers Council (Comment 7). The pituitary effect of DBP in pups as observed by Lee et al. (2004) was not identified as a critical endpoint for the male or female reproductive effects of DBP for MADL development, even though OEHHA believes it is relevant to the reproductive toxicity of this chemical. In the Initial Statement of Reasons and MADL supporting document (OEHHA, 2007), OEHHA has provided detailed discussion of the biological significance of histopathological changes in the mammary gland of males and females, and in the testis of male pups. As discussed above in OEHHA’s Response to Comment 7, OEHHA’s evaluation and conclusions regarding the findings by Lee et al. (2004) is completely consistent with the U.S. EPA Guidelines for Reproductive Toxicity Risk Assessment.

Comment 13

ACC concluded that the biological significance of the effects of DBP at low doses observed in the study by Lee et al. (2004) is “scientifically unfounded” and that this study is “of insufficient quality for use in setting the NOEL for DBP,” because: 1) the numbers of animals used in this study are too low to provide robust conclusions regarding the effects reported at low doses; 2) the effects were not reported in previous studies by the National Toxicology Program; 3) the effects reported cannot be compared to historical

control information; 4) the study cannot be peer reviewed to determine its validity; and 5) the effects reported are unlikely to reflect the mode of action (MOA) and potency of DBP.

Response

OEHHA disagrees with the arguments raised by the ACC. Lee et al. (2004) used 6-8 litters per group in their study. While the group is indeed smaller than used in other studies cited by the ACC in their comments (e.g., in the Wine et al. (1997) and Mylchreest et al. (2000) studies), this group size is large enough to detect DBP-caused abnormal changes in the testis and the mammary gland. In other words, the group size is large enough to provide sufficient statistical power to detect an effect of the magnitude observed in this study. Using a larger group of animals in the study would have increased the statistical power, and consequently might have detected a statistically significant effect on other parameters, but would not have reduced the likelihood of detecting the reported effects.

There are numerous studies in the literature that have consistently shown that perinatal exposure to DBP can cause alterations in the development of the testis and mammary gland of male pups. The findings by Lee et al. (2004) are consistent with the generally recognized effects of DBP in developing animals. However, according to the information available to OEHHA, detailed histopathological evaluation of the mammary gland of male and female pups and the testis of male pups during development, as conducted by Lee et al. (2004), has not been included in other studies, including those conducted by the National Toxicology Program (NTP). The Lee study with its histopathological evaluation of reproductive tissue used more sensitive measures to find effects, and therefore it is not surprising that the same findings have not been reported in other studies. To OEHHA's knowledge, there is no historical database available on the histopathological changes observed by Lee et al. (2004). While historical control data are generally recognized to be useful in interpretation of developmental and reproductive toxicological endpoints, it is also generally recognized that comparison of data from treated animals with concurrent controls should always take precedence over comparison with historical control data (e.g., see the U.S. EPA (1991) developmental toxicity guidelines. Thus, the statistically-significant effects in the study by Lee et al. meet the generally-accepted standards of scientific validity.

The study report by Lee et al. (2004) is a peer-reviewed publication in Toxicology, a pre-eminent international journal that publishes high quality original research and critical reviews dealing with the adverse effects of xenobiotics on the health of humans and animals. The findings by Lee et al. (2004) are highly consistent with the modes of action by which DBP exerts its reproductive effects, as proposed by many investigators (e.g., NTP-CERHR, 2003; Foster et al. 2005).

In conclusion, OEHHA disagrees with each reason advanced to call into question the study by Lee et al. (2004) and OEHHA instead finds this study is "of sufficient quality"

and that this sensitive study is the most appropriate basis for establishing MADLs for DBP, per Sections 12801 and 12803.

Comment 14

OEHHA's assessment does not take into account a recent study in marmosets suggesting that primates are less sensitive to effects of DBP than are rats, and another in mice suggesting that not all rodents respond in the same manner to DBP exposures. Together, these studies call into question the validity of basing the DBP MADL on effects reported in low doses in rats.

Response

As defined in Sections 12801 and 12803, a MADL is derived from a NOEL based on the most sensitive study deemed to be of sufficient quality. The Sprague-Dawley rat used in the study by Lee et al. (2004) is one of the most commonly used laboratory animals in biomedical and toxicological research. There is no scientific evidence indicating that the reproductive effects of DBP observed in rats are irrelevant to humans. In fact, there is substantial evidence indicating that marmosets may not be a good animal model to evaluate the male reproductive toxicity of chemicals for potential risks in men (Li et al. 2005). Therefore, there is no scientific basis for questioning the validity of the reproductive effects of DBP as observed by Lee et al. (2004).

Comment 15

A more scientifically justifiable NOEL for DBP is the 30 mg/kg/day determined by the U.S. EPA in its recent toxicological review of DBP. This NOEL, which is 200 times higher than the NOEL chosen by OEHHA, is itself conservative because it is based on an effect that has not reliably been shown to coincide with any adverse developmental effects at that dose, namely reduced fetal testicular testosterone.

Response

OEHHA reviewed the study by Lehmann et al. (2004) relied upon by U.S. EPA and provided detailed discussion of the findings from this study in the Initial Statement of Reasons and the MADL supporting document (OEHHA, 2007). OEHHA considered this study to be of sufficient quality. However, the NOEL observed in this study is higher than that in the study by Lee et al. (2004). Therefore, it is not the most sensitive study and OEHHA cannot use this study for MADL calculation, according to the provisions of Section 12801 and 12803.

Comment 16

ACC stated that the scientific inappropriateness of Lee et al. for setting the DBP NOEL is supported by a recent toxicological review performed by the U.S. Environmental Protection Agency (EPA) and the conclusions of an external peer review panel comprised

of independent experts. In addition, the “Australian DBP hazard assessment did not consider the low dose effects in Lee et al. to be adverse.”

In addition, the ACC stated that the “overly conservative nature of OEHHA's assessment and proposed MADL is demonstrated by assessments of DBP toxicity conducted by other government agencies, including the EPA (which was reviewed by an external peer review panel), the National Toxicology Program Center for Evaluation of Risks to Human Reproduction, the European Union, and the Australian Department of Health and Aging, all of which have reached more reasonable and scientifically valid conclusions regarding the toxicity of DBP.”

Response

OEHHA follows the provisions of Sections 12801 and 12803 in developing MADLs. OEHHA notes that, while there is uniform consensus that DBP causes developmental toxicity, other organizations have reached varying conclusions about the level of exposure that represents the NOEL. Since OEHHA has no basis for concluding that the study by Lee et al. (2004) is not of sufficient scientific quality, OEHHA has identified it as the most sensitive study and used it in establishing the MADL.

This study by Lee et al. (2004) is sensitive, of high quality, and its findings are consistent with the generally recognized effects of DBP in developing animals. Unlike other studies of reproductive effects of DBP, this study included detailed histopathological evaluation of the mammary gland of male and female pups and the testis of male pups during development. The study report by Lee et al. (2004) is a peer-reviewed publication in *Toxicology*, a pre-eminent international journal that publishes high quality original research and critical reviews dealing with the adverse effects of xenobiotics on the health of humans and animals. The findings by Lee et al. (2004) are entirely consistent with the modes of action by which DBP exerts its reproductive effects, as proposed by many investigators (e.g., NTP-CERHR, 2003; Foster et al. 2005). Thus, for the purpose of Proposition 65, this study is the most sensitive study of sufficient quality for establishing a NOEL for the reproductive effects of DBP.

Comment 17

ACC stated that OEHHA normally refers the acute or chronic Reference Exposure Levels (REL) for airborne toxicants developed by OEHHA to a Scientific Review Panel for review, and that “the MADL value is conceptually no different than the REL,” ACC requested that “OEHHA submits its assessment of DBP toxicity to a Scientific Review Panel” and predicted that “such a review would reach the same conclusions as have the EPA, the EPA’s external peer review panel, and the Australian Government – that the low dose effects reported in Lee et al. are not adverse, and should not be used to define the NOEL for DBP.”

Response

Section 39660(c)(3) of the Health and Safety Code which pertains to Reference Exposure Levels requires that “The scientific basis or scientific portion of the method used by [OEHHA] to assess the factors set forth in this subdivision shall be reviewed in a manner consistent with this chapter by the Scientific Review Panel on Toxic Air Contaminants,” and such action by OEHHA is therefore mandatory rather than discretionary. No such peer-review requirement exists for MADLs. However, OEHHA’s practice is to provide the members of the Proposition 65 Developmental and Reproductive Toxicant Identification Committee, the State’s Qualified Experts for reproductive toxicity under Proposition 65, with the opportunity to comment on draft MADLs and the documents supporting them. No comments on the draft DBP MADL or its supporting document were received from any member of the Committee.

References

The following references were cited above in the summary and responses to the three submissions.

European Food Safety Authority (EFSA, 2005 Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to Di-Butylphthalate (DBP) for use in food contact materials. The EFSA Journal 242: 1-17.

Foster PM (2005). Mode of action: impaired fetal leydig cell function--effects on male reproductive development produced by certain phthalate esters. Crit Rev Toxicol 35, 713-9.

Lee KY, Shibutani M, Takagi H, Kato N, Takigami S, Uneyama C et al. (2004). Diverse developmental toxicity of di-n-butyl phthalate in both sexes of rat offspring after maternal exposure during the period from late gestation through lactation. Toxicology 203, 221-38.

Lehmann KP, Phillips S, Sar M, Foster PM, Gaido KW (2004). Dose-dependent alterations in gene expression and testosterone synthesis in the fetal testes of male rats exposed to di(n-butyl) phthalate. Toxicol Sci 81, 60-8.

Li L-H, Donald JM, Golub MS (2005). A Review on Testicular Development, Structure, Function, and Regulation in Common Marmoset. Birth Defects Research Part B. Developmental and Reproductive Toxicology. 74(5):450-469.

Lucas JN, Rudmann DG, Credille KM, Irizarry AR, Peter A, Snyder PW (2007). The rat mammary gland: morphologic changes as an indicator of systemic hormonal perturbations induced by xenobiotics. Toxicol Pathol 35, 199-207.

Mylchreest E, Cattley RC, Foster PM (1998). Male reproductive tract malformations in rats following gestational and lactational exposure to di(n-butyl) phthalate: an antiandrogenic mechanism? Toxicol Sci 43, 47-60.

Mylchreest E, Wallace DG, Cattley RC, Foster PM. (2000). Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to Di(n-butyl) phthalate during late gestation. *Toxicol Sci* 55, 143-51.

National Toxicology Program-Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR, 2003). NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di-n-Butyl Phthalate (DBP). Center for the Evaluation of Risks to Human Reproduction, NTP, U.S. Department of Health and Human Services, Research Triangle Park, NC;

Office of Environmental Health Hazard Assessment (OEHHA, 2007). Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Di(n-butyl)phthalate (DBP). Available at <http://www.oehha.ca.gov/prop65/law/DBPnotice062907.html#downloads>

U.S. Environmental Protection Agency (U.S. EPA, 1991). Guidelines for Developmental Toxicity Risk Assessment, Federal Register 56:63798-826

U.S. Environmental Protection Agency (U.S. EPA, 1996) Guidelines for Reproductive Toxicity Risk Assessment, EPA/630/R-96/009 FRL-5630-6, Washington DC.

U.S. Environmental Protection Agency (U.S. EPA, 2006). Draft Toxicological Review of Dibutyl Phthalate (di-nButyl Phthalate). U.S. EPA, Washington DC.

Wine RN, Li LH, Barnes LH, Gulati DK, Chapin RE (1997). Reproductive toxicity of di-n-butylphthalate in a continuous breeding protocol in Sprague-Dawley rats. *Environ Health Perspect* 105, 102-7

Zhang Y, Jiang X, Chen B (2004). Reproductive and developmental toxicity in F1 Sprague-Dawley male rats exposed to di-n-butyl phthalate in utero and during lactation and determination of its NOAEL. *Reprod Toxicol* 18, 669-76.

ALTERNATIVES DETERMINATION

In accordance with Government Code section 11346.5(a)(7), OEHHA has, throughout the adoption process of this regulation, considered available alternatives to determine whether any alternative would be more effective in carrying out the purpose for which the regulations were proposed, or would be as effective and less burdensome to affected private persons than the proposed action. OEHHA has determined that no alternative considered would be more effective, or as effective and less burdensome to affected persons, than the proposed regulation.

For chemicals listed under the Act as known to cause reproductive toxicity, the Act exempts from its requirements discharges to sources of drinking water and exposures of people without provision of a warning if the exposure produces no observable effect on reproduction assuming exposure at 1,000 times the level in question, or the discharged

amount is at or below this level. The Act does not specify numerical levels of exposure where there would be no observable effect given an exposure 1,000 times the level in question, i.e., the maximum allowable dose level (MADL).

The purpose of this regulation is to provide “safe harbor” levels for certain chemical exposures. This regulation establishes MADLs for a chemical that causes reproductive toxicity. The discharge prohibition does not apply to exposures at or below these levels and warnings regarding reproductive toxicity concerns are not required for exposures at or below these levels. Thus, these levels will allow persons subject to the Act to determine whether a given discharge to sources of drinking water or exposure of people involving these chemicals is subject to the warning requirement and discharge prohibition provisions of the Act (Health and Safety Code sections 25249.6 and 25249.5 respectively).

Although Section 12803 describes principles and assumptions for conducting risk assessments to derive safe harbor levels, many businesses subject to the Act do not have the resources to perform these assessments. Yet each business with ten or more employees needs the ability to determine whether its activities or products are subject to the discharge prohibition or warning requirements of the Act. Given the wide use or occurrence of the chemicals covered by this regulation, the absence of this regulation would leave numerous businesses without an efficient way of determining if they are in compliance with the Act without the expenditure of significant resources on their part.

LOCAL MANDATE DETERMINATION

OEHHA has determined the 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 the proposed regulatory action. It should be noted that Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, the proposed regulations do not impose any mandate on local agencies or school districts.