FINAL STATEMENT OF REASONS
TITLE 22, CALIFORNIA CODE OF REGULATIONS

SECTION 12805. SPECIFIC REGULATORY LEVELS: REPRODUCTIVE TOXICANTS

This is the Final Statement of Reasons for specific regulatory levels for di(2-ethylhexyl)phthalate (DEHP) by oral exposure. DEHP 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 24, 2005, the Office of Environmental Health Hazard Assessment (OEHHA) published a Notice of Proposed Rulemaking (California Regulatory Notice Register, 2005) to adopt regulatory levels for DEHP by oral exposure pursuant to Title 22, California Code of Regulations, section 12000[1]. 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 8, 2005, and a public hearing was held on August 8, 2005. Written and oral testimony was accepted at the hearing. A total of eight sets of written comments, listed in Table 1 (page 2), were received.

On August 17, 2005, 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 rulemaking File OAL File No. Z-05-0614-06. This notice identified relevant documents that had not been previously included in the Rulemaking File OAL FILE No. Z-05-0614-06, but that had been reviewed by OEHHA in establishing the proposed MADLs for DEHP by oral exposure. Of these documents, 15 citations were not included in the MADL support document cited in the Initial Statement of Reasons published on June 24, 2005 (California Regulatory Notice Register, 2005). These 15 citations were papers that became available to OEHHA after preparation of the MADL document was completed. OEHHA reviewed these papers when they became available and determined that no revisions to the MADL document were necessitated by information contained in these papers. Although information provided in these recent papers did not contribute directly to the development of the MADLs (and thus these papers were not cited in the MADL document), these papers were reviewed and considered by OEHHA because they could be sources of potentially relevant information. All the documents identified in the notice of August 17, 2005, were made available for public inspection and comment between August 17 and September 1, 2005.

On August 23, 2005, on behalf of the American Chemistry Council (ACC), Price (2005b) submitted comments to OEHHA concerning the Notice of August 17, 2005, and requested that OEHHA provide a written explanation of the manner in which it was relying on the new documents identified in the notice and requested that OEHHA extend the comment period. In response to the request, OEHHA issued another Notice of Addition of Documents and Information to Rulemaking file, OAL FILE No. Z-05-0614-06, on August 30, 2005, and extended the comment period from September 1 through

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

September 15, 2005. One further set of comments from the ACC (Price, 2005c) was received.

On May 5, 2006, OEHHA issued two additional notices: "Notice of Modifications to Text of Proposed Regulations, Amendment to Title 22, California Code of Regulations, Section 12805 (OAL Rulemaking File No. Z-05-0614-06)" and "Notice of Addition of Documents and Information to OAL Rulemaking File No. Z-05-0614-06." A public comment period of fifteen days from May 5 through May 22, 2006, was provided. Two sets of written comments were received. One was from Schettler and Hall (2006) on behalf of Health Care Without Harm, and the other from Shah (2006) on behalf of the ACC.

This regulatory action hereby adopts maximum allowable dose levels for DEHP by oral exposure.

SUMMARY AND RESPONSE TO COMMENTS ON THE NOTICE OF PROPOSED RULEMAKING PUBLISHED ON JUNE 24, 2005.

Eight commenters, listed in Table 1, submitted comments on the Notice of Proposed Rulemaking. Comments from Gould et al. (2005), Schettler and Hall (2005), Chan (2005), Brody (2005), Schmitz (2005), Rizzo (2005), and Lunder (2005), respectively, are relatively brief. Comments from these seven commenters are summarized and responded to issue by issue in Comments 1 to 11. On behalf of the ACC's Phthalate Esters Panel, Price (2005a) submitted a set of comprehensive comments and expressed opinions that are generally different from the other seven commenters. The comments by Price (2005a) are summarized and responded to in Comment 12-22.

Table 1. List of Commenters for the Notice of Proposed Rulemaking Published on June 24, 2005

Commenter/Affiliation	Representing	Date Received	Submission No./Citation
Robert M. Gould, Julie Silas, SF Bay Area PSR Jimmy H. Hara, Felix Aguilar, PSR – Los Angeles	San Francisco Bay Area and Los Angeles Chapters of Physicians for Social Responsibility	Jul. 25, 2005	C-1/Gould et al., 2005
Ted Schettler Science and Environmental Network Anna G. Hall Health Care Without Harm	Health Care Without Harm	July 25, 2005	C-2/Schettler and Hall, 2005
Wilma Chan	Chairwoman, Assembly Committee on Health, California State Assembly	August 5, 2005	C-3/Chan, 2005
Charlotte Brody Commonweal	Commonweal	August 5, 2005	C-4/Brody, 2005
Mike Schmitz California League for Environmental	California League for Environmental Enforcement Now	August 5, 2005	C-5/Schmitz, 2005

Enforcement Now			
Jeanne Rizzo Breast Cancer Fund	Breast Cancer Fund	August 5, 2005	C-6/Rizzo, 2005
Sonya Lunder Environmental Working Group	Environmental Working Group	August 8, 2005	C-7/Lunder, 2005
Courtney M. Price CHEMSTAR	American Chemistry Council Phthalate Esters Panel	August 8, 2005	C-8/ Price, 2005a

Comment 1

Six commenters supported calculating specific and different MADLs for adults, infant boys and neonatal infant boys (Brody, 2005; Chan, 2005; Gould et al., 2005; Lunder, 2005; Schettler and Hall, 2005; Schmitz, 2005). A seventh, Rizzo (2005), stated that creating separate MADLs for adults, infants and neonates is a step in right direction. One commenter (Price, 2005a) opposed separate MADLs for infants and neonates.

Response

OEHHA acknowledges the agreement with its approach of calculating different MADLs for adults, infant boys, and neonatal infant boys.

Comments by Price (2005a) are summarized and responded to below (Comments 12-22).

Comment 2

Chan (2005) and Rizzo (2005) expressed concern that scientists employed by chemical industry groups conducted the studies used in developing the MADLs.

Response

The study used by OEHHA as the basis for the oral MADLs (David et al., 2000) was published in the peer-reviewed scientific literature. Section 12803(a)(4) requires that "the NOEL shall be based on the most sensitive study deemed to be of sufficient quality." The study was carefully reviewed by OEHHA and was found to meet this requirement.

Comment 3

Six commenters raised concerns about multiple sources of exposure to DEHP and suggested OEHHA consider regulations addressing aggregate exposure to DEHP (Brody, 2005; Chan, 2005; Lunder, 2005; Rizzo, 2005; Schettler & Hall, 2005; Schmitz, 2005).

Response

The methods for calculating the MADL are laid out in regulation (Section 12805). The extent to which exposures should be aggregated in evaluating whether or not a given exposure may require a warning is an issue separate from MADL development.

Comment 4

Three commenters (Brody, 2005; Lunder, 2005, and Rizzo, 2005) suggested that OEHHA consider regulations addressing exposure to multiple phthalates with similar reproductive toxicity.

Response

Although concurrent or consecutive exposures to chemicals that may act through similar mechanisms and exert the same adverse effects are a matter of considerable public health concern, these comments are beyond the scope of the current regulatory action.

Comment 5

Chan (2005) and Rizzo (2005) suggested that the MADLs for boys should apply for girls.

Response

DEHP is currently listed under the Proposition 65 program as known to the state to cause developmental and male reproductive toxicity, but not female reproductive toxicity. The MADL is derived on the basis of "the reproductive effect for which studies produce the lowest NOEL" (Section 12803(a)(1)). In the case of DEHP, that effect is male reproductive toxicity and, consequently, these MADLs cannot apply to girls. The MADL for adults applies to both adult men and pregnant women.

Comment 6

Chan (2005) suggested that there should be a separate MADL for women of childbearing age and this MADL should not be based on the weight of an adult male. Rizzo (2005) also suggested that pregnant women be used as the standard for determining the MADL.

Response

DEHP is known to the state to cause developmental and male reproductive toxicity. Section 12803(a)(1) states that "where multiple reproductive effects provide the basis for the determination that a chemical is known to the state to cause reproductive toxicity, the reproductive effect for which studies produce the lowest NOEL shall be utilized for the determination of the NOEL." As presented in OEHHA (2005, 2006), "the NOEL (5.8 mg/kg-day) for male reproductive toxicity as observed by David et al. (2000a) is lower than the NOEL (48 mg/kg-day) for the developmental toxicity of DEHP as observed by Price et al. (1988). Therefore, the oral study in rats reported by David et al. (2000a) was used as basis for establishing the MADL for DEHP via the oral route of exposure."

Comment 7

Chan (2005) suggested that there should be a zero tolerance level for exposure to DEHP. Similarly, Lunder (2005) and Rizzo (2005) suggested that OEHHA consider regulations that would eliminate exposure to DEHP from use of phthalate-containing medical devices.

Response

Both of these suggested actions are beyond the scope of OEHHA's current regulatory action and would likely require changes to the Proposition 65 statute through legislative action or the initiative process in order to provide OEHHA with the authority to take the actions suggested in these comments.

Comment 8

Lunder (2005) suggested that OEHHA should consider a MADL for premature infants based on a body weight of one kilogram. Rizzo (2005) also noted that there is not a specific MADL for premature infants, and noted that such infants are most at risk because their exposure is more intense.

Response

Section 12803(a) states that "the NOEL shall be converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL." Thus, MADLs could potentially be calculated for individuals of any assumed bodyweight. At this time OEHHA is adopting MADLs for neonatal infant boys, infant boys, and adults.

Comment 9

Lunder (2005) stated that newborn infants might have an existing burden of DEHP and its harmful metabolites resulting from pre-birth exposure during pregnancy. Thus, the commenter suggested that the MADLs for a newborn infant should be adjusted for this possibly preexisting background burden. Similarly, Brody (2005) stated that the MADLs as proposed do not adequately address prenatal exposure.

Response

Data are not available to address increased susceptibility to testicular effects that may result from pre-natal exposure to DEHP. DEHP has a short half-life, so from an exposure perspective there should not be a large body burden in the newborn from exposure of the mother during pregnancy. Also, the MADL applies to the level in question relative to knowing and intentional exposure in the course of doing business (Health and Safety Code sections 25249.6 and 25249.10). If the same party is responsible for both pre- and postnatal exposures, that party has responsibility for accounting for both those exposures

in determining if a warning is required. If the parties responsible for those exposures are different, each is responsible for providing a warning only for the exposure it caused knowingly and intentionally in the course of doing business.

Comment 10

Schmitz (2005) urged OEHHA to re-evaluate adopted MADLs when any new studies providing pre- and peri-natal data on DEHP toxicity become available.

Response

Any adopted MADL can potentially be re-evaluated if appropriate new data of sufficient quality become available.

Comment 11

Rizzo (2005) noted that the proposed MADLs were set on a linear scale taking only body weight into account, and that children are especially vulnerable and that should be taken into account.

Response

The MADLs for DEHP by oral exposure are based on a NOEL of 5.8 mg/kg-day as observed in rats in the study by David et al. (2000). This NOEL is lower than the lowest LOEL (10 mg/kg-day) for the male reproductive effects of DEHP as observed by Akingbemi et al. (2001; 2004) in rats of 21-34 days of age. Testis in rats at this age is still developing and has been shown to be more sensitive to DEHP than that of adult rats. Therefore, the NOEL that OEHHA relied on as the basis for the proposed MALDs for DEHP by oral exposure is lower than the LOEL for the male reproductive toxicity of DEHP in rats of sensitive ages. OEHHA considered the fact that developing animals are more susceptible to the male reproductive toxicity of DEHP in establishing MADLs for this chemical, even though OEHHA did not use a NOEL observed in rats younger than those used in study by David et al. (2000; six weeks or 42 days old at the beginning of treatment).

Comment 12

Price (2005a) submitted a total of 53 pages of comments on OEHHA's Notice of June 24, 2005. The commenter presented six main points and concluded that "OEHHA should eliminate the separate MADLs for infants and neonates and raise the oral DEHP MADL to reflect a more appropriate NOAEL for DEHP effects." These comments are summarized, issue-by-issue, and responded to in Comment 12-22 below.

In the first point, the commenter stated that "OEHHA should await the outcome of the National Toxicology Program Center for the Evaluation for Risks to Human Reproduction Expert Panel review, to be conducted October 10-12, before developing the

final oral MADL." The commenter notes that the [Panel] report is anticipated to provide up-to-date expert guidance on the reliability and significance of the various studies on DEHP reproductive toxicity and so will inform selection of the appropriate NOEL.

Response

OEHHA is the lead agency in implementing Proposition 65. The methods for calculating the MADL are laid out in regulation (Section 12805). The National Toxicology Program Center for the Evaluation for Risks to Human Reproduction (NTP-CERHR) Expert Panel is not charged with identifying the most appropriate NOEL to serve as the basis for a Proposition 65 MADL. Accordingly, OEHHA is not required to follow the conclusions by the NTP-CERHR Expert Panel, although OEHHA considered all relevant information, including that which is contained in the NTP-CERHR Expert Panel Report on DEHP and is available to OEHHA. OEHHA proceeded with development of the MADLs based on its own timeframe pursuant to Section 12805.

In the process of finalizing proposed MADLs for DEHP by oral exposure, OEHHA noted that the NTP-CERHR had released the "NTP-CERHR Expert Panel Update on the Reproductive and Developmental Toxicity of Di(2Ethylhexyl) Phthalate" in November, 2005 (CERHR, 2005). OEHHA also noted the following conclusions by the NTP-CERHR Expert Panel on Phthalates:

"The oral exposure studies of Akingbemi et al. (111, 179), Schilling et al. (151), and the NTP (114) are sufficient to conclude that DEHP is a reproductive toxicant in male rats at the indicated dose levels. All of those data are assumed relevant." [CERHR, 2005; page 168]

"The convergence of data from the NTP study, Akingbemi, Poon around the 10-30 mg/kg bw /day range gives added confidence that this is the range of the lowest effective dose level. It is the panel's view that the existing data support a NOAEL between 1 and 10 mg/kg bw/day for oral DEHP exposure in rats." [CERHR, 2005; page 169]

OEHHA's selection of the NOEL (5.8 mg/kg-day) is within the range of 1-10 mg/kg-day and is consistent with the opinions of the NTP-CERHR Expert Panel on Phthalates.

Comment 13

In the second point, Price (2005a) stated that "OEHHA's unprecedented decision to establish separate MADLs for infant and neonatal boys is overly conservative and unwarranted." The commenter presented three reasons in support of this statement:

a) The science does not indicate that young animals experience adverse effects at NOEL values in the range of those from high quality multi-generation reproductive toxicity studies or other sensitive studies.
b) Under Proposition 65, the method for calculating MADLs already includes a conservative 1000x safety factor that accounts for sensitive subpopulations, including infants and neonates.

c) OEHHA is not authorized, under Proposition 65, to establish separate age-based MADLs.

Under the first reason, the commenter first discussed NOELs and/or LOELs observed in a number of studies conducted in rats of different ages and concluded that "the scientific evidence shows that while young rats experience more severe testicular effects than adults at high oral DEHP doses, the effects in young rats are reversible and do not occur at oral DEHP doses in the range of the NOEL values found in high quality multi-generation and other sensitive studies." By citing experimental findings in primates or epidemiological observations in humans as discussed in other sections of the comments, the commenter concluded that "humans likely are much *less* [sic] sensitive to the potential reproductive effects of DEHP than are the rodents upon which the MADL is based," and that "establishing separate MADLs for infants and neonates is overly conservative and unwarranted."

Detailed comments under the second and third reasons are summarized and responded to below in Comments 14 and 15, respectively.

Response

As recognized by the commenter, there is clear evidence that developing animals are more sensitive to the testicular effects of DEHP following oral exposure than are adults. Moreover, the testicular effects of DEHP in neonatal and juvenile animals following relatively short periods of exposure are in general more severe than those observed in adult animals (e.g., CERHR, 2000; 2005; U.S. FDA, 2001; Cammack et al., 2003). It is generally recognized that the exact values for the NOELs and LOELs observed in animal studies are highly dependent on the experimental design. While the NOELs (i.e., the highest levels of exposure at which no effects were observed) for the testicular effects observed in some oral studies in rats of less than six weeks of age could be above the equivalent NOELs observed in adult animals because of the specific experimental doses used in some studies, it has been consistently observed in numerous studies that the LOELs (i.e., the lowest levels of exposure at which effects were observed) for the testicular effects of DEHP in neonatal or juvenile rats are markedly lower than those for the adult animals. These consistent findings clearly indicate that neonatal and juvenile rats are more sensitive to DEHP than are adults (e.g., CERHR, 2000; 2005; U.S. FDA, 2001; Boekelheide, 2004). However, OEHHA recognized that the NOEL observed in rats in the study by David et al. (2000) is still lower than the lowest LOEL (10 mg/kg-day) in rats in the studies by Akingbemi et al. (2001, 2004). Therefore, OEHHA concluded that it is appropriate to use the same NOEL for all MADLs for DEHP by oral exposure. In other words, OEHHA did not use the NOELs observed in developing rats for establishing MADLs for neonatal or infant boys. Instead, OEHHA used the NOEL observed in juvenile and adult animals for MADLs for all ages, including infants and neonatal infants.

Body weights of human infants and neonatal infants are greatly lower than that of an adult man. Because the MADL is expressed as "micrograms per day" according to the

regulations (Sections 12801 and 12803), exposure of an infant or neonatal infant to DEHP at a MADL calculated on the basis of an adult body weight of 70 kg from an exposure in animals expressed as µg/kg-day would result in a dose up to 20-fold higher than the corresponding dose in adults. Thus, it is scientifically inappropriate to apply a MADL calculated on the basis of an adult body weight of 70 kg to neonatal or infant boys, especially when there is clear evidence that the developing male reproductive system is more sensitive to the toxicity of DEHP than that in the adult. The age-specific MADLs simply normalize the exposure to the approximate body weight of the exposed individual. The exposure per unit bodyweight (kg body weight) at the corresponding MADL is the same for the neonatal infants, infants, and 70kg adults. Thus, to the extent that a MADL is "protective," the separate MADLs simply confer the same degree of "protectiveness" to each of these populations of different ages. However, it should be pointed out that OEHHA does not consider it appropriate to emphasize the health protectiveness for MADLs since this is inherent in the statutory requirement and the degree of health protectiveness depends on how the MADL is applied and exposures are calculated. See more discussions on the intent of MADLs in OEHHA's response to Comment 14 below.

With regard to the human and primate data as discussed in detail by this commenter in other sections (Section II and III, respectively) of the submission, the data are not sufficient at the present time to support ACC's conclusion that "humans likely are much less sensitive to the potential reproductive effects of DEHP than are the rodents upon which the MADLs is based." Detailed discussions on issues related to the non-human primate data have been provided in the supporting document for DEHP Oral MADL (OEHHA, 2005). The commenter largely repeated comments that had been previously submitted to OEHHA and provided no new data related to this issue. More detailed responses by OEHHA to issues related to the primate data are provided in OEHHA Responses to Comment 17 and 18 below.

Comment 14

Under the second reason to support ACC's statement that "OEHHA's unprecedented decision to establish separate MADLs for infant and neonatal boys is overly conservative and unwarranted," Price (2005a) stated that the 1000-fold factor that is required by statute is more conservative than the uncertainty factors typically applied by OEHHA and other agencies. The commenter stated that a typical uncertainty factor of 100 already is protective of infants. Since the primate data indicate that humans likely are less sensitive than rodents to DEHP, an appropriate interspecies factor would be less than 1, rather 10. Therefore, the 1000-fold factor used for the MADL is already extremely conservative and protective of humans, including infants and neonates, and the separate MADLs for infants and neonates are unwarranted.

Response

The 1000-fold factor is required by statute. The intent of developing a MADL is to establish a level of exposure where there would be "no observable effect assuming

exposure at one thousand (1,000) times the level in question" (Health and Safety Code section 25249.10(c)). Thus all MADLs are intended to be well below a level of exposure that would cause no observable effects.

U.S. EPA in its "Guidelines for Reproductive Toxicity Risk Assessment" (U.S. EPA, 1996) states that "application of adequate uncertainty factors to a NOAEL, LOAEL or benchmark dose will result in an exposure level for all humans that is not attended with significant risk above background." In other words, a level of exposure that will cause no observable effects under the U.S. EPA guidelines. Thus, application of a 1000-fold factor to a NOEL to derive a MADL cannot be directly compared to application of a variable uncertainty factor.

Issues related to the primate data will be addressed in Comment 17 and 18.

Comment 15

Under the third reason for ACC's conclusion that "OEHHA's unprecedented decision to establish separate MADLs for infant and neonatal boys is overly conservative and unwarranted," Price (2005a) stated that OEHHA is not authorized to develop separate MADLs for infants and neonates. The commenter provided the following arguments in support of this statement:

1. There is no mention of using body weights for infants or neonates in the regulatory language for MADL development (Section 12803(b)). The commenter stated that "the drafters of the Proposition 65 regulations clearly were aware that different parameters could be appropriate depending on age, but specifically chose not to include age-related weights for purposes of converting the NOEL to a MADL."
2. The two provisions in the regulations cited by OEHHA as regulatory basis for developing age-specified MADLs for DEHP do not apply. The commenter stated that "one is found at 22CCR section 12803(a)…," the commenter concluded that "that provision clearly related only to the next 7 subsections of 12803(a), explaining how to derive a NOEL. It does not related to section 12803(b) (quoted above), which explains how to convert a NOEL to a MADL."
3. Section 12801(a), cited by OEHHA, "does not give OEHHA carte blanche to deviate from its own regulatory procedure, as applied for 17 years. Language from two cases, "it is fixed law that an administrative agency is bound by its own regulations" from *Bonn v. California State University, Chico*, (1979) 88 Cal. App. 3d 985, 990, and "a school board cannot ignore its own rules and repudiate its method of procedure," from *Frates v. Burnett*, (1970) 9 Cal. App. 3d 63, 71, were cited to support the commenter's arguments.

Response

The arguments presented by the commenter are specifically contradicted by the plain language of the regulations (Sections 12801 and 12803) and the Final Statement of Reasons for Section 12803. The commenter recognizes that both Section 12801 and Section 12803 contain language specifically authorizing OEHHA to depart from the

default values specified in the regulations. Section 12801 states that "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," and expressly applies to the entire article. Section 12803 states that "in *the absence of* principles or assumptions scientifically more appropriate based upon the available data, the following default principles and assumptions shall apply in any such assessment." [Emphasis added by OEHHA.] This provision clearly contemplates that this subsection provides default assumptions that can be deviated from under appropriate situations. The purpose of including this language in both subsections of the regulations is explained in the Final Statement of Reasons for Section 12803, where it states that "'safe harbor' risk assessments need not be performed in a rigid fashion. Rather it is intended that *each* default assumption or principle set forth in Section 12803 apply *only in the absence of a scientifically more appropriate principle or assumption*" (emphasis added). The use of a default bodyweight of 70 kg based on an *adult* male to convert a µg/kg-day value to a µg/day value for an infant or neonatal infant is clearly not scientifically appropriate. Thus, OEHHA's action is entirely consistent both with the wording and the stated intent of the regulations. Since the intention of the regulation is to provide broadly-applicable default values for several parameters, and since it is also impossible to specify all of the possible alternative values that might be substituted for these default values when it is more scientifically appropriate to do so, the absence from the regulation of age-specific weights applicable to male reproductive endpoints does not preclude their use in an appropriate case.

Comment 16

Under the title "Human data provide no evidence that DEHP causes developmental or reproductive effects in humans," Price (2005a) agreed with "OEHHA's statement that no human studies are "of sufficient quality" for MADL development," but "disagreed with OEHHA's conclusion that the data in Fredricsson et al. (1993) and Duty et al. (2003a; 2003b; 2004) "provided limited evidence on an association between exposure to phthalates and damaged sperm quality." After briefly discussing some findings in a number of studies in humans, the commenter concluded that "data from several human studies provide no evidence of a link between DEHP exposure and reproductive effects in humans," and thus "the lack of evidence for such an association supports the Panel's position that primates are less sensitive to the reproductive effects of DEHP than are rodents and imbues further confidence that OEHHA's MADL based on rodent data is very conservative." The commenter also included a detailed critique of the study by Swan et al. (2005) as Appendix A to the comments submitted to OEHHA.

Response

OEHHA acknowledges that the commenter agrees with OEHHA's conclusion that there is no human study "of sufficient quality" to provide basis for MADL development. Except the studies by Hack et al. (2002), Jonsson et al. (2005), and Swan et al. (2005), respectively, all other studies discussed by the commenter (Fredricsson et al., 1993;

Modigh et al., 2002; Duty et al., 2003a; 2003b; 2004; Rais-Bahrami et al., 2004) were cited and discussed in OEHHA's DEHP oral MADL support document (OEHHA, 2005).

As recognized by the commenter, "Fredricsson et al. (1993) reported that the motility of sperm exposed to 1 mM DEHP was reduced by 25%." Similarly, the commenter recognized by the fact that Duty et al. (2003a; 2003b; 2004) found "a suggestion of a negative association between MEHP and two computer-aided sperm analysis parameters." These findings support OEHHA's conclusion that these studies provided limited evidence for possible adverse effects of DEHP or MEHP on human sperm quality. However, because of a variety of limitations in these studies, OEHHA did not use any of these human studies as basis for MADL calculation.

With regard to the studies (Hack et al., 2002; Jonsson et al., 2005; Swan et al., 2005) that were not cited in the OEHHA's DEHP oral MADL support document (OEHHA, 2005), OEHHA reviewed these studies in response to the comments. The study by Hack et al. (2002) did not collect any data on hormone levels, sperm production or quality, fecundity or fertility in very-low-birth-weight men at 20 years of age and thus provided little evidence with regard to the potential male reproductive effects of DEHP in humans. The studies by Jonsson et al. (2005) and Swan et al. (2005), respectively, provided limited evidence that there are associations of different degrees between exposure to some phthalates (e.g., diethyl phthalates or di-*n*-butyl phthalates) and alterations in biomarkers for male reproductive development or function in young men or male infants. However, neither study observed obvious association between exposure to DEHP and abnormal changes in the endpoints included in these studies to evaluate the male reproductive functions. Neither study is "of sufficient quality" to be used as basis for MADL calculation. Since both studies provided additional information relevant to the developmental and male reproductive toxicity of DEHP, they have been added to the Bibliography in the revised MADL support document (OEHHA, 2006).

OEHHA carefully considered the critiques by the commenter of the study by Swan et al. (2005) and agreed with the commenter that the study by Swan et al. (2005) has some limitations and thus it is not "of sufficient quality." However, OEHHA noted that many of the criticisms by the commenter of the Swan et al. study (2005) can also apply to other human studies cited by the commenter (e.g., Hack et al., 2002; Rais-Bahrami et al., 2004; Jonsson et al., 2005) in support of the ACC's conclusion. None of these studies provide convincing evidence that DEHP does not cause male reproductive damage in men. Therefore, while it is not incorrect to state that "data from several human studies provide no evidence of a link between DEHP exposure and reproductive effects in humans," it should also be noted that the studies do not provide evidence for lack of such an effect.

Because of the lack of human studies of sufficient quality on the male reproductive toxicity of DEHP, OEHHA relied upon studies in laboratory animals for MADL development.

Comment 17

After a brief description of the findings from laboratory studies conducted in non-human primates, the commenter listed the following three reasons in support of ACC's conclusion that "the body of science for DEHP indicates that primate data are a better model for humans than the rodent data."

1. "Mode of action data indicate that rats are not good models for humans."
2. "Physiological data indicates the primate is a better model than the rat for evaluating potential human reproductive effects."
3. "Pharmacokinetic and metabolic information indicate that primates are a better model than rats for human reproductive toxicity."

Response

For clarification, Section 12803(a)(4) requires that "the NOEL shall be based on the most sensitive study deemed to be of sufficient quality." In developing MADLs for DEHP by the oral route of exposure, OEHHA identified "the most sensitive study deemed to be of sufficient quality." In the case of DEHP, based on the findings from numerous relevant studies, OEHHA determined that the rodent data is relevant to humans and found that the study in rats by David et al. (2000) is "the most sensitive study deemed to be of sufficient quality."

With regard to the mode of action data, the commenter did not comment on OEHHA's detailed discussions on mechanistic data that are included in the MADL supporting document (OEHHA, 2005). Instead, the commenter proposed two possible modes of actions: one via PPARs, and the other through "cellular turn-over." Possible involvement of PPARs in DEHP-induced testicular damages has been recognized by the researchers in the toxicological field. OEHHA's key discussions and conclusions on this issue as presented in the MADL support document (2005; 2006) are quoted below:

> "Two modes of actions (MOAs) have been postulated by Klaunig et al. (2003) to describe the etiology of Leydig cell tumors in PPARα agonist-treated rats. The authors have concluded that 'the weight of evidence available to date to support virtually all of the postulated key events is weak overall, and moderate at best for only two or three of the postulated events.' Furthermore, Klaunig et al. (2003) concluded that 'the proposed animal MOAs - induction of aromatase secondary to liver induction (Pathway 1) and the direct inhibition of testosterone biosynthesis (Pathway 2) - are plausible mechanisms and could occur in humans. If PPARα is mediating the induction of aromatase, this mechanism could occur in humans due to the expression of PPARα in human liver. The inhibition of testosterone biosynthesis by PPAR agonists is better established than the induction of aromatase and is also plausible, as PPARα is present in human Leydig cells. The pathways for the regulation of the HPT [hypothalamic-pituitary-testicular] axis of rats and humans also are similar, in that compounds that decrease testosterone will increase LH levels. Hence, compounds that induce LCTs in rats by disruption of the HPT axis pose a potential risk to human health."

The weight of evidence does not indicate that the non-cancer testicular effects of DEHP are mainly mediated by PPARα. Even if PPARs including PPARα, β, and γ play any important role in DEHP-induced damage in testicular development and functions, as suggested by evidence summarized in a recent comprehensive review by Corton and Lapinskas (2004), PPARs are expressed in human male reproductive organs (e.g., Elbrecht et al., 1996; Schultz et al., 1999; Collett et al., 2000; Hase et al., 2002). Therefore, PPAR-mediated testicular effects of DEHP in rats are relevant to humans. Possible modes of actions underlying the induction of Leydig cell tumors in rodents, including those involving PPARs, are also plausible in humans.'"

The commenter inaccurately cited the findings and conclusions presented in the report by Klaunig et al. (2003). The commenter did not present any new data or express any opinion on OEHHA's conclusion about the potential role of PPARs in the testicular effects of DEHP, which is strongly supported by all relevant data that are available to OEHHA.

On the cellular "turn-over" hypothesis postulated by the commenter, there is no data either from the three papers cited by the commenter (Li et al., 2000; Richburg and Boekelheide, 1996; Richburg et al., 1999) or any in vivo study reviewed by OEHHA indicating that exposure to DEHP causes Sertoli cell apoptosis. There is simply no scientific evidence to support a "cell turnover" hypothesis.

Based on the mode of action data that is available to OEHHA, the testicular effects of DEHP observed in rats are relevant to humans. There are no data to support the commenter's conclusion that "mode of action data indicate that rats are not a good model for humans." In fact, there is substantial evidence indicating that marmoset is not a good model to predict the male reproductive toxicity of DEHP for humans, based on the mode of action data available at this time. More discussion on marmoset data is presented in the response to Comment 18.

It should be pointed out that the findings from the study by Pugh et al. (2000) indicate that DEHP at a dose that is effective in rats may cause testicular damage in cynomolgus monkeys, a non-human primate. These findings suggest that not all primates "are less sensitive to the reproductive effects of DEHP than are rodents," as concluded by the commenter. However, this study is not the most sensitive study of sufficient quality. It is thus not used as basis for calculating MADLs. [See discussions about this study in the MADL supporting document (OEHHA, 2005; 2006).]

With regard to pharmacokinetic and metabolic data, the commenter reiterated OEHHA's position that "similarities in the absorption, distribution, metabolism, and excretion (ADME) of DEHP in rats and humans are sufficient to strongly suggest that the testicular effects of DEHP observed in rats are relevant to humans." However, the commenter believed that "significant difference between rodents and primates in the ADME of DEHP that indicate that primates are a more appropriate model of human reproductive toxicity than rats."

OEHHA believes that a direct comparison of ADME data of DEHP between rodents and humans should be used as basis to determine if rodent data is relevant to humans in this regard. The commenter did not comment on the data that OEHHA relied upon, neither did the commenter compare rodent data to those observed in humans. OEHHA is aware of the difference in the ADME features between rodents and marmosets, but does not think that differences between these two animal species can be used as basis to determine if the marmoset is a better model than the rat to predict the male reproductive toxicity of DEHP in humans. It should be emphasized again that there is no requirement in the Proposition 65 regulations to determine if one animal model is more appropriate than the other. OEHHA relies on "the most sensitive study deemed to be of sufficient quality" (Section 12803) to derive a MADL.

Therefore, there is no scientific basis for OEHHA to "use primate data to set the NOEL." Even if "primate data are a better model for humans than the rodent data," which is not supported by scientific evidence for the male reproductive toxicity of DEHP in marmoset but may be true in cynomolgus monkeys, OEHHA has no regulatory authority to use an animal study that is not "the most sensitive study deemed to be of sufficient quality."

Comment 18

One critical issue Price (2005a) focused on in the current comments concerns the marmoset data. The majority of the comments on this issue were previously submitted to OEHHA during the process of listing DEHP as causing developmental or male reproductive toxicity under Proposition 65 (e.g., Price et al., 2003; Stanley, 2004). These comments were responded to in OEHHA's previous responses to ACC's comments (e.g., OEHHA, 2003) and were addressed in detail in the MADL support document (OEHHA, 2005; 2006). Therefore, OEHHA only highlighted three critical questions repeatedly raised by the commenter and responded to them in the current document.

Question One: Is the marmoset, as a non-human primate, in general a better model than rat for evaluating potential human reproductive effects?

Question Two: Are the findings from marmoset studies more appropriate than those from studies in rodents to predict the male reproductive effects of DEHP in humans and thus should marmoset data be used as basis for developing MADLs for DEHP?

Question Three: Should the high levels of vitamin C and E in the diets for marmosets used in the study by MCSI (2003) be taken into account in interpreting the lack of obvious testicular toxicity of DEHP in marmosets?

Response

Question One:

The commenter stated that the "primate is a better model than the rat for evaluating potential human reproductive effects." With regard to selection of animal models for

toxicological studies, OEHHA notes the following comments by the ACC (Stanley, 2004):

> "In the absence of adequate human data, experimental animals are assumed to provide appropriate information concerning potential human health effects. The default assumptions for use of experimental animals include:
>
> that the effect observed in animals reflect those that would occur in humans;
> that the effects on reproductive processes are similar between animals and humans, *unless demonstrated otherwise*;
> that, unless demonstrated otherwise, the most sensitive experimental species should be used (reflecting an assumption that humans are at least as or more sensitive than experimental animals).
>
> While "experimental animals" can be any species, toxicologists frequently use the rodent (rat or mouse) as the species of choice for a variety of reasons."

OEHHA believes that the defaults stated by the ACC represent some generally accepted practices in selecting an appropriate animal model in toxicological studies. According to these generally accepted practices, whether or not a particular animal model is appropriate to predict potential human health effects depends largely on the possible mode of actions of the chemical under testing. While under certain experimental conditions of toxicity testing for one chemical a particular animal species may be highly appropriate, that species may not be appropriate for testing another chemical under different conditions. In the case of DEHP, OEHHA considered these generally accepted scientific principles in determining if the rodent data on the male reproductive toxicity of DEHP are relevant to humans, and if the marmoset data are appropriate for use to predict the male reproductive toxicity of DEHP in humans. OEHHA did not make generalized conclusions on the overall value of the common marmoset as an animal model in the MADL support document for DEHP by oral exposure. Beyond the generally accepted defaults regarding animal models (e.g., use of rodents, "the effect observed in animals reflect that which would occur in humans," etc.), OEHHA does not consider it scientifically appropriate to draw a general conclusion on the value of a particular animal model in risk assessment for all chemicals.

Question Two:

In developing MADLs, OEHHA identifies "the most sensitive study" among all animal studies that are "deemed to be of sufficient quality" in selecting a NOEL for MADL calculations. In the case of DEHP, OEHHA did not determine if one animal model is more appropriate than the other to predict the male reproductive effects of DEHP in humans.

DEHP causes no obvious toxicity in the marmoset, one of the two non-human primate species that have been used in experimental animal studies on DEHP. Consequently, the relevance of rodent data to humans has been frequently raised as a critical issue. In

recognition of this, OEHHA had carefully reviewed a large amount of data relevant to the male reproductive toxicity of DEHP in non-human primates, including all the marmoset data submitted to OEHHA by the ACC. OEHHA observed the following:

1. With the exception of prosimian primates, humans and marmosets are as phylogenetically distant as is possible within the order Primata. OEHHA reviewed a large amount of data on physiological features of the male reproductive system in common marmosets (Li et al., 2005). As discussed in the MADL supporting document (OEHHA, 2005; 2006), the marmoset is different from humans in several important physiological features of the testis and numerous studies have shown that many of these features most likely play an important role in mediating the testicular effects of DEHP.
2. One of the critical effects of DEHP observed in neonatal rats is reduced Sertoli cell proliferation (CERHR, 2000; 2005). The male marmosets used in the MCSI study (MCSI, 2003) were 90 to 110 days old at the beginning of treatment. The population size of Sertoli cells in adult marmosets is already largely established by three months of age (e.g., Sharpe et al., 2000; 2003; Li et al., 2005). Therefore, none of the marmoset studies on DEHP, including that by MCSI (2003), provide any data on the potential effects of DEHP on Sertoli cell proliferation during the sensitive neonatal period.
3. Another critical effect of DEHP observed in developing rodents is reduction in testosterone production in Leydig cells and disruption of androgen-dependent development of the male reproductive system. Regulation of production and/or function of testosterone in male marmosets has substantial differences from that in rodents, cynomolgus monkeys and men (Zuhlke & Weinbauer, 2003; CERHR, 2005; Li et al., 2005). Therefore, it is not appropriate to use the marmoset as an animal model to predict an adverse effect of DEHP on testosterone production and/or function in humans. It should also be pointed out that none of the marmoset studies on DEHP, including that by MCSI (2003), investigated the effects of DEHP on establishment of the male reproductive system, which occurs before birth in marmosets.
4. The testicular toxicity of DEHP has been investigated in one study in four cynomolgus monkeys reported by Pugh et al. (2000). Based on considerations that were discussed in detail in the MADL supporting document (OEHHA, 2005), OEHHA concluded that DEHP may cause testicular damage in cynomolgus monkeys, a primate phylogenetically closer to humans than is the marmoset.

Therefore, the marmoset is not a good model to predict the male reproductive toxicity of DEHP in humans. OEHHA disagrees with the commenter that the marmoset study "provides a good basis for developing the MADL." Even if the marmoset data are relevant to humans, they cannot be used as the basis for MADL calculation, since they do not come from the "the most sensitive study deemed to be of sufficient quality."

Question 3:

According to the information ACC provided in the present comments, there is no question that vitamin C, alone or together with vitamin E, is protective against the

testicular effects of DEHP in rats or mice. The mechanism underlying the protective effects of vitamin C and/or E against the testicular effects of DEHP in rodents remains unknown, and there are no experimental data to show clearly that such a protective effect does not exist in marmosets or humans. OEHHA therefore raised a possibility that high amounts of vitamin C supplement in the diet and high serum levels of vitamin C may have contributed to the lack of obvious testicular effects of DEHP in the marmoset study. None of the information ACC provided in the present comments has clearly shown that such a possibility does not exist.

ACC pointed out that intracellular levels, not plasma levels, are probably responsible for any protective effect that vitamin C may afford. Thus, directly comparing plasma vitamin C levels across species is probably not a good indication of the relative degree of protection those plasma levels might afford each species. If ACC is correct in this regard, estimating the degree of possible protective effects of vitamin C in marmosets or humans by comparing serum or plasma vitamin C levels among rodents, primates, and humans may not be appropriate.

Several important facts regarding vitamin C in marmosets and humans are relevant and should be pointed out.

1. High amounts of vitamin C in the marmoset study is one of many possible factors that may explain the lack of testicular effects in this species. Unique physiological features in the testis of marmosets that are relevant to the testicular actions of DEHP, as discussed above, are clearly the major factors to consider. OEHHA's conclusions on this issue are actually consistent with one of the conclusions presented in the MCSI marmoset study report (MCSI, 2003), i.e.,

   > "It can no longer be assumed that [lack of effect on the testes in common marmoset, which has been observed in rodents after repeated exposure] is due to poor absorption. This difference is thought to arise from a difference in target organs physiology between the two animal species rather than from any significant differences in metabolic kinetics." (MCSI, 2003).

2. The marmosets used in the study by MCSI (2003) were given 80 g/head/day of the mixture of main diet and additives that contained 200g of water and 1 g of ascorbic acid (AA or vitamin C) per 1000 g of pellet diet. According to the information posted by the diet manufacturer (CLEA Japan Inc., Tokyo) on its website (http://www.clea-japan.com), the main diet (CMS-1M) contains 109 mg vitamin C per 100 g, or approximately 1000 ppm). The total concentration of vitamin C in the diet for marmosets in the MCSI study was likely at the same level (2000ppm) as that reported by Flurer et al. (1987) and Flurer and Zucker (1987). Therefore, the marmoset diet used in the MCSI study indeed contained high levels of vitamin C.

3. There are numerous studies showing that vitamin C plays important roles in maintaining normal male fertility or protecting the male reproductive system from damage caused by environmental chemicals (e.g., Hampl et al., 2004). There are no data to support the ACC statement that vitamin C may have little impact on the testicular toxicity of DEHP in rodents. The commenter stated that "it is possible that

vitamin C had little impact on testicular toxicity, and that vitamin E played the larger role in the protective effect observed by Ishihara et al. in rats." The diets used in the study also contained a high level of vitamin E (31.9 mg per 100 g pellet). If vitamin E indeed played a role in the protective effects of vitamins against the testicular effects of DEHP in rodents, the high level of this vitamin in the marmoset diet may as well be protective against the testicular effects of DEHP. These findings clearly support OEHHA's consideration that lack of testicular effects in marmosets may due to the protective effect of high levels of vitamin C and E in the marmoset diet.

4. It has been consistently shown that mean vitamin C intake for men and women in the United States is higher than median intake, suggesting that some people ingest much more vitamin C than the median. A considerable number (approximately 20-30%) of children and adults in the United States are vitamin C deficient or depleted (e.g., Hampl et al., 2004). If vitamin C indeed plays a protective role in the testicular effects of DEHP or other phthalates, children or men who are vitamin C-deficient or depleted may be at a higher risk of the testicular effects of phthalates.

In conclusion, there is sufficient evidence to indicate that the marmoset is not a good model to predict the male reproductive toxicity of DEHP in humans. Even if the marmoset is an appropriate model for studying human reproductive health, none of the existing non-human primate studies on DEHP is "the most sensitive study deemed to be of sufficient quality." Therefore, OEHHA concluded and continues to believe that the marmoset study by the MCSI (2003) should not be used as the basis for establishing MADLs for DEHP by the oral route of exposure.

Comment 19

Price (2005a) stated that "the studies of Akingbemi et al. (2001; 2004) have deficiencies that make them of insufficient quality for MADL development." To support this statement, the commenter discussed two methods used in the studies and concluded that limitations or methodological deficiencies in these two methods made the studies by Akingbemi et al. (2001; 2004) of insufficient quality.

Response

For clarification, the studies by Akingbemi et al. (2001; 2004) are used in the process of selecting "the most sensitive study", but are not used as the basis for MADL calculation.

The commenter pointed out that multiple blood samples should be collected and analyzed from each animal over several hours during the peak phase of the circadian cycle of blood testosterone levels, in order to accurately measure the blood testosterone levels for comparison between individual animals. While the suggested method is likely an ideal one, it is technically difficult and has not been commonly used in toxicological studies. Instead, single-point measurement of testosterone has generally been used and was also used in the studies recommended by the commenter as the basis for MADL calculation; i.e., the marmoset study by MCSI (2003) or the multi-generation reproductive study by Wolfe and Layton (2005).

The in vitro model of Leydig cells used by Akingbemi et al. (2001; 2004) is also a well-established model and has been widely used by many researchers in numerous studies. There are a variety of limitations in almost every experimental model that is being currently used in biomedical and toxicological research. To OEHHA's knowledge, all the methods used in the studies by Akingbemi et al. (2001; 2004) are well established and have been commonly used in relevant studies. Therefore, these studies are of sufficient quality according to generally accepted principles, even though certain limitations in the methods do exist. OEHHA considers that the studies by Akingbemi et al. (2001; 2004) utilized appropriate designs and are of sufficient quality.

Comment 20

The commenter concluded that the study by Poon et al. (1997) is "not of sufficient quality for MADL development", because the adverse effects reported in this study "have not been corroborated by other multi-generation studies."

Response

The study by Poon et al. (1997) had been reviewed by the U.S. FDA (2001) and the NTP-CERHR Expert Panel (CERHR, 2000), respectively. The NOEL identified in this study, 3.7 mg/kg-day, was used by the U.S. FDA (2001) as the basis for calculation of the oral Tolerable Intake. The NTP-CERHR Expert Panel (CERHR, 2000) concluded that this study is "thorough in its design and execution, including verification of dose" and further concluded that "it is the Panel's view that the existing data support a NOAEL within the range of 3.7-14 mg/kg bw /day for oral exposure in rats." OEHHA's conclusion about this study is totally consistent with those of the U.S. FDA and the NTP-CERHR, as is its use of this study in the process of selecting "the most sensitive study". OEHHA continues to believe that the study by Poon et al. (1997) is of sufficient quality, even though this study per se is not used for calculating MADLs.

Comment 21

The commenter stated that the study by "David et al. (2000) is not the most appropriate study for MADL development", since: 1) it is a chronic toxicity bioassay, not a reproductive or developmental toxicity study, and 2) the reproductive toxicity endpoint giving the NOEL of 5.8 mg/kg/day is not relevant for human risk assessment.

Response

As defined in regulation, a MADL is derived from a No Observable Effect Level (NOEL) based on the most sensitive study deemed to be of sufficient quality (Section 12803). Therefore, "the most appropriate study" is the one that meets these criteria.

The study by David et al. (2000) observed a number of adverse testicular effects in rats exposed to DEHP for up to 104 weeks. This study is of sufficient quality and provided

clear evidence that oral exposure to DEHP causes male reproductive toxicity in rats. Aspermia is a severe male reproductive effect that most likely results from testicular atrophy. The commenter provided no scientific basis for the statement that DEHP-induced aspermia in rats is irrelevant to humans, nor is OEHHA aware of any such basis.

In the comments submitted to OEHHA (Stanley et al., 2004), the ACC suggested a NOAEL of 4 mg/kg-day for calculating a MADL of 280 μg/day for DEHP, based on the studies by Poon et al. (1997) and David et al. (2000). OEHHA's use of the study by David et al. (2000) is fully consistent with the comments previously submitted by the ACC.

Comment 22

The commenter discussed four recent multi-generation reproductive studies of DEHP in rodents (Wolfe and Layton, 2005; Schilling et al., 2001; Tanaka, 2002; 2005) and concluded that "based on these recent multi-generation studies, a conservative overall NOAEL for DEHP DART effects in male rats is 46 mg/kg-day, the NOAEL derived from Wolfe and Layton (2005)." The commenter further stated that a NOAEL of 46 mg/kg-day observed in recent multi-generation rodent studies is "more appropriate" than 5.8 mg/kg-day "proposed by OEHHA" and thus suggested OEHHA "raise the adult MADL to reflect a more appropriate NOAEL for DEHP effects."

Response

Based on the information contained in the comments, all four studies cited by the commenter provided clear evidence that DEHP causes developmental and reproductive toxicity in rats or mice following oral exposure. The remaining question is that if any of these four studies should be considered as "the most sensitive study deemed to be of sufficient quality."

The full report by Schilling et al. (2001) is not available to OEHHA, but OEHHA has reviewed this study in an abstract format (Schilling et al., 1999; OEHHA, 2005). The study by Tanaka (2002) had been reviewed and was included in the MADL supporting document (OEHHA, 2005). Neither study was identified as "the most sensitive study deemed to be of sufficient quality."

The NTP-sponsored study was first reported in abstract form by Wolfe and Layton (2002). OEHHA had reviewed the abstract, since the full report was not available to OEHHA when the MADL support document was prepared. In response to the comments, OEHHA has reviewed the full report of this study as well as the study report by Tanaka (2005) and have the following findings:

The study by Tanaka (2005) was in mice, a species that has been shown to be less sensitive to the male reproductive toxicity of DEHP than are rats (CERHR, 2000).

With regard to the NTP study (Wolfe and Layton, 2005), OEHHA has the following findings:

1. This is a well-designed "reproductive assessment by continuous breeding" (RACB) study sponsored by the NTP. The study is "of sufficient quality".
2. Mating of F1 animals exposed to 10,000 ppm DEHP in feed (equivalent to 543 mg/kg-day DEHP) did not produce any offspring, indicating complete infertility in these animals (both males and females) exposed to DEHP.
3. At 7500 ppm (equivalent to 391 mg/kg-day or 359 mg/kg-day in F1 or F2 animals, respectively), DEHP caused abnormal changes in almost all the major endpoints indicative of developmental or male reproductive toxicity in F1-, F2-, and/or F3-general animals.
4. At 300 ppm (equivalent to 14 mg/kg-day in F1 or F2 animals), compared to the control group, the number of rats having small testes by gross necropsy examination among male animals that were not used for mating in the F1 (3 of 45) and F2 (1 of 21) generations were slightly increased. Although this effect was not observed in the next higher dose (1000 ppm), it was consistent with observations in the 7500-ppm group and with the anticipated testicular effects of DEHP in rodents. Preputial separation and testis descent were also delayed in F2-generation males at this and the next two lower (30 and 100 ppm) dose levels.
5. The authors concluded that "the findings obtained in this study indicate that DEHP is clearly a reproductive and developmental toxicant at 7500 and 10,000 ppm based upon changes in fertility and pregnancy indices, litter data, sperm parameters, sexual development, and/or histopathological changes in testes. The authors also stated that "there was no reproductive toxicity observed at doses lower than 7500 ppm except for a possible increase of small testes and prostates which may represent an increased incidence of developmental abnormalities in the male reproductive organs at 300 and/or 1000 ppm."

Therefore, the recent NTP-sponsored RACB study reported by Wolfe and Layton (2005) provided further clear evidence that exposure to DEHP causes a variety of adverse effects on the male reproductive system in rats. Increased incidence of male reproductive abnormalities (small testes, small prostates, delayed preputial separation or testicular descent) indicates that 300 ppm (equivalent to 14 mg/kg-day) indicates likely adverse effects at this level. This gives a NOEL of 100 ppm, equivalent to approximately 5.0 mg/kg-day. This NOEL is higher than that (3.7 mg/kg-day) observed in the study by Poon et al. (1997), but lower than that (5.8 mg/kg-day) in the study by David et al. (2000). It is also lower than the lowest LOEL (10 mg/kg-day) observed in the studies by Akingbemi et al. (2001; 2004). Thus, oral MADLs for DEHP based on the study by David et al. (2000) as proposed by OEHHA have met the requirements of the relevant regulations and are scientifically appropriate.

Findings from the studies listed by the commenter in this subsection of submission do not support the commenter's statement that a NOAEL of 46 mg/kg-day observed in recent multigeneration rodent studies is more appropriate than 5.8 mg/kg-day that is used by

OEHHA as basis for MADL calculation. There are no new data to support an action to "raise the adult MADL to reflect a more appropriate NOAEL for DEHP effects."

SUMMARY AND RESPONSE TO COMMENTS ON THE NOTICE OF ADDITION OF DOCUMENTS AND INFORMATION PUBLISHED ON AUGUST 17, 2005, AND THE CLARIFICATION OF NOTICE OF ADDITION OF DOCUMENTS AND INFORMATION TO RULEMAKING FILE PUBLISHED ON AUGUST 30, 2005

Comment 23

In response to OEHHA's Notice of Addition of Documents and Information to Rulemaking File OAL File No. Z-01-1019-06 and Z-05-0614-06, released on August 17, 2005, Price (2005b) on behalf of the ACC made three requests to OEHHA:

> That OEHHA await the outcome of the National Toxicology Program's Center for Evaluation of Risks to Human Reproduction (NTP-CERHR) Expert Panel Review of DEHP before identifying the appropriate NOEL to serve as the basis for the MADL. The commenter notes that the Panel's report is anticipated to provide up-to-date expert guidance on the reliability and significance of the various studies on DEHP reproductive toxicity, and so will inform selection of the appropriate NOEL.
>
> That if OEHHA does not await the outcome of the NTP-CERHR Expert Panel deliberations, it extend the period for comment on the documents placed in the rulemaking file by the notice of August 17, 2005 until at least 30 days after OEHHA publishes a written explanation of the manner in which it is relying on new documents. The commenter states that there are 16 citations for the oral MADL and 24 citations for the i.v. MADLs that were not included in the MADL support documents published on June 24, 2005.
>
> That if OEHHA will not grant the foregoing request, OEHHA grant an extension of 60 days for comment on the documents added to the rulemaking file. The commenter offers several reasons why a two-week comment period is inadequate.

Response

In response to the comments by Price (2005b), OEHHA published a notice on August 30, 2005. This new Notice explained the intention of the August 17 Notice and extended the commenting period to September 15, 2005. In addition, OEHHA sent Price a letter, dated August 30, 2005, containing the following responses:

With regard to the first recommendation made by the commenter, OEHHA notes that the NTP CERHR Expert Panel is not charged with identifying the most appropriate NOEL to serve as the basis for a Proposition 65 MADL. Accordingly, OEHHA will proceed with development of the MADLs within the prescribed timeframe.

With regard to the second recommendation, OEHHA does not consider it necessary or appropriate to publish a written explanation of the manner in which it is relying on new documents. The 15 citations for the oral MADL and 18 citations for the i.v. MADL (rather than the 16 and 24, respectively, stated by the commenter) that were not included in the MADL support documents published on June 24, 2005, were papers that became available to OEHHA after preparation of the MADL documents was completed. OEHHA reviewed these papers as they became available, and determined that no revision to the MADL documents was necessitated by these papers. Had any such revision been required, a revised MADL document would have been prepared and released for the requisite comment period. The purpose of the August 17, 2005, notices was to enter these papers into the rulemaking record as sources of potentially relevant information that had been considered by OEHHA but which did not directly contribute to the development of the MADLs and which were not cited in the MADL documents. It should be noted that numerous such papers had previously been identified in the Bibliography section of the oral MADL support document.

With regard to the third recommendation, OEHHA did not consider it necessary or appropriate to extend the comment period by 60 days, since the documents in question did not directly contribute to development of the MADLs. OEHHA extended the comment period by an additional 15 days.

Comment 24

In response to OEHHA's Clarification of Notice of Addition of Documents and Information to Rulemaking File OAL File No. Z-01-1019-06 and Z-05-0614-06, released on August 30, 2005, Price (2005c) on behalf of the ACC submitted the following comments:

> The extension of commenting period was shorter than 60 days as requested by the commenter in previous comments submitted on August 23, 2005 (see comment 29 above) and thus the commenter was unable to thoroughly review and comment on the new documents OEHHA has added to the rulemaking files and their significance for the MADLs within the given extension period.
>
> The MEHP serum level results of the Koch et al. (2005) study, conducted using very low doses of DEHP in a single human, cannot be extrapolated to higher human doses or compared to results of high-dose animals studies due to the markedly different toxicokinetic patterns for DEHP metabolism at these widely disparate doses.
>
> Among the new documents are two new human studies: Swan et al. (2005) and Jönsson et al. (2005). As discussed in the Panel's August 8, 2005 comments, neither of these studies found a correlation between urinary levels of the DEHP metabolite, MEHP, and parameters related to male reproductive development or function. These studies add to the weight of evidence that DEHP is unlikely to cause reproductive toxicity in humans at reasonably anticipated exposures, and further support the Panel's belief that the science justifies higher adult MADLs for DEHP than those

proposed by OEHHA, and that the proposed MADLs for infants and neonates are overly conservative and unwarranted.

In addition to the studies the commenter discussed above, a new study by Main et al. (2005) was listed as one of the four references but not discussed in the comments.

Response

As stated in OEHHA's clarification notice of August 30, 2005, none of the documents listed in the Notice of August 17, 2005, "directly contribute to the development of the MADLs." However, these papers were reviewed as potential sources of relevant information.

OEHHA reviewed the four papers cited by the commenter, including the new study by Main et al. (2005), which was not included in any of OEHHA's notices prior to May 5, 2006. These very recent studies provide additional information relevant to the developmental or male reproductive toxicity of DEHP in humans. OEHHA found discrepancies between the commenter's conclusions and some of the scientific findings in these studies. As noted in the August notice, OEHHA has found that none of the studies directly contribute to the development of the MADLs. OEHHA continues to make that finding and makes it for the additional study of Main et al. (2005) as well. Therefore, no substantial revision to the MADL calculation is necessary.

SUMMARY AND RESPONSE TO COMMENTS ON TWO NOTICES PUBLISHED ON MAY 5, 2006.

Comment 25

On behalf of Health Care Without Harm (HCWH), Schettler and Hall (2006) supported the revisions to the proposed MADLs for oral DEHP exposure in adults, infants, and neonates. In addition, the commenters requested that OEHHA add the "NTP-CERHR Expert Panel Update on the Reproductive and Developmental Toxicity of Di(2-Ethylhexyl) Phthalate" to the record.

Response

OEHHA acknowledges the comments received. Since the NTP-CERHR report (CERHR, 2005) was included in the comments, that report is now part of the administrative record for this regulatory action.

Comment 26

On behalf of the American Chemistry Council Phthalate Esters Panel, Shah (2006) submitted a 5-page letter of comments with four attachments as the following:

Attachment A: Letter from C. Price, ACC to S. Luong, OEHHA, regarding Proposed MADL for DEHP by oral exposure (August 8, 2005), and attached comments: Comments of the Phthalate Esters Panel of the American Chemistry Council on Notice of Proposed Rulemaking Establishing Oral MADLs for Di(2-Ethylhexyl) Phthalate under Proposition 65 (August 8, 2005).

Attachment B: Letter from H. C. Shah, ACC to Dr. Michael D. Shelby, CERHR, with attached comment by the ACC Phthalate Esters Panel on the final NTP-CERHR Expert Panel update on the reproductive and developmental toxicity of DEHP (February 3, 2006).

Attachment C: Curriculum Vitae and Opinion of Dr. Stefan Schlatt entitled: Evaluation of the marmoset (Callithrix jacchus) as model for reproductive toxicity (January 30, 2006).

Attachment D: Opinion of Dr. Suzetter Tardif entitled: Findings regarding female reproductive physiology from the Mitsubishi Study #B000496, "Sixty-five week repeated oral dose toxicity study of DEHP in juvenile common marmosets (January 19, 2006).

After briefly reiterating previous comments by Price (2005a; Attachment A), Shah (2006) stated that "the Panel concluded that OEHHA should eliminate the separate MADLs for infants and neonates and raise the oral DEHP MADL to reflect a more appropriate NOAEL for DEHP effects." In addition, by citing comments submitted to the NTP-CERHR (Attachment B, C, and D) with regard to the marmoset as a "valuable model for human reproductive toxicity," the commenter reiterated ACC's belief that "OEHHA should use existing primate data as the basis for developing the oral DEHP MADL, or at the very least, recognize that the primate data demonstrate the highly conservative nature of the rodent data and use that recognition to guide its development of the MADL."

With regard to OEHHA's revisions to the proposed regulations and additions of document and information announced in the Notices of May 5, 2006, Shah (2006) noted that "these revisions by OEHHA do not address the Panel's August 2005 comments, which demonstrated that OEHHA's development of separate neonatal and infant MADLs are not supported by science or by the text of Proposition 65, no matter how the terms "neonatal" and "infant" are defined." The commenter had no other comments on OEHHA's revisions to the proposed regulations and additions of document and information announced in the Notices of March 3, 2006.

Response

None of the Shah (2006) comments submitted addressed OEHHA's revisions of the proposed regulations announced in the Notices of March 3, 2006.

With regard to previous comments submitted to OEHHA from the American Chemistry Council by Price (2005a; Attachment A in the current submission), OEHHA has considered all of them and provided detailed responses as presented above in Comment 12-22 in this Final Statement of Reasons.

With regard to comments on the marmoset as an animal model and use of marmoset data on DEHP in developing MADLs for DEHP by oral exposure, the commenter basically reiterated previous comments from the ACC on this issue. As discussed in detail in OEHHA's responses in Comment 17 and 18, OEHHA has carefully and thoroughly considered the marmoset-related issues and experimental data. The commenter provided no additional data to demonstrate that the marmoset study by the MCSI (2003) is "the most sensitive study deemed to be of sufficient quality." None of the comments suggest that the rodent data on the male reproductive toxicity of DEHP are not relevant to humans. Therefore, OEHHA's decision to use the study in rats by David et al. (2000) as the basis for establishing MADLs for DEHP by oral exposure is scientifically sound.

With regard to comments by Dr. Stefan Schlatt, OEHHA made no conclusion on the general value of the marmoset as an animal model. OEHHA also considered the marmoset study by the MCSI (2003) "carefully and critically" as requested by Dr. Schlatt. OEHHA's conclusions on the value of marmoset data on DEHP in establishing MADLs for this chemical by oral route are based on considerations presented in the MADL support document (2005; 2006) and again in OEHHA's responses to Comment 17 and 18 above. OEHHA's conclusions on the findings from the MCSI study are generally consistent with those made by the NTP-CERHR Expert Panel as presented in the "NTP-CERHR Expert Panel Update on the Reproductive and Developmental Toxicity of Di(2-Ethylhexyl) Phthalate" (CERHR, 2006).

Comments from Dr. Suzette Tardif focused on the findings from the marmoset study by the MCSI (2003) on the female reproductive toxicity of DEHP. DEHP is currently listed as causing developmental and male reproductive toxicity under Proposition 65. Evidence on the female reproductive toxicity of DEHP is therefore irrelevant to the development of MADLs for DEHP by oral exposure. Therefore, no response to Dr. Tardif's comments is necessary.

CONCLUSIONS ON COMMENTS AND RESPONSE

As presented above, all the comments submitted to OEHHA have been reviewed and considered by OEHHA. Based on relevant scientific evidence and regulatory provisions that OEHHA relied upon in developing MADLs for DEHP by oral route of exposure, OEHHA determined that the MADLs for DEHP by oral exposure as proposed by OEHHA (2005) meet the requirements of Article 8 of the regulations. No further revision is made.

CITATIONS

Below are given the full citations of documents referred to in the comments and responses to comments.

Akingbemi BT, Ge R, Klinefelter GR, Zirkin BR, Hardy MP (2004). Phthalate-induced Leydig cell hyperplasia is associated with multiple endocrine disturbances. *Proc Natl*

Acad Sci U S A **101**, 775-80.

Akingbemi BT, Youker RT, Sottas CM, Ge R, Katz E, Klinefelter GR, Zirkin BR, Hardy MP (2001). Modulation of rat Leydig cell steroidogenic function by di(2-ethylhexyl)phthalate. *Biol Reprod* **65**, 1252-9.

Boekelheide K (2004). Cracking the nut. *Toxicol Sci* **81**, 1-2 .

Brody C (2005). Comments on proposed MADLs for DEHP on behalf of the Commonweal. Submitted to the Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency, Sacramento, on August 5, 2005. Available upon request.

California Regulatory Notice Register (2005). Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency, Notice of Proposed Rulemaking. Title 22, California Code of Regulations. Amendment to Section 12805 Specific Regulatory Levels: Chemicals Causing Reproductive toxicity. Vol. No. 25-Z, pp. 899-902.

Cammack JN, White RD, Gordon D, Gass J, Hecker L, Conine D, Bruen US, Friedman M, Echols C, Yeh TY, Wilson DM (2003). Evaluation of reproductive development following intravenous and oral exposure to DEHP in male neonatal rats. *Int J Toxicol* **22**, 159-74.

Center for the Evaluation of Risks to Human Reproduction (CERHR, 2000). NTP-CERHR Expert Panel Report on Di (2-ethylhexyl) Phthalate. National Toxicology Program, U.S. Department of Health and Human Services, Research Triangle Park, NC, October.

Center for the Evaluation of Risks to Human Reproduction (CERHR, 2005). NTP-CERHR Expert Panel Update on the Reproductive and Developmental Toxicity of Di (2-ethylhexyl) Phthalate. National Toxicology Program, U.S. Department of Health and Human Services, Research Triangle Park, NC, November.

Chan W (2005). Comments on the proposed MADL for the reproductive toxicant DEHP by intravenous and oral exposure. Submitted to the Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency, Sacramento, on August 5, 2005. Available upon request.

Collett GP, Betts AM, Johnson MI, Pulimood AB, Cook S, Neal DE *et al.* (2000). Peroxisome proliferator-activated receptor alpha is an androgen-responsive gene in human prostate and is highly expressed in prostatic adenocarcinoma. *Clin Cancer Res* **6,** 3241-8.

Corton JC, Lapinskas PJ (2005). Peroxisome proliferator-activated receptors: mediators of phthalate ester-induced effects in the male reproductive tract? *Toxicol Sci* **83,** 4-17.

David RM, Moore MR, Finney DC, Guest D (2000). Chronic toxicity of di(2-ethylhexyl)phthalate in rats. *Toxicol Sci* **55**, 433-43.

Duty SM, Calafat AM, Silva MJ, Brock JW, Ryan L, Chen Z *et al*. (2004). The relationship between environmental exposure to phthalates and computer-aided sperm analysis motion parameters. *J Androl* **25,** 293-302.

Duty SM, Silva MJ, Barr DB, Brock JW, Ryan L, Chen Z *et al*. (2003a). Phthalate exposure and human semen parameters. *Epidemiology* **14,** 269-77.

Duty SM, Singh NP, Silva MJ, Barr DB, Brock JW, Ryan L *et al*. (2003b). The relationship between environmental exposures to phthalates and DNA damage in human sperm using the neutral comet assay. *Environ Health Perspect* **111,** 1164-9.

Elbrecht A, Chen Y, Cullinan CA, Hayes N, Leibowitz M, Moller DE *et al*. (1996). Molecular cloning, expression and characterization of human peroxisome proliferator activated receptors gamma 1 and gamma 2. *Biochem Biophys Res Commun* **224,** 431-7.

Flurer CI, Kern M, Rambeck WA, Zucker H (1987). Ascorbic acid requirement and assessment of ascorbate status in the common marmoset (Callithrix jacchus). *Ann Nutr Metab* **31,** 245-52.

Flurer CI, Zucker H (1987). Difference in serum ascorbate in two species of Callithricidae. *Int J Vitam Nutr Res* **57,** 297-8.

Fredricsson B, Moller L, Pousette A, Westerholm R (1993). Human sperm motility is affected by plasticizers and diesel particle extracts. *Pharmacol Toxicol* **72,** 128-33.

Gould RM, Silas J, Hara JH, and Aguilar F (2005). Comments on proposed MADLs for DEHP on behalf of the San Francisco Bay Area and Los Angeles Chapters of Physicians for Social Responsibility. Submitted to the Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency, Sacramento, on July 25, 2005. Available upon request.

Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E, Klein N (2002). Outcomes in young adulthood for very-low-birth-weight infants. *N Engl J Med* **346,** 149-57.

Hampl JS, Taylor CA, Johnston CS (2004). Vitamin C deficiency and depletion in the United States: the Third National Health and Nutrition Examination Survey, 1988 to 1994. *Am J Public Health* **94**, 870-5.

Hase T, Yoshimura R, Mitsuhashi M, Segawa Y, Kawahito Y, Wada S *et al*. (2002). Expression of peroxisome proliferator-activated receptors in human testicular cancer and growth inhibition by its agonists. *Urology* **60,** 542-7.

Jonsson BA, Richthoff J, Rylander L, Giwercman A, Hagmar L (2005). Urinary phthalate metabolites and biomarkers of reproductive function in young men. *Epidemiology* **16**,

487-93.

Klaunig JE, Babich MA, Baetcke KP, Cook JC, Corton JC, David RM *et al*. (2003). PPARalpha agonist-induced rodent tumors: modes of action and human relevance. *Crit Rev Toxicol* **33,** 655-780.

Koch HM, Bolt HM, Preuss R, Angerer J (2005). New metabolites of di(2-ethylhexyl)phthalate (DEHP) in human urine and serum after single oral doses of deuterium-labelled DEHP. *Arch Toxicol* **79,** 367-76.

Li LH, Jester WF Jr, Laslett AL, Orth JM (2000). A single dose of Di-(2-ethylhexyl) phthalate in neonatal rats alters gonocytes, reduces sertoli cell proliferation, and decreases cyclin D2 expression. *Toxicol Appl Pharmacol* **166**, 222-9.

Li LH, Donald JM, Golub MS (2005). Review on testicular development, structure, function, and regulation in common marmoset. *Birth Defects Res B Dev Reprod Toxicol* **74,** 450-69.

Lunder S (2005). Comments on proposed MADLs for DEHP on behalf of the Environmental Working Group. Submitted to the Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency, Sacramento, on August 5, 2005. Available upon request.

Main KM, Mortensen GK, Kaleva MM, Boisen KA, Damgaard IM, Chellakooty M, Schmidt IM, Suomi A-M, Virtanen HE, Petersen JH, Andersson A-M, Toppari J, Skakkebæk NE (2006). Human breast milk contamination with phthalates and alterations of endogenous reproductive hormones in three months old infants. *Environ Health Perspect* **114,** 270-6. [Published online on September 7, 2005].

Mitsubishi Chemical Safety Institute Ltd. (MCSI, 2003). Sixty-five week repeated oral dose toxicity study of di(2-ethylhexyl) phthalate (DEHP) in juvenile common marmosets. Mitsubishi Chemical Safety Institute Ltd., Study No. B000496. [A copy of the final study report was provided to OEHHA by the American Chemistry Council.]

Modigh CM, Bodin SL, Lillienberg L, Dahlman-Hoglund A, Akesson B, Axelsson G (2002). Time to pregnancy among partners of men exposed to di(2-ethylhexyl)phthalate. *Scand J Work Environ Health* **28,** 418-28.

Office of Environmental Health Hazard Assessment (OEHHA, 2003). Letter from George V. Alexeeff on behalf of OEHHA to Courtney M. Price, ACC, with attached "Response to Comments from the American Chemistry Council on Notice of Intent to List Di(2-ethylhexyl) Phthalate under Proposition 65," on October 14, 2003. Available upon request.

Office of Environmental Health Hazard Assessment (OEHHA, 2005). Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity of Di(2-ethylhexyl)phthalate (DEHP) by Oral Exposure. OEHHA, California Environmental

Protection Agency, Sacramento, California, June.

Office of Environmental Health Hazard Assessment (OEHHA, 2006). Revised Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity of Di(2-ethylhexyl)phthalate (DEHP) by Oral Exposure. OEHHA, California Environmental Protection Agency, Sacramento, California, April.

Poon R, Lecavalier P, Mueller R, Valli VE, Procter BG, Chu I (1997). Subchronic oral toxicity of di-n-octyl phthalate and di(2-Ethylhexyl) phthalate in the rat. *Food Chem Toxicol* **35**, 225-39.

Price CM (2003). Comments from the American Chemistry Council Phthalate Esters Panel to the Office of Environmental Health Hazard Assessment (OEHHA) on OEHHA's Notice of Intent to List Di(2-Ethylhexyl) Phthalate (DEHP) under the Proposition 65. Submitted to OEHHA, California Environmental Protection Agency, Sacramento, on June 9, 2003. Available upon request.

Price CM (2005a). Comments from the American Chemistry Council Phthalate Esters Panel to the Office of Environmental Health Hazard Assessment (OEHHA) on Proposed MADL for DEHP by Oral Exposure. Submitted to OEHHA, California Environmental Protection Agency, Sacramento, on August 8, 2005. Available upon request.

Price CM (2005b). Comments from the American Chemistry Council Phthalate Esters Panel to the Office of Environmental Health Hazard Assessment (OEHHA) on OEHHA's Notice of Addition of Documents and Information to Rulemaking File OAL file No. Z-01-1019-06 and OAL File No. Z-05-0614-06. Submitted to OEHHA, California Environmental Protection Agency, Sacramento, on August 23, 2005. Available upon request.

Price CM (2005c). Comments from the American Chemistry Council Phthalate Esters Panel to the Office of Environmental Health Hazard Assessment (OEHHA) on OEHHA's Clarification of Notice of Addition of Documents and Information to Rulemaking file, OAL FILE Z-01-1019-06 and OAL File No. Z-05-0614-06. Submitted to OEHHA, California Environmental Protection Agency, Sacramento, on September 14, 2005. Available upon request.

Price CJ, Tyl RW, Marr MC, Myers CB, Sadler BM, Kimmel CA (1988). Reproductive and fertility evaluation of diethylhexyl phthalate (CAS No. 117-81-7) in CD-1 mice exposed during gestation NTP Report No. 88-092.

Pugh G Jr, Isenberg JS, Kamendulis LM, Ackley DC, Clare LJ, Brown R *et al*. (2000). Effects of di-isononyl phthalate, di-2-ethylhexyl phthalate, and clofibrate in cynomolgus monkeys. *Toxicol Sci* **56,** 181-8.

Rais-Bahrami K, Nunez S, Revenis ME, Luban NL, Short BL (2004). Follow-up study of adolescents exposed to di(2-ethylhexyl) phthalate (DEHP) as neonates on extracorporeal membrane oxygenation (ECMO) support. *Environ Health Perspect* **112,** 1339-40.

Richburg JH, Boekelheide K (1996). Mono-(2-ethylhexyl) phthalate rapidly alters both Sertoli cell vimentin filaments and germ cell apoptosis in young rat testes. *Toxicol Appl Pharmacol* **137,** 42-50.

Richburg JH, Nanez A, Gao H (1999). Participation of the Fas-signaling system in the initiation of germ cell apoptosis in young rat testes after exposure to mono-(2-ethylhexyl) phthalate. *Toxicol Appl Pharmacol* **160,** 271-8.

Rizzo J (2005). Comments on proposed MADL for DEHP on behalf of the Breast Cancer Fund. Submitted to the Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency, Sacramento, on August 5, 2005. Available upon request.

Schettler T and Hall AG (2005). Comments on proposed MADLs for DEHP on behalf of the Health Care Without Harm. Submitted to the Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency, Sacramento, on July 25, 2005. Available upon request.

Schettler T and Hall AG (2006). Comments on re-proposed MADLs for DEHP on behalf of the Health Care Without Harm. Submitted to the Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency, Sacramento, on May 9, 2006. Available upon request.

Schilling K, Gembardt C, Hellwig J (1999). Reproduction toxicity of di-2-ethylhexyl phthalate (DEHP). *Toxicologist* **48(1-S),** 147-8.

Schilling K, Gembardt C and Hellwig J (2001). Di-2-ethylhexyl phthalate – two-generation reproduction toxicity study in Wistar rats. Continuous dietary administration. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, D-67056 Ludwigshafen, FRG. Laboratory project identification 70R0491/97139.

Schmitz M (2005). Comments on proposed MADLs for DEHP on behalf of the California League for Environmental Enforcement Now. Submitted to the Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency, Sacramento, on August 5, 2005. Available upon request.

Schultz R, Yan W, Toppari J, Volkl A, Gustafsson JA, Pelto-Huikko M (1999). Expression of peroxisome proliferator-activated receptor alpha messenger ribonucleic acid and protein in human and rat testis. *Endocrinology* **140,** 2968-75.

Shah HC (2006). Comments from the American Chemistry Council Phthalate Esters Panel to the Office of Environmental Health Hazard Assessment (OEHHA) on Re-proposed MADL for DEHP by Oral Exposure. Submitted to OEHHA, California Environmental Protection Agency, Sacramento, on May 22, 2006. Available upon request.

Sharpe RM, McKinnell C, Kivlin C, Fisher JS (2003). Proliferation and functional

maturation of Sertoli cells, and their relevance to disorders of testis function in adulthood. *Reproduction* **125,** 769-84.

Sharpe RM, Walker M, Millar MR, Atanassova N, Morris K, McKinnell C *et al*. (2000). Effect of neonatal gonadotropin-releasing hormone antagonist administration on sertoli cell number and testicular development in the marmoset: comparison with the rat. *Biol Reprod* **62,** 1685-93.

Stanley MK (2004). Letter from the American Chemistry Council Phthalate Esters Panel to the Office of Environmental Health Hazard Assessment, with attached "information pertaining to development of a maximum allowable dose level for di(2-ethylhexyl) phthalate." Submitted to the Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, on May 12, 2004. Available upon request.

Swan SH, Main KM, Liu F, Stewart SL, Kruse RL, Calafat AM, Mao CS, Redmon JB, Ternand CL, Sullivan S, Teague JL, Drobnis EZ, Carter BS, Kelly D, Simmons TM, Wang C, Lumbreras L, Villanueva S, Diaz-Romero M, Lomeli MB, Otero-Salazar E, Hobel C, Brock B, Kwong C, Muehlen A, Sparks A, Wolk A, Whitham J, Hatterman-Zogg M, Maifield M , and The Study for Future Families Research Group (2005). Decrease in anogenital distance among male infants with prenatal phthalate exposure**.** *Environ Health Perspect* **113,** 1056-61. [Published online on May 27, 2005].

Tanaka T (2002). Reproductive and neurobehavioural toxicity study of bis(2-ethylhexyl) phthalate (DEHP) administered to mice in the diet. *Food Chem Toxicol* **40,** 1499-506.

Tanaka T (2005). Reproductive and neurobehavioural effects of bis(2-ethylhexyl) phthalate (DEHP) in a cross-mating toxicity study of mice. *Food Chem Toxicol* **43,** 581-9.

U.S. Environmental Protection Agency (U.S. EPA, 1996). Guidelines for reproductive toxicity risk assessment. *EPA/630/R-96/009* FRL-5630-6.

U.S. Food and Drug Administration (U.S. FDA, 2001). Safety Assessment of Di (2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices. Centers for Devices and Rediological Health. U.S. Food and Drug Administration. Rockville, MD.

Wolfe GW, Layton K, Nehrebeckyj L, Wang Y, Chapin R, Rousselle SD, and Bishop J (2002). Reproductive effects of diethylhexylphthalate (DEHP) in Sprague-Dawley rats when assessed by the continuous breeding protocol. *Toxicologist* **66(1-S),** 234

Wolfe GW and Layton K (2005). Diethylhexylphthalate: Multigenerational reproductive assessment by continuous breeding when administered to Sprague-Dawley rats in the Diet. Final Report submitted to National Toxicology Program. TRC Study No. 7244-200, NTP-RACB 98-004.

Zuhlke U, Weinbauer G (2003). The common marmoset (Callithrix jacchus) as a model in toxicology. *Toxicol Pathol* **31 Suppl**, 123-7.

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 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 (Id.). 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.