REVISED 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 intravenous (i.v.) injection. 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; Health and Safety Code, Section 25249.5 *et seq*.). On October 29, 2004, the Office of Environmental Health Hazard Assessment (OEHHA) published a Notice of Proposed Rulemaking (California Regulatory Notice Register, 2004) to adopt a regulatory level for DEHP by i.v. injection pursuant to Title 22, California Code of Regulations, Section12000[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 was provided from the publication of the Notice until December 13, 2004, and a public hearing was held on December 13, 2004. Written and oral testimony was accepted at the hearing. A total of six sets of written comments, listed in Table 1 (page 3), were received.

OEHHA reviewed the comments and revised the proposed Maximum Allowable Dose Levels (MADLs) for di(2-ethylhexyl)phthalate (DEHP) by i.v. injection (OEHHA, 2005). Pursuant to the requirements of Government Code, Section 11346.8(c), and Section 44 of Title 1 of the California Code of Regulations, on June 24, 2005, OEHHA issued a Notice of Modifications to Text of Proposed Regulations, Title 22, California Code of Regulations, Section 12805 (OAL Rulemaking File No. Z-01-1019-06). A public comment period of 45 days from June 24 through August 8, 2005, was provided and a public hearing was held on August 8, 2005. Written and oral testimony was accepted at the hearing. A total of ten sets of written comments, listed in Table 2 (page 14), 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-01-101906. This notice identified 43 citations that had not been previously included in the Rulemaking File OAL FILE No. Z-01-1019-06, but that had been reviewed by OEHHA staff in establishing the proposed MADLs for DEHP by i.v. injection. Among the 43 citations included in the Notice of August 17, 2005, were 18 research papers that became available to OEHHA after preparation of the MADL document was completed. OEHHA staff reviewed these papers when they became available and determined that no revisions to the MADL document were necessitated by the 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

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

papers were reviewed and considered by OEHHA staff because they could be sources of potentially relevant information. All the documents identified in the notice of August 17 were made available for public inspection and comment between August 17 and September 1, 2005.

On August 23, 2005, the American Chemistry Council (Price, 2005b) submitted comments to OEHHA on the Notice of August 17, 2005 and requested OEHHA to publish a written explanation of the manner in which it is relying on new documents and to extend the commenting period. In response to the request, OEHHA issued a Clarification of Notice of Addition of Documents and Information to Rulemaking file, OAL FILE Z-01-1019-06, on August 30, 2005 and extended the comment period from September 1 to September 15, 2005. One further set of comments from the American Chemistry Council (Price, 2005c) was received.

On October 29, 2005, OEHHA submitted the proposed regulations to the Office of Administrative Law (OAL). On December 13, 2005, OAL disapproved the proposed regulation for failing to comply with the "clarity" standard and for failing to follow certain procedures required by the Administrative Procedure Act ("Decision of Disapproval of Regulation Action", OAL File No. 05-1027-05 S).

OEHHA addressed issues raised by the OAL by revising the proposed regulations and issued two additional notices on March 3, 2006: "Notice of Modifications to Text of Proposed Regulations, Amendment to Title 22, California Code of Regulations, Section 12805 (OAL Rulemaking File No. 05-1027-05 S)" and "Notice of Addition of Documents and Information to Rulemaking File OAL File 05-1027-05 S," respectively. Both Notices provided a public comment period of 15 days from March 3 through March 20, 2006. A total of three sets of written comments, listed in Table 3 (page 25), were received.

This regulatory action hereby adopts maximum allowable dose levels for DEHP by i.v. injection.

SUMMARY AND RESPONSE TO COMMENTS ON THE NOTICE OF PROPOSED RULEMAKING PUBLISHED ON OCTOBER 29, 2004.

Table 1 lists six sets of comments on the Notice of Proposed Rulemaking (California Regulatory Notice Register, 2004). Summaries and detailed responses to these comments are provided below.

Table 1. List of Commenters on the Notice of Proposed Rulemaking Published on October 29, 2004

Commenter/Affiliation	Representing	Date Received	Submission No. /Citation
Courtney M. Price CHEMSTAR	American Chemistry Council Phthalate Esters Panel	December 13, 2004	C-1/ Price, 2004
Michael Green Center for Environmental Health	Center for Environmental Health	December 9, 2004	C-2/ Green, 2004
Carol Rene Brophy Nosssaman, Guthner, Knops & Elliott	California Medical Association; California Healthcare Association, Inc.	December 13, 2004	C-3/ Brophy, 2004
Gary Whitmyre Risksciences, LLC	Not stated	December 13, 2004	C-4/ Whitmyre, 2004
Robert M. Gould and Julie Silas Physicians for Social Responsibility, San Francisco Bay Area Chapter	Physicians for Social Responsibility San Francisco Bay Area Chapter	December 7, 2004	C-5/ Gould and Silas, 2004
Ted Schettler Science and Environmental Health Network Anna G. Hall Health Care Without Harm	Health Care Without Harm	December 8, 2004	C-6/ Schettler and Hall, 2004

Comment 1

Price (2004) stated that it is appropriate to develop a separate MADL for DEHP for the i.v. injection route of exposure.

Response

Comment acknowledged. OEHHA is developing a separate set of MADL's for DEHP by the i.v. route of exposure.

Comment 2

One commenter supported the selection of the Cammack et al. 2003 study, four did not state an objection to it, and one commenter appeared to object to it.

Price (2004) stated that the study by Cammack et al. (2003) provides an appropriate NOEL for the calculation of the MADL. Commenters Gould and Silas (2004), Green (2004), Schettler and Hall (2004) and Whitmyre (2004) did not state opposition to development of the MADL for DEHP by i.v. injection based on the study of Cammack et al. (2003). Brophy (2004) stated that "OEHHA's failure to consider the recovery effect [in Cammack et al. (2003)] is fatal to the selection and interpretation of a representative study."

Response

The basis for the i.v. MADL is the study by Cammack et al. (2003), as indicated in OEHHA (2004, 2005a) which lays out the basis for the MADL presented and referred to in the Initial Statement of Reasons and in the Notice of Modifications to Text of Proposed Regulations (OEHHA, 2004, 2005a).

Contrary to the statement in Brophy (2004), and as discussed in detail in the MADL document for DEHP by i.v. injection (OEHHA, 2004), OEHHA considered all relevant data reported in the study by Cammack et al. (2003), including the data reported from animals at the end of a 64-66 day recovery period. Detailed discussion of this issue is presented in OEHHA's responses to Comments 10-12.

Comment 3

Three of the six commenters (Gould and Silas, 2004; Schettler and Hall, 2004; Green, 2004) opposed the calculation of proposed MADL of 4,200 μg/day based on an adult male body weight of 70 kg. The commenters requested OEHHA to recalculate the proposed MADL based on a realistic body weight for the vulnerable populations (i.e., male fetuses, neonates, or infants).

Response

OEHHA revised the MADL calculation and developed MADLs for different age groups. These were proposed in the Notice of Modifications to Text of Proposed Regulations released on June 24, 2005, and are shown in the revised MADL document referenced therein (OEHHA, 2005).

Comment 4

Two commenters, Schettler and Hall (2004) and Green (2004), urged OEHHA to develop a MADL for enteral exposures.

Response

The MADLs for DEHP by i.v. injection apply to exposure to DEHP by the i.v. route of exposure. OEHHA has proposed separate MADLs for DEHP by the oral (enteral) route of exposure, as noticed in the Initial Statement of Reasons published on June 24, 2005 in the California Regulatory Notice Register).

Comment 5

Two comments, Schettler and Hall (2004) and Green (2004), urged OEHHA to consider aggregate exposures in developing MADLs for DEHP, noting that in the hospital setting patients can be concurrently exposed to DEHP that leaches from multiple medical products.

Response

The methods for calculating the MADL are laid out in regulation (Title 22, California Code of Regulations., 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 and is addressed in other parts of the regulations.

Comment 6

Green (2004) was concerned about OEHHA's discounting of the study by Sjoberg et al. (1985).

Response

The study by Sjoberg et al. (1985) was one of the two studies considered by OEHHA in selecting a study as the basis for MADL calculation (OEHHA, 2004; 2005). OEHHA did not discount this study. The reason for using the study by Cammack et al. (2003) instead of that by Sjoberg et al. (1985) was presented in the last paragraph of the "Study Selection" section in the MADL development documents (OEHHA, 2004; 2005), and is quoted below:

"Although the LOEL of 250 mg/kg-day observed in the study by Sjoberg et al. (1985b) is lower than that (300 mg/kg-day) in the study by Cammack et al., the NOEL (60 mg/kg-day) in the study by Cammack et al. (2003) is still below 250 mg/kg-day. Therefore, for the purpose of Proposition 65, the study by Cammack et al. (2003) is identified as "the most sensitive study deemed to be of sufficient quality" for the male reproductive effects of DEHP following i.v. injection."

In other words, although effects were observed both at 250 mg/kg-day (Sjoberg et al., 1985) and at 300 mg/kg-day (Cammack et al., 2003), the highest level of exposure at which effects were not observed was 60 mg/kg-day. Consequently, this NOEL is the basis for the MADL, as required by Title 22, California Code of Regulations, Section 12803(a)(4).

Comment 7

Green (2004) suggested that the NOAEL observed in the study by Cammack et al. (2003) should be 14.8 mg/kg-day, derived by averaging the lowest dose used in the study (60 mg/kg-day) from 21 days (dosing period) to 85 days (total observation period, including 64-66 days of post-dosing recovery).

Response

The generally accepted practice in reproductive toxicology and dose response assessment is to calculate a daily dose for the period of exposure by averaging doses administered to laboratory animals according to dosing frequency (e.g., from five days per week to daily) and/or duration (e.g., from eight hours per day to 24 hours per day in inhalation studies). A variable period of time (e.g., days to months) post exposure is sometimes included depending on the nature of a biological effect (e.g., delayed occurrence or reversibility); sometimes, pharmacokinetic adjustments are applied. DEHP has a relatively short half-life and does not accumulate significantly in rats or humans (CERHR, 2000). Thus, animals used in the study by Cammack et al. (2003) during the recovery period were unlikely exposed to DEHP either by direct exposure or as a result of residual amounts of DEHP or its metabolites. Based on these considerations, OEHHA decided that no further recalculation of the NOEL as observed in the study by Cammack et al. (2003) is necessary.

Comment 8

Brophy (2004) stated that OEHHA should not adopt a DEHP MADL for i.v. injection unless and until OEHHA establishes a Proposition 65 safe harbor regulation that recognizes patient "warnings" for medical treatment are the sole province of the treating physician and governed by the law of "informed consent."

Response

This comment is outside the scope of the proposed rulemaking. The requirement for clear and reasonable warning about exposures to DEHP is currently in force because the chemical has been on the Proposition 65 list for more than 12 months (Health and Safety Code, Section 25249.10(b)). Adoption of a MADL will simply clarify the level of exposure at which a warning must be provided. In cases where warnings must be provided, however, adoption of a MADL will have no effect on the manner in which the warning will have to be provided.

Comment 9

Brophy (2004) stated that OEHHA's DEHP MADL document did not adhere to either the legal or the scientific standards that govern promulgation of a MADL. A footnote to this statement indicates that the basis for the statement is the commenter's opinion that OEHHA failed to properly evaluate human data, and failed to use a weight-of-evidence analysis when listing DEHP as a reproductive toxicant. Brophy (2004) also stated that:

1. "Few, if any, reports exist suggesting that DEHP exposure adversely affects humans."
2. The U.S. Food and Drug Administration (U.S. FDA) is required to maintain a database of adverse effects resulting from the use of medical devices and drugs.

3. OEHHA has never requested human data from the U.S. FDA and has not even discussed the human data with U.S. FDA.

The commenter concluded that OEHHA failed to properly evaluate human data and to use a weight-of-the-evidence analysis when listing DEHP as a reproductive toxicant, and that OEHHA has wrongly determined that FDA and NIOSH made a "finding" that DEHP is a reproductive toxicant. The commenter requested OEHHA take no further action regarding DEHP, until it fully evaluates "all relevant evidence."

Response

Addition of DEHP to the Proposition 65 list is not the subject of the current regulation. If the commenter believes that the listing does not meet the requirements of Title 22, California Code of Regulations, Section12306, the commenter may request that OEHHA reconsider the listing under the provisions of Title 22, California Code of Regulations, Section12306(j).

The commenter does not identify which aspects of the legal or the scientific standards that govern promulgation of a MADL were not adhered to by OEHHA, but rather refers to the listing process. The listing process and MADL development process are quite separate, with the exception of the regulatory provision of Title 22, California Code of Regulations, Section12801(a), i.e., "The determination of whether a level of exposure to a chemical known to the state to cause reproductive toxicity has no observable effect for purposes of Section 25249.10(c) of the Act shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of a chemical as known to the state to cause reproductive toxicity." The commenter gave no indication of or reason for considering the study by Cammack et al. (2003) not to be of comparable scientific validity to the studies which formed the basis for adding DEHP to the Proposition 65 list. Thus, there appears to be no factual support for the comment.

The U.S FDA is designated an authoritative body for purposes of Proposition 65 (Title 22, California Code of Regulations, Section12306(l)). The addition of DEHP to the Proposition 65 list was based on the U.S. FDA document "Safety Assessment of Di(2-ethylhexyl)phthalate (DEHP) Released from PVC Medical Devices" (U.S. FDA, 2001), in addition to a document by the National Institute for Occupational Safety and Health (NIOSH, 1990). In the U.S. FDA document, U.S. FDA derived Tolerable Intake values for humans "from the results of studies conducted using experimental animals." OEHHA notes that it is a generally accepted scientific practice to develop such values on the basis of animal data when human data are insufficient or unavailable, and that all of the MADLs adopted to date have been based on animal data. U.S. FDA also noted that "the dose of DEHP received by some infants from device-related sources could be 20-fold greater than the dose of DEHP that is not expected to result in adverse effects following intravenous exposure." As presented in the document entitled Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Di(2-ethylhexyl)phthalate (DEHP) by Intravenous Injection (OEHHA, 2004), OEHHA has

evaluated all of the relevant data subject to the provisions of Title 22, California Code of Regulations, Sections12306(g) and 12306(h), including any human data identified in the documents by the U.S. FDA (2001) or NIOSH (1990) or in the comments submitted to OEHHA**.**

Comment 10

After briefly discussing some aspects of observations in the study by Cammack et al. (2003), Brophy (2004) stated that "OEHHA has disregarded the conclusions of the authors and focused on certain evidence of microscopic changes to cell in rat tentacles (*sic*) and decreased tentacle (*sic)* weight. Considering the compelling exculpating evidence in this study and other human data, OEHHA's conclusions concerning DEHP are without merit as a matter of law and science."

Response

OEHHA assumes that the commenter intended to refer to rat testicles rather than tentacles. The effects noted by OEHHA in the study by Cammack et al. (2003) were "absolute testis weights in the 300 and 600 mg/kg-day i.v. groups were significantly decreased by approximately 33% and 48%, respectively (0.326±0.013g and 0.253±0.011g in the 300 and 600 mg/kg-day groups, respectively, compared to 0.486±0.016g in the vehicle-only control group). Histopathological changes, consisting of partial depletion of the germinal epithelium and/or decreased diameter of the seminiferous tubules, were present in all animals of the 300 and 600 mg/kg-day i.v. groups" (OEHHA, 2004; 2005). These parameters are generally recognized to be clear indicators of male reproductive toxicity. For example, in the U.S. Environmental Protection Agency's "Guidelines for Reproductive Toxicity Risk Assessment" (U.S. EPA, 1996), it is stated that "a significant increase or decrease [in testis weight] is indicative of an adverse effect", and that "histological evaluations can be especially useful by providing a relatively sensitive indicator of damage." OEHHA concurs with U.S. FDA that the human data available do not provide an adequate basis for risk assessment.

Comment 11

Brophy (2004) stated that "OEHHA's findings when it listed DEHP as a reproductive toxicant, and the present MADL proposal appear to contradict FDA's findings and conclusions when reviewing the same scientific data." The commenter further stated that "OEHHA's proposed MADL for i.v. exposures is clearly inconsistent with FDA regulatory mandates. Consequently, compliance with Proposition 65 is likely to render affected medical devices misbranded under federal law, and within the scope of *Dowhal*." The commenter concluded that "to avoid wasteful and costly litigation, CHA and CMA respectfully request that OEHHA work cooperatively with FDA, both with respect to adopting a MADL and addressing the manner in which appropriate warnings should be provided."

Response

As noted above on the response to comment 9, DEHP is currently on the Proposition 65 list of chemicals known to the State to cause reproductive toxicity largely because it was formally identified as causing reproductive toxicity by U.S. FDA, a Proposition 65 authoritative body. The subject of the current regulation is development of a MADL. The issues raised by the commenter pertain to the warning requirement consequent to the chemical being on that list, not to the specific exposure level at which the warning requirement comes into force (i.e., the MADL). Thus, the comments are not relevant to the current regulatory action.

Comment 12

Whitmyre (2004) submitted a total of eight pages of comments. This commenter agreed with OEHHA that the study by Cammack et al. (2003) is the key study for evaluation of the potential male reproductive effects of DEHP. However, the commenter charged that OEHHA ignored the results from the recovery groups, focused upon parameters that are not reliable indicators of reproductive impact, and incorrectly identified 60 mg/kg-day as the "NOAEL". The commenter concluded that "the evaluation by OEHHA that forms the basis for the proposed MADL does not meet the standard of scientific rigor required to support a MADL", and suggested that that 600 mg/kg-day should be used as NOAEL and a MADL of 42,000 micrograms/day should be proposed.

Response

The commenter agreed with OEHHA that the study by Cammack et al. (2003) is one of the key studies used as basis for the MADL development for DEHP by i.v. injection. Thus, OEHHA assumes that the commenter agrees with OEHHA that this study is "the most sensitive study deemed to be of sufficient quality" (Title 22, California Code of Regulations, Section 12803(a)(4)). The issues raised by the commenter appear to be based on a number of factual errors. OEHHA's detailed responses to the relevant issues are provided below:

1. The commenter stated that OEHHA ignored the results of the recovery group in selecting a NOAEL.

As explained in OEHHA's supporting document for proposed MADLs for DEHP by i.v. injection (OEHHA, 2004; 2005), OEHHA fully considered all the data, including those observed in animals from the recovery groups. OEHHA stated that "at the end of the 21-day treatment period, seven animals from each group were necropsied and nine animals from each group were allowed to recover until 90 days of age." OEHHA further stated that "at the end of recovery (90 days of age, approximately 64-66 days of recovery), absolute testis weight in rats treated with 300 or 600 mg/kg-day were still significantly lower than those of the control animals. No treatment-related histopathological changes were observed in the testis, epididymis, or prostate."

For the purpose of clarification, it should be pointed out that OEHHA used the No Observable Effect Level (NOEL), not the NOAEL, for calculation of the proposed MADLs, as required by Title 22, California Code of Regulations, Section 12803.

2. The commenter stated that "OEHHA focused upon parameters that are not reliable indicators of reproductive impact." The commenter further stated that "lack of any functional effects on sperm parameters in the recovery group indicate no functional impairment at any dose for intravenous-administered DEHP." After acknowledging the fact that DEHP administered for 21 days caused decreases in the diameter of the seminiferous tubules and a mild depletion of germinal epithelial cells in the testes, the commenter stated that "these effects in the testes are without toxicological significance for the case at hand because no impairment of sperm function (the ultimate metric for measuring male reproductive toxicity) occurred."

The main endpoints used in the study by Cammack et al. (2003) for the testicular effects of DEHP include testis weight, histopathological evaluations, testicular spermatid counts, and evaluation of epididymal sperms. All of these endpoints have been commonly used in numerous studies to investigate the male reproductive toxicity of chemicals (CERHR, 2000; Thomas and Thomas, 2001; Creasy, 2001; 2003;) and, as noted in the response above to Comment 10, the U.S. Environmental Protection Agency's "Guidelines for Reproductive Toxicity Risk Assessment" (U.S. EPA, 1996) state that "a significant increase or decrease [in testis weight] is indicative of an adverse effect", and that "histological evaluations can be especially useful by providing a relatively sensitive indicator of damage." OEHHA is not aware of any data to support the commenter's conclusion that testicular weights and histopathological evaluation are not "reliable indicators of reproductive impact", nor did the commenter provide or cite to any such data.

The commenter stated that "after a mixture of germ cells are released in various stages of development from the seminiferous tubules of the testes, they travel through the epydidymis, …. external to the testes." This statement appears to reflect a fundamental error in understanding of the process of sperm production and maturation. Only elongated spermatids, not "a mixture of germ cells in various stages of development", are continuously released from the seminiferous epithelium into the lumen and then are transferred into the epididymis (Thomas and Thomas, 2001; Creasy, 2001). In fact, one adverse histopathological change observed in the testis of rats treated with DEHP was the release of a mixture of germ cells into the lumen of the seminiferous tubules, resulting from sloughing of the seminiferous epithelium (CERHR, 2000; Creasy, 2001; Boekelheide, 2004).

The commenter stated "OEHHA made note of the sperm counts in the epididymis as a benchmark of male reproductive toxicity" and that "what is much more meaningful (*sic*) measure of impact on male reproductive function are sperm motility and morphology." In the OEHHA MADL document (OEHHA, 2004; 2005), OEHHA simply summarized the findings by the authors by stating that "no effect on sperm motility or morphology or

testicular sperm count was observed, but epididymal sperm counts were significantly increased in rats treated with 300 or 600 mg/kg-day." OEHHA based identification of the NOEL on a number of observations, including testis weights and histopathological changes in the testis. In the study by Cammack et al. (2003), rats treated by i.v. injection with 300 or 600 mg/kg-day of DEHP had higher epididymal sperm counts than those in the control group. This observation is not consistent with decreased testicular weights with histopathological damages in the seminiferous epithelium in the same group of animals (Cammack et al., 2003; Thomas and Thomas, 2001; Creasy, 2001; 2003). OEHHA agrees with the study authors that the changes in epididymal sperm count are unlikely to be a treatment-related effect (Cammack et al., 2003).

With regard to the value of sperm motility and morphology in measurement of impact on male reproductive function, these are two parameters among numerous endpoints listed by Thomas and Thomas (2001) as "potentially useful tests of male reproductive toxicity for laboratory animals and/or humans." To OEHHA's knowledge, there are no data to support the commenter's conclusion that these two parameters are more meaningful than other endpoints, such as testis weights or histopathological evaluation, in measuring the impact of a chemical on the male reproductive function.

3. The commenter stated that "the vast majority of patients would encounter medical devices infrequently for a few hours or a few days followed by a long period of non-use," and thus "the treatment profile for rats from the recovery group in the Cammack et al. (2003) study is very similar to the anticipated time profile for use of medical devices by patients." The commenter concluded that "the recovery group results from the Cammack et al. (2003) study suggest that, given sufficient time, the male reproductive effects of DEHP (if they occur at all) are anticipated to be repaired and reversed in patients exposed to DEHP through the use of PVC-containing medical devices."

The data observed in animals from the recovery groups by Cammack et al. (2003) indicate that some testicular effects of DEHP in animals exposed for 21 days postnatally may be reversible to some extent. These data do not contradict the fact that exposure to DEHP causes damages in the testis. Therefore, there is no basis to exclude the data observed during the exposure period. It would be against the generally accepted principles in toxicology and risk assessment to only use the data collected during the recovery period, in which no exposure occurs.

4. Based on lack of obvious effects on epididymal sperm parameters in the recovery group, the commenter suggested that the NOAEL observed in the study by Cammack et al. (2003) is 600 mg/kg-day, instead of 60 mg/kg-day as identified by OEHHA (2004), and a MADL of 42,000 micrograms/day should be proposed.

As discussed above, data collected during the whole experimental period, especially those collected when the animals were dosed, have been considered in this MADL development. Testicular weight and histopathological evaluation of the male reproductive organs are routine and reliable endpoints for the assessment of male

reproductive toxicity. Moreover, the testis weights in the 300 and 600 mg/kg-day groups were still significantly lower than those in the control group at the end of recovery period, clearly indicating potential long-term effects of DEHP on the testis in rats treated within the first three-weeks after birth. Therefore, even if the data observed in treated animals at the end of more than two months of recovery are used, 60 mg/kg-day, the lowest dose used in the study, is still the NOEL for this study.

Based on the considerations discussed above, OEHHA disagrees with Whitmyre on identification of the NOEL observed in the study by Cammack et al. (2003). No revision to the proposed MADLs for DEHP by i.v. injection or to the supporting document is required.

Comment 13

Whitmyre (2004) suggested that the proposed MADL for DEHP be reviewed by an independent panel comprised of individuals not affiliated with OEHHA as staff or consultants. The commenter listed a number of reasons for this suggestion.

Response

The technical process for development of MADLs by OEHHA is specified in regulations (Title 22, California Code of Regulations, Sections12801 and 12803). The procedure followed for adoption of a MADL into regulation is consistent with the Administrative Procedure Act, and provides for comment by interested parties on the proposed regulation. OEHHA provides the draft MADLs to the members of the Developmental and Reproductive Toxicant Identification Committee, the designated State's qualified experts for reproductive toxicity (Title 22, California Code of Regulations, Section 12306(l)), so that they may comment if they wish on the proposal. OEHHA declines to take the extraordinary step of convening an additional review panel to review the MADL's for a single chemical.

Comment 14

Price (2004) disagreed with OEHHA's conclusion that "the data from studies in common marmosets cannot be used as basis for MADL development for DEHP, nor can they be used as a basis for adjusting the rat NOEL." Price (2004) presented a number of reasons for disagreeing with OEHHA on this conclusion, and stated that the differences discussed by OEHHA are not sufficient to completely discount the primate data.

Response

OEHHA's conclusion as quoted above was based on the fact that the testis in the common marmoset is different from that in rats, cynomolgus monkeys, and men in some physiological characteristics that may also play an important role in the testicular actions of DEHP (CERHR, 2000; Akingbemi et al., 2001; 2004; U.S. FDA, 2003; Boekelheide, 2004). In the supporting document for proposed MADLs for DEHP by i.v. injection

(OEHHA, 2004; 2005), OEHHA reviewed numerous studies to determine the relevance of marmoset data and gave one line of evidence as examples to indicate the fundamental differences in the testis between the marmoset and humans. Thus, OEHHA has not discounted the primate data, but rather has carefully evaluated it and concluded that it does not provide a scientifically valid basis for either developing a MADL or for modifying the MADL's developed on the basis of rodent data.

Comment 15

Based on the marmoset data, Price (2004) concluded that "at the least, the marmoset data provide a basis for OEHHA to acknowledge in its documentation that a MADL based on rat data is likely very conservative – that is, health protective – and the Panel requests that OEHHA do so."

Response

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 could cause observable effects. OEHHA does not consider it appropriate to emphasize the health protectiveness of this MADL 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. Also, as discussed in the response to Comment 14, OEHHA disagrees with Price (2004) on the significance of the marmoset data in determining the relevance of rodent data to humans.

SUMMARY AND RESPONSE TO COMMENTS ON THE NOTICE OF MODIFICATIONS TO TEXT OF PROPOSED REGULATIONS ISSUED ON JUNE 24, 2005

Table 2 lists ten sets of comments received during the period from June 24 to August 8, 2005, on the Notice of Modifications to Text of Proposed Regulations. In addition, two sets of written comments from Courtney M. Price on behalf of the American Chemistry Council (Price, 2005b; 2005c) were received on August 23 and September 14, 2005, in response to Notices released by OEHHA on August 17 and 30, 2005, respectively. Summaries of and detailed responses to these comments are provided below.

Table 2. List of Commenters on the Notice of Modifications to Text of Proposed Regulations Issued 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	C2-1/Gould et al., 2005
Ted Schettler Science and Environmental Network Anna G. Hall Health Care Without Harm	Health Care Without Harm	July 25, 2005	C2-2/Schettler and Hall, 2005
Wilma Chan	Chairwoman, Assembly Committee on Health, California State Assembly	August 5, 2005	C2-3/Chan, 2005
Charlotte Brody Commonweal	Commonweal	August 5, 2005	C2-4/Brody, 2005
Mike Schmitz California League for Environmental Enforcement Now	California League for Environmental Enforcement Now	August 5, 2005	C2-5/Schmitz, 2005
Jeanne Rizzo Breast Cancer Fund	Breast Cancer Fund	August 5, 2005	C2-6/Rizzo, 2005
Courtney M. Price CHEMSTAR	American Chemistry Council Phthalate Esters Panel	August 8, 2005	C2-7/ Price, 2005a
Sonya Lunder Environmental Working Group	Environmental Working Group	August 8, 2005	C2-8/Lunder, 2005
Roger Richter California Hospital Foundation	California Hospital Association	August 8, 2005	C2-9/Richter, 2005
Hans Lee California Medical Association	California Medical Association	August 8, 2005	C2-10/Lee, 2005

Comment 16

Eight commenters supported OEHHA's proposal to develop MADLs specifically for i.v. injection. Two, Lee (2005) and Richter (2005), did not. By re-submitting the comments by Brophy (2004), Richter (2005) and Lee (2005) reiterated their opposition to proposed MADLs for DEHP by i.v. injection.

Response

OEHHA determined that it is appropriate to develop MADLs for DEHP by i.v. injection. The comments by Brophy (2004) are summarized and responded to in the responses to Comments 8-11 above.

Comment 17

Six of the ten commenters supported calculating specific and different MADLs for adults, infants and neonates (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.

Response

OEHHA acknowledges the agreement with its approach of calculating different MADLs for infants, neonates and adults.

Comment 18

Price (2005a) reiterated comments by Price (2004) submitted on December 13, 2004, as summarized in Comment 14 and 15 above.

As presented in the MADL document (), OEHHA determined that developing animals are sensitive to the testicular effects of DEHP and a MADL based on 70 kg for an adult man is not appropriate for infants and neonates. Price (2005a) challenged OEHHA's scientific judgment on this issue and stated that there is no scientific basis to develop separate age-specific MADLs for DEHP by i.v. exposure. Price (2005a) made the following arguments:

1. The sensitivity studies cited by OEHHA are based on oral exposures in which the reported testicular effects were reversible and occurred only at high oral doses (100-1000 mg/kg-day).
2. The NOELs for effects on juvenile rats were generally above the NOELs for testicular effects on adults, indicating that young individuals are not more sensitive than adults to DEHP at oral doses approximating the NOEL for adults.
3. Any sensitivity of young animals to oral DEHP is likely due to significant pharmacokinetic differences, not pharmacodynamic differences (i.e., tissue susceptibility), and oral sensitivity is of little relevance to i.v. exposure.
4. The LOELs and NOELs for the testicular effects of DEHP following i.v. exposure in rats aged 3-5 days (Cammack et al., 2003), 25 or 40 days (Sjoberg et al., 1985) were comparable. Therefore, age-related testicular effects do not occur in rats following intravenous DEHP exposure.
5. U.S. FDA stated that "it's not clear whether age-related differences in DEHP-induced testicular toxicity would occur following parental exposure." The factors that the U.S. FDA considered and that may make children more sensitive to

DEHP, such as higher gastrointestinal lipase activity, are not always relevant to intravenous exposures, and are not unique to humans.

Response

With regard to reiteration of the comments by Price (2004) on the Initial Statement of Reasons, see Comments 14 and 15 and the respective responses presented above.

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 likely to be more sensitive to the toxicity of DEHP than that in the adult. Body weights of human neonates and infants are dramatically lower than that of an adult man. Because the MADL is expressed as "micrograms per day" according to the regulations (Title 22, California Code of Regulations, Sections 12801 and 12803), exposure of an infant or neonate 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. The age-specific MADLs simply normalize the exposure to the approximate body weight of the exposed individual.

The commenter's five arguments are repudiated by weight of scientific evidence that has been generated in numerous laboratory studies and that has been generally accepted in the scientific community.

There is evidence that developing animals are more sensitive to the testicular effects of DEHP following oral exposure. 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. This clearly indicates that neonatal and juvenile rats are more sensitive to DEHP than are adults (e.g., CERHR, 2000; Li, et al., 2000; U.S. FDA, 2001; Boekelheide, 2004).

The reasons for the age-dependent sensitivity to the testicular effects of DEHP remain to be determined (CERHR, 2000; U.S. FDA, 2001). Significant pharmacokinetic differences between young and adult animals have been shown to be involved. Moreover, dramatic differences in the physiological characteristics of the testis between neonatal, juvenile, and adult animals have also been shown to play an important role. For example, as shown in many *in vitro* studies using cultures of testicular tissues or cells isolated from rats of different ages, Sertoli cells and/or germ cells from neonatal or juvenile animals are more sensitive to mono(2-ethylhexyl) phthalate (MEHP, the active metabolite of DEHP) than are those from older or adult animals (CERHR, 2000; U.S.

FDA, 2001). Therefore, experimental evidence clearly indicates that both pharmacokinetic and pharmacodynamic differences are likely involved.

It is important to point out that 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; Li, et al., 2000; U.S. FDA, 2001; Cammack et al., 2003). For example, this commenter stated the damage to the testes of adult rats exposed to DEHP for 104 weeks as observed by David et al. (2000) was so minor that the NOEL should be 29 mg/kg-day, rather than 5.8 mg/kg-day as determined by OEHHA (Stanley, 2004). On the other hand, a single oral dose of 100-1000 mg/kg DEHP caused severe damage to the testes of neonatal rats (Li et al., 2000). Comparison of these two studies clearly demonstrates that neonatal rats are much more sensitive to the testicular effects of DEHP than are young and adult animals following oral treatment. Similarly, the testicular effects (cytoplasmic vacuolization in Sertoli cells in plastic tissue sections) in young rats (25 or 40 days of age) following i.v. treatment as observed by Sjoberg et al. (1985) were much more minor, compared to those (persistent decrease in testicular weights and severe histopathological damage) in rats treated from 3-5 days of age (Cammack et al., 2003). Therefore, regardless of route of exposure (oral or i.v.), neonatal rats are more sensitive to the testicular effects of DEHP than are young or adult animals.

OEHHA's development of separate MADLs for neonates and infants and the scientific basis for this determination do not contradict the statement by the U.S. FDA as cited by the commenter. In fact, OEHHA's approach is fully consistent with numerous statements by the U.S. FDA (2001) and with those by the Phthalate Expert Panel of the NTP-CERHR (CERHR, 2000).

Comment 19

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. A typical uncertainty factor of 100 already is protective of infants. Citing the comments by the American Chemistry Council on oral DEHP MADLs, the commenter stated that primate data indicate that humans likely are less sensitive than rodents to DEHP and thus 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

As recognized by the commenter, and as noted in the response to Comment 14 by the same commenter, the 1000-fold factor is required by the statute. As also noted in the response to Comment 15, 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. 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.

OEHHA staff have reviewed the primate data in detail and determined that the data in marmoset are not appropriate for use in determining if humans are less or more sensitive than rodents to DEHP. At the present time, there is no convincing evidence indicating that humans of different ages are indeed less sensitive to the testicular effects of DEHP than are rodents. Thus, OEHHA has neither the regulatory authority nor a solid scientific basis for modifying the 1000-factor required by the Proposition 65 statute.

With regard to the separate MADLs for neonates and infants, the exposure per unit bodyweight at the corresponding MADL is the same for the neonate, infant and 70kg adult. Exposure of a neonate weighing 3.5 kg to the MADL of 210 µg/day results in a dose of 60 µg/kg-day, exactly the same dose that results from exposure of an adult male weighing 70 kg to the MADL of 4200 µg/kg-day. 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.

Comment 20

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. The other provision, Section 12801(a), cited by OEHHA, "does not give OEHHA carte blanche to deviate from its own regulatory procedure, as applied for 17 years. Languages from two cases (Bonn v. California State University, Chico, 88 Cal. App. 3d 985, 990, 1979: "it is fixed law that an administrative agency is bound by its own regulations" and Frates v. Burnett, 9 Call Appl. 3d 63, 71, 1970: "a school board cannot ignore its own rules and repudiate its method of procedure") was cited.

Response

The arguments advanced by the commenter are specifically contradicted by the plain language of the regulations (Title 22, California Code of 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)" This provision clearly contemplates that this subsection provides default assumptions that can be deviated from in 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 neonate is clearly less scientifically appropriate than using the average bodyweight for a male infant or neonate. Thus, OEHHA's action is entirely consistent both with the clear wording and the stated intent of the regulations. Since it is clear that the intention of the regulation is to provide broadly-applicable default values for several parameters, and since it is also clearly 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 21

Schmitz (2005) reiterated the comments submitted by Green (2004) in December 2004 about re-calculation of the NOEL as observed in the study by Cammack et al. (2003). The commenter suggested again that the NOEL should be 14.8 mg/kg-day, derived by averaging the lowest dose used in the study (60 mg/kg-day) from 21 days (dosing period) to 85 days (total observation period, including 64-66 days of post-dosing recovery).

Response

See Comment 7 and OEHHA's response to Comment 7 above.

Comment 22

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

See Response to Comment 5 above.

Comment 23

Brody (2005), Lunder (2005), and Rizzo (2005), respectively, 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 is a matter of considerable public health concern, these comments are beyond the scope of the current regulatory action.

Comment 24

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

Response

DEHP is 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" (Title 22, California Code of Regulations, Section 12803(a)(1)). In the case of DEHP, that effect is male reproductive toxicity and, consequently, these MADLs cannot apply to girls.

Comment 25

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

As noted in the response to Comment 24, DEHP is known to the state to cause developmental and male reproductive toxicity. Title 22, California Code of Regulations, 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." The studies producing the lowest NOEL are those

demonstrating male reproductive toxicity. As discussed in OEHHA (2005), there are currently insufficient data for developmental effects of DEHP by i.v. injection to establish a separate MADL for pregnant women based on the developmental toxicity of DEHP.

Comment 26

Chan (2005) suggested that there should be a zero tolerance level for exposure to DEHP by i.v. injection. 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 occur.

Comment 27

Lunder (2005) suggested that OEHHA consider a MADL for premature infants based on a body weight of one kg. Rizzo (2005) also noted that the 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

Title 22, California Code of Regulations, 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 neonates, infants, and adults, and may develop a different value for premature infants at a future date.

Comment 28

Lunder (2005) stated that newborn infants may 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 to the mother during pregnancy.

Comment 29

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 30

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 i.v. injection are based on the NOEL observed in rats in the study by Cammack et al. (2003). Rats used in this study were three to five days of age when the treatment with DEHP started. Rats at this age are considered to be one of the most sensitive populations to the testicular effects of DEHP (CERHR, 2000; Li et al., 2000; U.S. FDA, 2001). Therefore, the MADLs not only take into account of the difference in body weights between the adult and children, they are also based on the NOEL that was observed in animals of a sensitive age.

Comment 31

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

Response

The study used by OEHHA as the basis for the i.v. MADLs (Cammack et al., 2003) was published in the peer-reviewed scientific literature. Title 22, California Code of Regulations, Section12803(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.

<u>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</u>

Comment 32

Price (2005b) submitted a set of comments in response to OEHHA's Notice of Addition of Documents and Information to Rulemaking File OAL File No. Z-01-1019-06, released on August 17, 2005. The commenter made three recommendations to OEHHA:

> That OEHHA await the outcome of the National Toxicology Program 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. MALDs 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 33

In response to OEHHA's Clarification of Notice of Addition of Documents and Information to Rulemaking File OAL File No. Z-01-1019-06, released on August 30, 2005, on behalf of the Phthalate Esters Panel of the American Chemistry Council, Price (2005c) 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 staff 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 previous notices. OEHHA notes that the commenter's conclusions about the scientific findings in these studies are inconsistent with or contradictory to those made by the study authors. These very recent studies provide additional information relevant to the developmental or male reproductive toxicity of DEHP in humans. However, OEHHA determined that these studies do not provide data appropriate for the derivation of a MADL, so no revision to the MADL document is necessary.

SUMMARY AND RESPONSE TO COMMENTS ON THE NOTICES ISSUED ON MARCH 3, 2006

Table 3 lists three sets of comments received during the period from March 3 to March 20, 2006, on OEHHA's two notices issued on March 3, 2006. Summaries of and responses to these comments are provided below.

Table 3. List of Commenters on the Notice of Modifications to Text of Proposed Regulations Issued on March 3, 2006

Commenter/Affiliation	Representing	Date Received	Submission No. /Citation
Robert M. Gould, Julie Silas, SF Bay Area PSR Jimmy H. Hara, Donald Broder, PSR – Los Angeles	San Francisco Bay Area and Los Angeles Chapters of Physicians for Social Responsibility	March 13, 2006	C3-1/Gould et al., 2006
Ted Schettler Science and Environmental Network Anna G. Hall Health Care Without Harm	Health Care Without Harm	March 17, 2006	C3-2/Schettler and Hall, 2006
Hasmukh C. Shah CHEMSTAR	American Chemistry Council Phthalate Esters Panel	March 20, 2006	C3-3/ Shah, 2006

Comment 34

Gould et al. (2006) and Schettler and Hall (2006) stated their support for OEHHA's Modifications to Text of Proposed Regulations. In addition, Schettler and Hall (2006) submitted a copy of the "NTP-CERHR Expert Panel Update on the Reproductive and

Developmental Toxicity of Di(2-Ethylhexyl) Phthalate" (CERHR, 2005) and requested OEHHA to enter this report into 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 35

On behalf of the American Chemistry Council Phthalate Esters Panel, Shah (2006) re-submitted previous comments submitted to OEHHA from the American Chemistry Council by Price (2004, 2005a, 2005b, 2005c, respectively). After briefly reiterating those previous comments, Shah (2006) stated that "the Panel strongly believes that OEHHA should eliminate the separate i.v. DEHP MADLs for neonatal infant and infant males." With regard to OEHHA's revisions to the proposed regulations and additions of document and information announced in the Notices of March 3, 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 (2004, 2005a, 2005b, 2005c, respectively), OEHHA has considered all of them and provided detailed responses as presented above in this Final Statement of Reasons. Specifically, comments from Price (2004) are summarized and responded to in Comment 1, 14 and 15, Price (2005a) in Comment 18, 9, and 20, Price (2005b) in Comment 32, and Price (2005c) in Comment 33.

CONCLUSIONS ON COMMENTS AND RESPONSE

As presented above, all the comments submitted to OEHHA have been reviewed and considered by OEHHA staff. Modifications to the original proposed regulation have been made; in each case the modifications were noticed, comments were received and response to those comments are provided in this Final Statement of Reasons. Based on relevant scientific evidence and regulatory provisions that OEHHA relied upon in developing MADLs for DEHP by i.v. injection, OEHHA determined that the MADLs for DEHP by i.v. injection as proposed and modified by OEHHA in previous notices

(October 29, 2004; June 24, 2005; March 3, 2006) meet the requirements of Article 8. No further modification is needed.

CITATIONS

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

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.

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.

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

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

Brophy CR (2004). Comments on behalf of the California Healthcare Association and the California Medical Association. Submitted to the Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency, Sacramento, on December 13, 2004. Available upon request.

California Regulatory Notice Register (2004). Office of Environmental Health Hazard Assessment (OEHHA), Notice of Proposed Rulemaking. Title 22, California Code of Regulations. Amendment to Section 12805 Specific Regulatory Levels: Chemicals Causing Reproductive toxicity. Vol No. 44-Z, pp1491-1493.

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.

Creasy DM (2001). Pathogenesis of male reproductive toxicity. *Toxicol Pathol* **29**, 64-76.

Creasy DM (2003). Evaluation of testicular toxicology: a synopsis and discussion of the recommendations proposed by the Society of Toxicologic Pathology. *Birth Defects Res Part B Dev Reprod Toxicol* **68**, 408-15.

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ALTERNATIVES DETERMINATION

In accordance with Government Code § 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 Title 22, California Code of Regulations, Section12803 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.