FINAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

SECTION 25805, SPECIFIC REGULATORY LEVELS: CHEMICALS CAUSING REPRODUCTIVE TOXICITY

MAXIMUM ALLOWABLE DOSE LEVELS (ORAL EXPOSURE) FOR ATRAZINE, PROPAZINE, SIMAZINE, AND THEIR CHLOROMETABOLITES 2,4-DIAMINO-6-CHLORO-*S*-TRIAZINE (DACT), DES-ETHYL ATRAZINE (DEA), AND DES-ISOPROPYL ATRAZINE (DIA)

This is the Final Statement of Reasons for the adoption of Maximum Allowable Dose Levels (MADLs) for oral exposure to atrazine, propazine, simazine, and their chlorometabolites 2,4 –diamino-6-chloro-*s*-triazine (DACT), des-ethyl atrazine (DEA), and des-isopropyl atrazine (DIA), under Proposition 65[1] in Title 27, California Code of Regulations, section 25805(b)[2]. On July 15, 2016, these chemicals were added to the Proposition 65[3] list as known to the State of California to cause reproductive toxicity (developmental and female endpoints). On June 10, 2016, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to adopt MADLs for these six chemicals. Specifically, OEHHA proposed an oral MADL of 100 micrograms per day for atrazine. Propazine, simazine, DACT, DEA and DIA are considered to be of equal potency to atrazine with respect to their common mechanism of reproductive toxicity[4]. Consequently, 100 micrograms/day is also being established as the oral MADL for each of these chemicals. The Initial Statement of Reasons set forth the grounds for the adoption of the MADLs into regulation. A public comment period was provided from June 10, 2016 to July 25, 2016. The Notice stated that a public hearing would be held only on request. No request for a public hearing was received.

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[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 et seq., hereafter referred to as “Proposition 65” or “The Act”.

[2] All subsequent citations are to Title 27, California Code of Regulations, unless otherwise noted.

[3] These six chemicals were added to the list effective July 15, 2016, via the authoritative bodies mechanism (Section 25306).

[4] US EPA, 2005. Propazine: Revised HED Risk Assessment for the Tolerance Reassessment Eligibility Decision (TRED) which Includes a New Use on Grain Sorghum. PC Code: 080808, DP Barcode: D323271 Memorandum from J. Morales et al. Office of Pesticide Programs and Toxic Substances (OPPTS) Health Effects Division to D. Sherman OPPTS, December 13, 2005, Page 4.
US EPA, 2006c. Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision (TRED) for Propazine. Office of Prevention, Pesticides and Toxic Substances , EPA 738-R-06-009, Page 4.
Available at http://www.epa.gov/opp00001/reregistration/status_page_p.htm
US EPA, 2006b. Triazine Cumulative Risk Assessment (March 28, 2006), Pages 21 and 32.
Available at http://www.epa.gov/pesticides/cumulative/common_mech_groups.htm#triazine

General Background and Information

The listing of atrazine, propazine, simazine, and their chlorometabolites DACT, DEA, and DIA is based on formal identification by the US Environmental Protection Agency (US EPA). The US EPA is a body recognized as authoritative for the listing of chemicals as known to cause reproductive toxicity under Proposition 65 (Section 25306 (l)). On February 7, 2014, OEHHA published the notice of intent to list atrazine, propazine, simazine, DACT, DEA, and DIA[5]. On March 24, 2015, OEHHA provided notice that these compounds would be added to the list of chemicals known to the state to cause reproductive toxicity for purposes of Proposition 65 with a delayed effective date due to pending litigation. Atrazine, propazine, simazine, DEA, DIA and DACT were added to the Proposition 65 list on July 15, 2016.

On June 12, 2015, OEHHA started the regulatory process to adopt the proposed MADLs. Because of delays in the effective date of the listings due to the litigation, OEHHA extended the deadline for submitting public comments to December 14, 2015.[6] On June 10, 2016, pursuant to Government Code Section 11347, OEHHA gave notice that it had decided to withdraw the rulemaking action because it could not be completed within the one-year period required by the Administrative Procedure Act. OEHHA concurrently opened a new rulemaking record by publishing a new notice of proposed rulemaking on June 10, 2016 to adopt MADLs for these chemicals. OEHHA also published on its website the notice of the proposed regulation, the proposed regulatory text, and the Initial Statement of Reasons.. The public comment period closed on July 25, 2016. Five sets of written comments were received by OEHHA regarding this proposed regulation[7].

Peer Review

On July 14, 2015, OEHHA provided the notice of proposed rulemaking and the Initial Statement of Reasons for the proposed MADLs to the members of the Developmental and Reproductive Toxicant Identification Committee for their peer review as required by Section 25801(f). No comments were received from any committee members. The proposal was not resubmitted to the Committee when the regulatory process was

[5] DACT was incorrectly identified as 2,3-diamino-6-chloro-s-triazine (instead of 2,4-diamino-6-chloro-s-triazine) in the Feb. 7, 2014 notice of intent to list the chemical and in the March 24, 2015 notice of listing.
[6] *Syngenta v OEHHA*, Third District Court of Appeal case #C0082128 (The listing of the triazines was initially to be effective on August 3, 2015 but was delayed due to this litigation. OEHHA was successful in the trial court. The case is currently on appeal but no stay of the listing was granted.)
[7] All comments were received during an earlier comment period on the same regulation (see http://oehha.ca.gov/proposition-65/crnr/proposed-madl-atrazine-propazine-simazine-23-diamino-6-chloro-s-triazine-dact.) One was resubmitted during this rulemaking, but OEHHA is nevertheless providing responses all comments received regarding this proposed MADL.

restarted because the scientific basis for the proposal had not changed.

Supplement to the Economic Impact Analysis

Impact on the Creation or Elimination of Jobs in California: This regulatory proposal will not affect the creation or elimination of jobs within the State of California, but instead provides a "safe harbor" value that aids businesses in determining if they are complying with the law. Proposition 65 requires businesses with ten or more employees to provide warnings when they expose people to chemicals that are known to cause cancer or reproductive harm. The law also prohibits the discharge of listed chemicals into sources of drinking water. Atrazine, propazine, simazine, DEA, DIA and DACT are listed under Proposition 65; therefore, businesses and individuals who manufacture, distribute or sell products with these chemicals in the state must provide a warning if their product or activity exposes the public or employees to this chemical.

Impact on the Creation of New Businesses or Elimination of Existing Businesses within the State of California

This regulatory action will not impact the creation of new businesses or the elimination of existing businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a "safe harbor" value that aids businesses in determining if they are complying with the law.

Impact on Expansion of Businesses within the State of California

This regulatory action will not impact the expansion of businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides a "safe harbor" value that aids businesses in determining if they are complying with the law.

Summary and Response to Comments

Written comments from a private citizen, Theresa Ryan Stueve, were received via email. A summary of her comments along with OEHHA's responses to those comments are presented below, as comment and response number 1.

OEHHA received two letters proposing a different value for the MADLs. One letter was from the Center for Environmental Health (CEH) and the Center for Biological Diversity. The other was from the American Congress of Obstetricians and Gynecologists (ACOG)

California Chapter, Dr. Tyrone Hayes, and 19 other scientists and health professionals. The contents of the two letters from these groups are largely the same. A summary of these comments along with OEHHA's responses are presented below, as comment and response numbers 2 to 5.

OEHHA received written comments from Syngenta Crop Protection via Stanley W. Landfair on the proposed MADLs for triazines. A summary of Syngenta's comments and OEHHA's responses are presented below, numbered 6 to 10.

Other comments containing essentially the same text were received via email from 30 private citizens. Those comments along with OEHHA's responses are presented below, as comment and response number 11.

Comment 1
The commenter opposes the proposed MADLs because she considers them to be based on three false hypotheses: (1) "Atrazine does not promote mammary carcinogenesis in the SD [Sprague-Dawley] rat but only promotes earlier onset of MTs [mammary tumors] in a 'uniquely susceptible' species above the MTD [maximum tolerated dose]"; (2) "Atrazine crosses the blood-brain barrier to suppress LH [luteinizing hormone] pulsatility and induce 'reproductive senescence' in the SD rat, which itself secondarily promotes MT formation"; and (3) "Mechanisms of rat ovarian aromatase/estrogen induction by atrazine are irrelevant to humans", as it relates to breast cancer development.

Response 1
The first hypothesis identified by the commenter pertains entirely to carcinogenicity. Atrazine, propazine, simazine, and their chlorometabolites DACT, DEA and DIA are listed under Proposition 65 as known to cause reproductive toxicity (developmental and female endpoints), not cancer. Because MADLs are developed based on reproductive and developmental toxicity endpoints, a hypothesis pertaining to carcinogenicity is not relevant to establishment of a MADL.

The second hypothesis addresses effects on luteinizing hormone (LH). US EPA concluded that "[n]euroendocrine effects are considered the critical endpoints for assessing the health effects of the CMG [common mechanism group] triazines", and identified a 1996 study in female Sprague-Dawley rats by Morseth, as showing attenuation of the pre-ovulatory LH surge as a biomarker indicative of hypothalamic disruption of function. US EPA identified this study as demonstrating the critical effects of atrazine. US EPA also noted that the hypothalamic-pituitary-gonadal axis is involved in the development of the reproductive system, and its maintenance and functioning in adulthood. The MADL for atrazine was calculated using the NOEL of 1.8 mg/kg/d from

the Morseth study. Thus, although the second hypothesis identified by the commenter addresses the LH surge, that hypothesis was described by the commenter as it may pertain to the relationship between suppression of the LH surge and carcinogenicity (i.e., promotion of mammary tumors). That carcinogenicity endpoint is not relevant to establishing the MADL.

The third hypothesis identified by the commenter is based on comparison of lifetime exposures to estrogen and its relationship to putative mechanisms of induction of breast cancer in humans and rodents. As with the first hypothesis, this comment was made regarding carcinogenicity and is not relevant to establishment of a MADL, which is for reproductive toxicity endpoints.

Comment 2

The commenters assert that the study relied upon by OEHHA as the basis for the MADL is subject to conflict of interest and bias because it was conducted by the original registrants of the pesticide. The commenters also note that the study was never published nor did it undergo peer review, which the commenters consider to be an essential part of the scientific process. The commenters further note that the study is almost 20 years old.

Response 2

The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) requires registrants of pesticides to submit studies conducted under specified regulatory guidelines for prenatal developmental toxicity and for reproduction and fertility effects. Such studies are submitted with complete data records compiled under the requirements of Good Laboratory Practice (GLP), are thoroughly evaluated by US EPA and are routinely used for regulatory purposes.[8] Although the study by Morseth (1996) was not a required study under FIFRA, it was conducted under the same requirements for data recording and submission to US EPA, and was evaluated under the same statutory provisions.

Studies conducted for submission under FIFRA are generally not published in the peer-reviewed scientific literature, or are published only in greatly condensed form. However, the data sets required to be submitted to US EPA are far more complete than those provided in published papers and allow regulatory scientists to objectively and thoroughly evaluate the studies. Unless a specific deficiency in the design, conduct or reporting of the study is identified, the length of time since the study was conducted has no relevance to the toxicity of the chemical.

[8] Master List of Test Guidelines for Pesticides and Toxic Substances. Available at https://www.epa.gov/sites/production/files/2016-12/documents/ocspp-testguidelines_masterlist-2016-12-28.pdf

Comment 3

The commenters state that the proposed MADLs of 100 µg/day for the triazines are based on an outdated scientific study[9] that "does not adequately reflect the findings of newer studies of comparable or better quality"[10,11,12,13]. The four cited studies demonstrate that low-level exposure to atrazine causes endocrine effects in mammals. All four studies show the lowest observable adverse effect level (LOAELs) below the no observable effect level (NOAEL) used by OEHHA for the proposed MADLs.

Response 3

OEHHA reviewed the four studies referenced in the comments. These are discussed below.

Enoch et al. (2007) is a study of a mixture of atrazine and several of its metabolites (hydroxyatrazine, diaminochlorotriazine, deethylatrazine, and deisopropylatrazine). This atrazine metabolite mixture (AMM) was administered orally to pregnant Long-Evans rats on gestation days (GD) 15-19 at exposure levels of 0.09, 0.87 or 8.73 mg/kg-d. Atrazine was also administered as a positive control at 100 mg/kg-d. Enoch et al. found acute exposure to the complex mixture AMM and to atrazine caused persistent alterations in the mammary gland of female offspring, and that these effects do not appear to be related to body weight or associated with pubertal timing. The complex AMM mixture contained 20% hydroxyatrazine, a chemical that is not identified as causing reproductive toxicity under Proposition 65. Although this complex mixture is composed primarily of chemicals listed as known to cause reproductive toxicity under Proposition 65, the AMM itself is not listed under Proposition 65 and contains a substantial proportion of an unlisted chemical. For that reason, this study is not considered to be of comparable scientific validity to the studies of the listed chemicals which formed the basis for listing, and therefore it was not used as the basis for a MADL for the listed triazines. Although atrazine also caused a developmental and female reproductive effect in this study, the dose of 100 mg/kg-d used was markedly higher

[9] Morseth , S. L. (1996) Evaluation of the Luteinizing Hormone (LH) Surge in Atrazine-Exposed Female Sprague-Dawley Rats – (Final) 6-month Interim Report: Lab Project Number: CHV 2386-111:2386-111:6791E, prepared by Corning Hazleton Inc., as cited by US EPA (2002a), page 27.

[10] Enoch, R.R., et al., Mammary gland development as a sensitive end point after acute prenatal exposure to an atrazine metabolite mixture in female Long-Evans rats. Environ Health Perspect, 2007. 115(4): p. 541-7.

[11] Giusi, G., et al., The endocrine disruptor atrazine accounts for a dimorphic somatostatinergic neuronal expression pattern in mice. Toxicol Sci, 2006. 89(1): p. 257-64.

[12] Lin, Z., et al., Gestational and lactational exposure to atrazine via the drinking water causes specific behavioral deficits and selectively alters monoaminergic systems in C57BL/6 mouse dams, juvenile and adult offspring. Toxicol Sci, 2014. 141(1): p. 90-102.

[13] Gojmerac, T., et al., Reproductive disturbance caused by an S-triazine herbicide in pigs. Acta Vet Hung, 1999. 47(1): p. 129-35.

than the no observable effect level of 1.8 mg/kg-d that serves as the basis for the proposed MADLs.

Giusi et al. (2006) and Lin et al. (2014) are both neurobehavioral toxicity studies, the developmental components of which have significant post-natal exposures in their study designs. The Guisi et al. 2006 study showed atrazine accounted for a dimorphic somatostantinergic neuronal expression pattern in CD-1 mice after exposure to 1 or 100 micrograms/kg-d from GD 14 to postnatal day (PND) 21. Lin et al., 2014 showed that exposure of C57BL/6 mice offspring and dams to 3 mg/L (estimated 1.4 mg/kg-d) atrazine from GD 6-PND 23 induced sex-selective changes involving motor and emotional functions in juvenile offspring, and decreases cognitive ability of adult female offspring, with the latter possibly associated with altered perirhinal cortex serotonin homeostasis. Neurobehavioral effects in the dams involved alterations in cognitive performance and were unrelated to reproductive behaviors. These studies are not suitable for MADL development since no reproductive effects were reported in the dams and the developmental effects cannot be attributed to prenatal exposure due to the substantial postnatal exposures of offspring in both these studies.

The Gojmerac et al. (1999) study shows reproductive disturbance caused by atrazine in pigs. A group of nine gilts (F_1 generation of Swedish Landrace × Large Yorkshire) were treated with 1 mg atrazine/kg body mass daily, mixed in the feed for 19 days before the onset of expected estrus. The authors concluded that insufficient serum estradiol concentration of the treated gilts resulted in a failure of expected estrus. This study was not cited by the US EPA in any of the documents that formed the basis for listing the triazines under Proposition 65[14], so it is not part of the body of evidence that led to the listing. Gojmerac et al. used only a single dose in this study, so no dose-response relationship could be established. Gojmerac et al. also published two related studies[15,16] not identified by the commenters, which also used only a single dose and which reported effects on LH levels and reproductive disturbance, respectively. Although these studies provide information relevant to identification of the reproductive hazard of atrazine, they have limitations in study design and there are no corroborative findings from other laboratories. The study identified by the commenters therefore cannot be considered to be “of comparable scientific validity to the evidence and standards which form the scientific basis for the listing”[17], as required by statute, so it

[14] Notice of Intent to List: Atrazine, Propazine, Simazine and their Chlorometabolites DACT, DEA and DIA. Available at https://oehha.ca.gov/proposition-65/crnr/notice-intent-list-atrazine-propazine-simazine-and-their-chlorometabolites-dact
[15] Gojmerac et al. Serum Leuteinizing Hormone Response to Administration of Gonadotropin-Releasing Hormone to Atrazine-Treated Gilts. Vet Human Toxicol. 2004. 46(5): 245-247.
[16] Gojmerac et al. Serum biochemical changes associated with cystic ovarian degeneration in pigs after atrazine treatment. Toxicology Letters. 1996. 85: 9-15.
[17] Health and Safety Code section 25249.10(c).

cannot form the basis for a MADL.

Comment 4
The commenters suggest a MADL no higher than 8 micrograms per day, and recommend an even lower MADL of 0.06 micrograms per day. The commenters additionally state that the importance of a health protective MADL is reinforced by epidemiological studies that correlated low-level atrazine exposure with adverse pregnancy outcomes and reproductive toxicities in women. The commenters also cite studies that demonstrate effects such as hermaphroditism, feminized behavior in males and presence of eggs in testes and decreased fertility in both sexes in amphibian and molluscan wildlife species.

Response 4
The commenters do not specifically explain how the recommended values of 8 or 0.06 micrograms per day were calculated. However, a MADL of 8 micrograms per day would be calculated from a NOEL of 0.14 mg/kg-day, which is consistent with the LOEL of 1.4 mg/kg-day identified in the study by Lin et al. (2014)[18] (divided by 10, since no NOEL was identified in that study[19]). Similarly, a MADL of 0.06 micrograms per day would be calculated from a NOEL of 0.001 mg/kg-day, which is consistent with the NOEL of 0.001 mg/kg-day identified in the study by Giusi et al. (2006)[20]. Neither study can form the basis for a MADL as discussed above in response to Comment 3.

Epidemiologic studies in humans and studies in non-mammalian species may provide important information for identification of hazard. However, the exposures in human epidemiologic studies are often insufficiently quantifiable to establish a NOEL or LOEL for purposes of MADL development. Similarly, data from studies in non-mammalian wildlife species may establish an ecotoxicological hazard and may be indicative of potential effects in mammals, but do not provide data on a dose-response relationship in mammals that could form the basis for a MADL because of differences in exposure pathways and potential differences in physiologic and metabolic parameters.

Comment 5
The commenters noted that the current maximum contaminant level (MCL) for atrazine

[18] Lin, Z., et al., Gestational and lactational exposure to atrazine via the drinking water causes specific behavioral deficits and selectively alters monoaminergic systems in C57BL/6 mouse dams, juvenile and adult offspring. Toxicol Sci, 2014. 141(1): p. 90-102.
[19] Title 27, California Code of Regulations, section 25803(a)(8) states: “When data do not allow the determination of a NOEL, the lowest observed effect level shall be divided by 10 to establish a NOEL for purposes of assessment.”.
[20] Giusi, G., et al., The endocrine disruptor atrazine accounts for a dimorphic somatostatinergic neuronal expression pattern in mice. Toxicol Sci, 2006. 89(1): p. 257-64.

in drinking water established by the US EPA is based on potential reproductive effects and cardiovascular effects at 3.0 micrograms per liter (ppb). With the primary mode of exposure to atrazine likely being through water consumption, and the average person consuming about 2 liters of water per day, an oral MADL of 100 micrograms per day is an exposure 16 times greater than that resulting from EPA's MCL. Therefore, a considerably lower MADL would more closely correlate with exposure criteria set forth by the federal government.

Response 5

The MCL for atrazine was adopted in 1995[21] based on atrazine's potential to cause "weight loss, cardiovascular damage, retinal and some muscle degeneration, and mammary tumors from a lifetime exposure at levels above the MCL". Currently, the "Potential Health Effects from Long-Term Exposure Above the MCL" identified by US EPA for atrazine[22] are "cardiovascular system or reproductive problems". The explanatory text on health effects of atrazine[23] accompanying the MCL value states that "some people who drink water containing atrazine *well in excess* of the maximum contaminant level (MCL) for many years could experience problems with their cardiovascular system or reproductive difficulties" (emphasis added).

The quantitative basis for the MCL relative to reproductive hazard is unclear. In contrast, US EPA has established reference doses (RfDs) explicitly to be protective of reproductive and developmental hazards. Those RfDs formed one of the bases for formal identification by US EPA of atrazine and the other triazines as causing reproductive toxicity, as specified in the Notice of Intent to List Atrazine, Propazine, Simazine and their Chlorometabolites DACT, DEA and DIA[24]. OEHHA agrees with US EPA that the six-month LH surge study in rats (Morseth, 1996, as described by US EPA[25]) is a robust study that provides an appropriate point of departure for quantitative dose response assessment. For purposes of Proposition 65, this is the most sensitive study of sufficient quality to serve as the basis for the MADLs.

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[21] US EPA. National Primary Drinking Water Regulations: Atrazine. Available at https://nepis.epa.gov/Exe/tiff2png.cgi/9100PO32.PNG?-r+75+-g+7+D%3A%5CZYFILES%5CINDEX%20DATA%5C95THRU99%5CTIFF%5C00002435%5C9100PO32.TIF

[22] US EPA. Table of Regulated Drinking Water Contaminants. Available at https://www.epa.gov/ground-water-and-drinking-water/table-regulated-drinking-water-contaminants#Organic

[23] Available at https://safewater.zendesk.com/hc/en-us/articles/212077797-3-What-are-atrazine-s-health-effects-

[24] Available at https://oehha.ca.gov/proposition-65/crnr/notice-intent-list-atrazine-propazine-simazine-and-their-chlorometabolites-dact

[25] Morseth, S. L. (1996) Evaluation of the Luteinizing Hormone (LH) Surge in Atrazine-Exposed Female Sprague-Dawley Rats – (Final) 6-month Interim Report: Lab Project Number: CHV 2386-111:2386-111:6791E, prepared by Corning Hazleton Inc., as cited by US EPA (2002a), page 27.

Comment 6

The commenter acknowledges that the US EPA used a NOEL of 1.8 mg/kg/d based on atrazine's effects on the pre-ovulatory LH surge in female rats in the study by Morseth et al., 1996[26] as the basis for its risk-based regulation of the triazine compounds. The commenter asserts that this effect is an inappropriate basis on which to calculate a MADL.

The commenter argues that "an effect on a biomarker such as luteinizing hormone (LH) in itself is not "reproductive toxicity" as required by Section 25801. Hormonal changes, without corresponding reproductive changes, may not be an adverse reproductive outcome due to species differences in reproduction and feed-back compensatory mechanisms inherent to the physiologic role of hormones. Adverse consequences on reproduction as determined by reliable reproduction studies conducted according to applicable U.S. EPA test guidelines do not occur at any dose levels of atrazine dietary exposure (DeSesso et al., 2014)."

Response 6

This issue was addressed in depth in the OEHHA Response to Comments Pertaining to the Notice of Intent to List [27] (pages 19-24). As summarized by US EPA, "atrazine-induced changes in the hormonal milieu lead to a cascade of effects on reproductive function in male and female rats. The decrease in LH is a precursor event to reproductive effects both on a quantitative (i.e., occurs at lower doses) and temporal basis (occurs after 4 days of exposure). An atrazine related suppression of suckling-induced prolactin release in the lactating dams, is another hormonal change leading to an adverse effect (prostatitis) in the rat animal model."[28] As explained by US EPA in this passage[29], it is clear that atrazine-induced hormonal alterations lead to adverse reproductive effects in experimental animals. That conclusion constitutes an identification of the chemical as causing reproductive toxicity in animals.

The commenter questioned whether hormonal changes in rats without corresponding reproductive changes could be considered a plausible adverse outcome in humans "due

[26] *Ibid.*

[27] Response to Comments Pertaining to the Notice of Intent to List Atrazine, Propazine, Simazine and their Chlorometabolites DACT, DEA and DIA as Causing Reproductive Toxicity under Proposition 65 Office of Environmental Health Hazard Assessment California Environmental Protection Agency March 2015. Available at: http://oehha.ca.gov/media/downloads/crnr/comments/032415triazinesrtc.pdf

[28] Re-Evaluation of Human Health Effects of Atrazine: Review of Cancer Epidemiology, Non-cancer Experimental Animal and In vitro Studies and Drinking Water Monitoring Frequency. Presented Jointly To The FIFRA Scientific Advisory Panel By: U.S. Environmental Protection Agency Office of Pesticide Programs Health Effects Division and Environmental Fate and Effects Division in collaboration with the Office of Research and Development. Presented On: July 26-29, 2011. Available at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2011-0399-0013.

[29] *Ibid.*

to species differences in reproduction and feed-back compensatory mechanisms inherent to the physiologic role of hormones." US EPA's Guidelines for Reproductive Toxicity Risk Assessment[30] state that "[a]n agent that produces an adverse reproductive effect in experimental animal studies is assumed to pose a potential reproductive threat to humans. This assumption is based on comparisons of data for agents that are known to cause human reproductive toxicity. In general, the experimental animal data indicated adverse reproductive effects that are also seen in humans."[31] It should also be noted that the US EPA Guidelines for Reproductive Toxicity Risk Assessment specifically recognizes changes in LH levels among the "female-specific endpoints of reproductive toxicity" (U.S. EPA 1996, table 5)[32].

As stated in the Initial Statement of Reasons for this regulatory action, OEHHA determined that the six-month LH surge study in rats (Morseth et al., 1996, as described by US EPA[33]) is the most sensitive study of sufficient quality identified by the US EPA[34,35], as required by Section 253803(a)(5), and that there were no subsequently published studies that were more sensitive. OEHHA used the NOEL of 1.8 mg/kg/d based on atrazine's effects on the pre-ovulatory luteinizing hormone (LH) surge in female rats from this study as the basis for the oral MADLs for atrazine, propazine, simazine, DACT, DEA, and DIA.

With regard to the De Sesso et al. study[36], rather than reporting an absence of reproductive effects at any dose level, the study reported that "small increases in abnormal sperm were noted at doses of 25 mg/kg/day and above, and reductions in testicular weights were noted after lactational exposure at 125 mg/kg/day". On that basis, De Sesso et al. concluded that "although there were some effects of a high bolus dose of atrazine on the development of the male reproductive system, the NOELs following prenatal (5 mg/kg/day) and postnatal (25 mg/kg/day) exposure were much higher than would be expected in humans under normal use conditions". OEHHA notes that these male reproductive toxicity parameters did not form the basis for formal

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[30] Guidelines for Reproductive Toxicity Risk Assessment. EPA/630/R-96/009. October 1996. Published on October 31, 1996, Federal Register 61(212):56274-56322. Available at: https://www.epa.gov/sites/production/files/2014-11/documents/guidelines_repro_toxicity.pdf

[31] *Ibid.* (page 2).

[32] *Ibid.*

[33] US EPA, 2002a. Atrazine (PC Code: 080803). Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document (Second Revision). April 11, 2002.

[34] *Ibid*.

[35] US EPA, 2006a. Decision Documents for Atrazine. Office of Prevention, Pesticides and Toxic Substances. Available at http://www.epa.gov/pesticides/reregistration/REDs/atrazine_combined_docs.pdf

[36] DeSesso,J.M., Scialli, A.R., White, T.E.K. and Breckenridge, C.B. (2014). Multigeneration Reproduction and Male Developmental Toxicity Studies on Atrazine in Rats. Birth Defects Research (Part B) 101:237–253.

identification by US EPA of the triazines as causing reproductive toxicity, or the consequent addition of the triazines to the Proposition 65 list, and thus are not relevant to calculation of the MADLs.

Comment 7

The commenter states that the Sprague-Dawley rat is not relevant for providing a NOEL for human health risk assessment because of physiological differences in reproductive senescence in humans and the Sprague Dawley rat. The commenter further states that atrazine's effects on the LH surge accelerates the reproductive aging process in Sprague Dawley rats, but is not expected to have an effect on human menopause. And, "the effect observed in aging Sprague Dawley rats in the Morseth study is therefore not predictive of a similar effect in the human female."

Response 7

OEHHA's Response to Comments Pertaining to the Notice of Intent to List [37] (pages 25 - 27) addressed this issue in detail. Briefly, there are differences in the induction of the LH surge in rats and humans. However, there is a 'common mechanism' underlying the reproductive effects of suppression of the LH surge, which occurs in both rodents and humans.

While both US EPA and OEHHA recognize that there are differences between rodent and human reproductive physiology, US EPA considered these differences and concluded, on the basis of animal data, that the triazines cause reproductive and developmental toxicity and further concluded that those data are relevant to humans. OEHHA has examined the record before US EPA and has determined that there is sufficient scientific evidence to support US EPA's conclusions and that the data meet the criteria pursuant to Proposition 65. Although the commenter considers the differences between the rat and human female reproductive hormone cycle to be significant, US EPA does not agree, and OEHHA cannot substitute its scientific judgment for that of the authoritative body[38], nor can OEHHA substitute the judgment of other scientists for that of the authoritative body.

OEHHA concurs with US EPA that (i) attenuation of the pre-ovulatory LH surge in female Sprague-Dawley rats by atrazine is a biomarker indicative of hypothalamic disruption of

[37]Response to Comments Pertaining to the Notice of Intent to List Atrazine, Propazine, Simazine and their Chlorometabolites DACT, DEA and DIA as Causing Reproductive Toxicity under Proposition 65 Office of Environmental Health Hazard Assessment California Environmental Protection Agency March 2015. Available at: http://oehha.ca.gov/media/downloads/crnr/comments/032415triazinesrtc.pdf http://oehha.ca.gov/media/downloads/crnr/comments/032415triazinesrtc.pdf

[38] Final Statement of Reasons. 22 California Code of Regulations Division 2. Sections 12701, et seq. - No Significant Risk Levels, Sections 12801, et seq. -No Observable Effect Levels. Available at https://oehha.ca.gov/media/downloads/crnr/art78fsrjune1989.pdf .

function and (ii) the hypothalamic-pituitary-gonadal (HPG) axis is involved in the development of the reproductive system, and its maintenance and functioning in adulthood, in rats and humans. Thus, disruption of the HPG axis by atrazine in female Sprague-Dawley rats is predictive of atrazine's ability to disrupt the HPG axis in humans. The MADL for atrazine was calculated using the NOEL from the Morseth study, which was deemed to be of adequate quality and considered the most sensitive endpoint. OEHHA acknowledges that there are additional studies where reproductive endpoints are observed. For purposes of Proposition 65, the study by Morseth et al. is the most sensitive study deemed to be of sufficient quality[39].

Comment 8
The commenter states that estrus cycle alterations associated with the LH surge suppression in the Sprague Dawley rat are not predictive of an adverse effect in humans because the biological mechanisms controlling the estrus and menstrual cycles differ in humans and rats in fundamental ways.

Response 8
Although the commenter's observation that there are several significant differences in the reproductive physiology between rats and humans is correct, the 'common mechanism' underlying the reproductive effects of atrazine and the five other triazine compounds is suppression of the LH surge, which occurs in both rodents and humans.

As noted in the responses to comments submitted by Syngenta in opposition to the Proposition 65 listing of the triazines, US EPA cited evidence that enabled the Agency to conclude that it is biologically plausible that triazines pose a reproductive and developmental hazard to humans:

> "Neuroendocrine effects are considered the critical endpoints for assessing the health effects of the CMG [Common Mechanism Group] Triazines. The CMG triazines have been shown to lead to various endocrine-related changes as a result of an effect on the hypothalamic-pituitary-gonadal axis. The consequences of this action include a diminishment of hypothalamic gonadotrophin releasing hormone (GnRH) and norepinephrine levels. These triazines also increase dopamine level [sic] which can result in a diminished pituitary secretion of PRL [prolactin]. Therefore, the CMG triazines operate at the level of the hypothalamus. *In both humans and rats*, hypothalamic GnRH controls pituitary hormone secretion (e.g., luteinizing hormone and PRL)."

[39] Section 25803(a)(5)

> "In particular, the triazine-mediated changes in the HPG relating to neuroendocrine and neuroendocrine-related developmental and reproductive toxicity *are considered relevant to humans*, and these adverse effects were identified as endpoints for the exposure scenarios selected for consideration in the quantitative cumulative assessment"[40] (emphasis added)

Comment 9

The commenter suggests there is a "more appropriate study [Coder 2011; Foradori et al 2014][41,42] to use for the purpose of deriving a NOEL for a MADL" than the Morseth study. The commenter states that the NOEL observed in Long-Evans rats in the oral gavage portion of the Coder study was 50 mg/kg/d. Dosing in that study was by oral gavage and resulted in exaggerated peak plasma levels of atrazine and metabolites compared to what would occur from environmental exposures". The commenter further states that "dietary dosing of rats had no effect on reproductive parameters in reproductive studies", and thus the NOEL observed in the Coder gavage study is considered to represent "a conservative and health protective basis for establishing a MADL".

Response 9

MADLs must be "based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing"[43]. MADLs must also be "based on the most sensitive study deemed to be of sufficient quality"[44]. The evidence and standards which form the scientific bases for the listings of atrazine, propazine, simazine, DACT, DEA and DIA as causing reproductive toxicity via the authoritative bodies listing mechanism are discussed in several US EPA documents (2002a, 2002b, 2005, 2006a,b,c,d)[45].

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[40] US EPA, 2006b. Triazine Cumulative Risk Assessment (March 28, 2006). Available at http://www.epa.gov/pesticides/cumulative/common_mech_groups.htm#triazine

[41] Coder, P.S. An Oral (Gavage and Dietary) Study of the Effects of Atrazine on Fertility and Reproductive Performance in Female Long Evans and Sprague-Dawley Rats. 2011. WIL Research Laboratories, LLC., Wil Study Number 639090. Owned by: Syngenta Crop Protection AG.

[42] Foradori, C.D., Coder, P.S., Tisdel, M.O., Yi, K.D., Simpkins, J.W., Handa, R.J., and Breckenridge, C.B. The Effect of Atrazine Administered by Gavage or in Diet on the LH surge and Reproductive Performance in Intact Female Sprague-Dawley and Long Evans Rats. Birth Defects Research Part B: Developmental and Reproductive Toxicology. 2014. 101: 262-275.

[43] Health and Safety Code section 25249,10(c) and Title 27, California Code of Regulations section, 25803(a)

[44] Section, 25803(a)(5)

[45] US EPA (2002b). Office of Pesticide Programs. Special Docket for Pesticide Reregistration Risk Assessments. Memorandum on ATRAZINE/DACT - Fourth Report of the Hazard Identification Assessment Review Committee. TXR NO. 0050592

US EPA (2005). Propazine: Revised HED Risk Assessment for the Tolerance Reassessment Eligibility Decision (TRED) which includes a New Use on Grain Sorghum. PC Code: 080808, DP Barcode: D32327 Memorandum from J. Morales et al. Office of Pesticide Programs and Toxic Substances (OPPTS) Health Effects Division to D. Sherman OPPTS, December 13, 2005.

OEHHA determined that the six-month LH surge study in rats (Morseth, 1996, as described by US EPA[46]) is the most sensitive study of sufficient quality identified by the US EPA[47,48], as required by Section 253803(a)(5), and that there were no subsequently published studies that were more sensitive.

OEHHA notes that the study by Morseth (1996)[49] was specifically utilized by US EPA[50] in reaching the conclusion that the triazines cause reproductive toxicity. This same study was used by US EPA[51] as the basis for the Agency's reference dose for atrazine. Thus, OEHHA agrees with US EPA[52] that the Morseth (1996) study is the most sensitive study of sufficient quality to serve as the basis for a quantitative dose response assessment. The Morseth (1996) study provides a NOEL of 1.8 mg/kg-day, while the commenter proposes a NOEL of 50 mg/kg-day based on the Coder study[53,54]. The Morseth (1996) study is clearly a more sensitive study than the Coder study, and is therefore selected as the basis for the MADLs.

Comment 10

US EPA (2006a). Decision Documents for Atrazine. US EPA OPPTS. Available at http://www.epa.gov/pesticides/reregistration/REDs/atrazine_combined_docs.pdf
US EPA (2006b). Triazine Cumulative Risk Assessment (March 28, 2006). Available at http://www.epa.gov/pesticides/cumulative/common_mech_groups.htm#triazine
US EPA (2006c). Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision (TRED) for Propazine. US EPA OPPTS , EPA 738-R-06-009 Available at http://www.epa.gov/opp00001/reregistration/status_page_p.htm
US EPA (2006d). Reregistration Eligibility Decision Document for Simazine. US EPA OPPTS. EPA 738-R-06-008. Available at http://www.epa.gov/opp00001/reregistration/status_page_s.htm
[46] US EPA, 2002a. Atrazine (PC Code: 080803). Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document (Second Revision). April 11, 2002.
[47] *Ibid*.
[48] US EPA, 2006a. Decision Documents for Atrazine. Office of Prevention, Pesticides and Toxic Substances. Available at http://www.epa.gov/pesticides/reregistration/REDs/atrazine_combined_docs.pdf
[49] Morseth, S. L. (1996) Evaluation of the Luteinizing Hormone (LH) Surge in Atrazine-Exposed Female Sprague-Dawley Rats – (Final) 6-month Interim Report: Lab Project Number: CHV 2386-111:2386-111:6791E, prepared by Corning Hazleton Inc., as cited by US EPA (2002a), page 27.
[50] US EPA, 2006a. Decision Documents for Atrazine. Office of Prevention, Pesticides and Toxic Substances. Available at http://www.epa.gov/pesticides/reregistration/REDs/atrazine_combined_docs.pdf
[51] *Ibid.*
[52] *Ibid.*
[53]Coder, P.S. An Oral (Gavage and Dietary) Study of the Effects of Atrazine on Fertility and Reproductive Performance in Female Long Evans and Sprague-Dawley Rats. 2011. WIL Research Laboratories, LLC., Wil Study Number 639090. Owned by: Syngenta Crop Protection AG.
[54] Foradori, C.D., Coder, P.S., Tisdel, M.O., Yi, K.D., Simpkins, J.W., Handa, R.J., and Breckenridge, C.B. The Effect of Atrazine Administered by Gavage or in Diet on the LH surge and Reproductive Performance in Intact Female Sprague-Dawley and Long Evans Rats. Birth Defects Research Part B: Developmental and Reproductive Toxicology. 2014. 101: 262-275.

With regard to the MADL calculation, the commenter states “in Section 25803 (6)…if other scientific considerations can be applied in the assessment with confidence, they may be used.” The commenter further states that in the case of atrazine, a physiologically based pharmacokinetic model has been developed: “This model allows the replacement of the interspecies pharmacokinetics component of the default value of ten with a chemical-specific value of three. Because the 1,000-fold includes ten-fold as an interspecies component, that ten-fold can be reduced to three-fold in this case. The default value of 1,000 (10 x 10 x 10) can therefore be replaced by 300 (10 x 10 x 3) based on chemical-specific data.”

Response 10

The statutory provision that allows development of a MADL is that “the exposure will have no observable effect assuming exposure at one thousand (1000) times the level in question”[55]. Section 25803 provides practical guidance in the implementation of that provision.

The commenter asserts that the 1,000-fold factor includes a ten-fold sub-factor as an interspecies component, but provides no explanation or support for that assertion. Nothing in the statute or regulations indicates that the mandatory 1,000-fold factor includes such a sub-factor or that the 1,000-fold factor can be modified in the way the commenter proposes.

Section 25803(a)(7) states “when available data are of such quality that anatomic, physiologic, pharmacokinetic and metabolic considerations can be taken into account with confidence, they may be used in the assessment.” The Final Statement of Reasons for this regulation[56] clarifies that this provision “allows the use of such data to explain scientifically differential responses among animal species when determining the relative sensitivity of humans", because “certain chemicals are known to cause adverse reproductive outcomes in some test species but not humans because of differences in anatomy, physiology, metabolism, and other factors". Thus, these considerations may be used in selecting the most appropriate animal models but they do not provide a basis for altering the mandatory 1,000-fold factor.

Comment 11

[55] Health and Safety Code section 25249,10(c)

[56] Final Statement of Reasons for 22 California Code of Regulations Sections 12801 et seq. – No Observable Effect Levels. Available at http://oehha.ca.gov/media/downloads/crnr/art78fsrjune1989.pdf. 22 California Code of Regulations Section 12803 was subsequently changed to 27 California Code of Regulations Section 25803, and subsection (a)(6) to subsection (a)(7).

Multiple comments from 30 private individuals contained essentially the same text supporting adoption of MADLs for the triazines. However, the commenters stated that the proposed MADLs were not protective of neonates, children and infants or of rural residents and farmworkers, and urged that lower MADLs be adopted based on the best available science. The commenters considered the proposed MADLs to be based on flawed assumptions and outdated science, particularly the Syngenta study on which the current proposed MADLs are based.

Response 11

For the reasons described in the Initial Statement of Reasons for this regulatory action[57], OEHHA determined that the six-month LH surge study in rats (Morseth, 1996, as described by US EPA[58]) is the most sensitive study of sufficient quality to serve as the basis for the MADLs. As discussed in the responses to comments 3 and 4, OEHHA has reviewed additional studies including those identified by several commenters, and has determined that none of those additional studies provide an appropriate basis for a MADL. OEHHA will therefore continue to use the NOEL of 1.8 mg/kg/d based on atrazine's effects on the pre-ovulatory LH surge in female rats from the study by Morseth (1996) as the appropriate basis for the oral MADLs for atrazine, propazine, simazine, DACT, DEA, and DIA.

The studies cited in this final rulemaking only contains studies cited by commenters.

Local Mandate Determination

OEHHA has determined this regulatory action will not impose 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. Local agencies and school districts are exempt from Proposition 65.

Alternatives Determination

In accordance with Government Code section 11346.9(a)(4), OEHHA has, throughout the adoption process for this regulation, considered available alternatives to determine whether any alternative would be more cost effective in carrying out the purpose for which the regulation was proposed, or would be as cost effective and less burdensome to affected private persons than the proposed action.

[57] Available at https://oehha.ca.gov/media/downloads/crnr/isortriazines2006122015.pdf
[58] Morseth, S. L. (1996) Evaluation of the Luteinizing Hormone (LH) Surge in Atrazine-Exposed Female Sprague-Dawley Rats – (Final) 6-month Interim Report: Lab Project Number: CHV 2386-111:2386-111:6791E, prepared by Corning Hazleton Inc., as cited by US EPA (2002a), page 27.

OEHHA has determined that no other reasonable alternative considered by OEHHA or that has otherwise been identified or brought to the attention of OEHHA would either be more effective in carrying out the purpose for which the action is proposed, or would be as effective and less burdensome to affected private persons, or would be more cost effective to affected private persons and equally effective in implementing the statutory policy or other provision of law than the proposed regulation.