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March 24, 2014

VIA E-MAIL AND FIRST CLASS MAIL

Ms. Cynthia Oshita
Office of Environmental Health Hazard
Assessment
P.O. Box 4010, MS-19B
Sacramento, California 95812

Re: ***Notice of Intent to List Atrazine, Propazine, Simazine and Their Chlorometabolites DACT, DEA and DIA***

Dear Ms. Oshita:

This letter and its attachments are submitted on behalf of Syngenta Crop Protection LLC ("Syngenta") in response to the Office of Environmental Health Hazard Assessment's ("OEHHA") February 8, 2014 Notice of Intent to List ("NOIL") Atrazine, Propazine, Simazine, DACT, DEA and DIA (collectively, "chlorotriazines" or "chlorotriazine compounds") as chemicals known to the state of California to cause reproductive toxicity pursuant to the "authoritative bodies listing mechanism" under California's Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65").

As summarized below and as explained in detail in the attachments to this letter, the chlorotriazine compounds do not qualify for listing "as causing reproductive toxicity" under the authoritative bodies listing mechanism, for three independent reasons:

I. The authoritative body cited in OEHHA's NOIL, the United States Environmental Protection Agency ("U.S. EPA"), has not "formally identified" any chlorotriazine compound "as causing reproductive toxicity" as required for listing under the authoritative bodies listing mechanism by California Code of Regulations Title 27, Section 25306(d);

II. The animal studies referenced in the U.S. EPA documents cited in the OEHHA NOIL do not satisfy the requirements of 27 CCR Section 25306(g)(2) that such studies constitute sufficient evidence to indicate that adverse reproductive effects in humans are biologically plausible; and

III. Numerous studies performed more recently than the studies referenced in the relevant U.S. EPA documents constitute "scientifically valid data which were not considered by the authoritative body" which "clearly establish that the chemical [chlorotriazines] does not satisfy the criteria of [27 CCR Section 25306(g)(2)]."

The attachments to this letter are:

(A) a letter from McKenna Long & Aldridge LLP to Dr. Lauren Zeise of OEHHA, dated October 4, 2013 ("October 4, 2013 letter");

(B) a Report dated October 2, 2013 entitled "Rationale for Not Listing Atrazine, Simazine, Propazine, Deethylatrazine, Deisopropylatrazine or Diaminochloroatrazine as Developmental or Reproductive Toxicants in Humans Under the Provisions of Proposition 65," ("Syngenta science paper") authored by Charles B. Breckenridge, Ph. D. (Syngenta, LLC), Anthony R. Schialli, M.D., (Tetra Tech Sciences, Inc.), and James W. Simpkins, Ph. D. (West Virginia University);

(C) a letter dated March 21, 2014 from Debra Edwards, Ph.D., formerly the Director of U.S. EPA's Office of Pesticide Programs ("OPP"), describing that agency's the risk-based approach to the regulation of pesticides;

(D) a letter dated March 21, 2014 from Tina E. Levine, Ph.D., formerly the Director of OPP's Health Effects Division, describing the risk assessment process followed by U.S. EPA's OPP, HED and HIARC;

(E) a letter dated March 21, 2014 from Edwin F. Tinsworth (Exponent), formerly the Director of U.S. EPA's OPP Registration, Special Review and Reregistration Divisions, describing U.S. EPA's risk assessment and pesticide registration processes and mandates;

(F) a letter dated March 21, 2014 from Jack Fowle, Ph.D., formerly the Deputy Director of the Health Effects Division, again describing OPP's pesticide regulatory processes;

(G) a letter dated March 21, 2014 from Gary Burin, Ph.D. (Technology Sciences Group, Inc.), formerly Chairman of OPP's Developmental and Reproductive Toxicity Peer Review Committee, describing U.S. EPA's approach to pesticide risk assessment and regulation;

(H) An abstract of a peer-reviewed article to be published in Birth Defects Research, Part B. Developmental and Reproductive Toxicology by Anthony R. Schialli, M.D (Tetra Tech Sciences, Inc.) summarizing the results of two recent atrazine developmental toxicity studies in rats;

(I) an abstract of a peer-reviewed article to be published in Birth Defects Research, Part B. Developmental and Reproductive Toxicology by Chad. D. Foradori, Ph. D., *et al.,* summarizing the differential effects on the LH surge in rats caused by bolus dosing compared to temporally distributed dosing in feed;

(J) an abstract of a peer-reviewed article to be published in Birth Defects Research, Part B. Developmental and Reproductive Toxicology by John M. DeSesso, Ph. D. (Exponent), *et al.*, discussing the findings of recent multi-generation reproduction and developmental toxicity studies on atrazine;

(K) a letter dated March 24, 2014 from Charles B. Breckenridge, Ph.D. (Syngenta LLC), *et al.*, describing the results of recent animal studies including dietary studies, life-stage studies, and pharmacokinetic studies; and

(L) a letter dated March 21, 2014 from James C. Lamb, Ph.D. (Center for Toxicology and Mechanistic Biology), discussing issues including route of administration, maternal toxicity, and interspecies differences.

I. U.S. EPA Has Not "Formally Identified" Any of the Chlorotriazine Compounds "As Causing Reproductive Toxicity"

The record, *i.e.*, the documents to which OEHHA points as the basis for listing, demonstrate that U.S. EPA, the "authoritative body" at issue here, did not "formally identify" the chlorotriazine compounds as "causing reproductive toxicity" within the meaning of Proposition 65, as that is not part of the agency's process for regulating pesticides. Furthermore, the federal agency's statements in the documents and decisions to which OEHHA points as the basis for listing, made from 2002-2006, cannot be construed as "final" for purposes of Proposition 65, where U.S. EPA currently is conducting a "***Re***evaluation" of chlorotriazines.

A. U.S. EPA Did Not Formally Identify Any Chlorotriazine as a Reproductive Toxicant in the Documents Cited in the NOIL

OEHHA's NOIL states that "OEHHA is relying on the U.S. EPA's conclusion that the triazine pesticides . . . cause developmental and reproductive effects...This conclusion meets the requirements of Section 26306(d)(1) and is made in a number of U.S. EPA documents . . ." NOIL at 1. OEHHA states that U.S. EPA has established acute and chronic reference doses for chlorotriazine compounds on the basis of developmental and reproductive effects observed in certain rodent studies, and quotes excerpts from several U.S. EPA documents that OEHHA characterizes as U.S. EPA's "conclusions" that the chlorotriazines cause developmental and reproductive harm in humans.

OEHHA's legal position that these statements and/or U.S. EPA's calculation of reference doses based on animal studies represent "conclusions" or "formal identifications" that the chlorotriazines cause developmental or reproductive harm to humans is incorrect and is based on a fundamental misunderstanding of U.S. EPA's, and in particular EPA's Office of Pesticide Programs' approach to risk assessment and mitigation in the regulation of pesticides. U.S. EPA/OPP is not primarily concerned with "hazard identification," that is, with reaching a definite conclusion as to whether a particular pesticide is "clearly shown" or "known" to cause cancer, reproductive harm, or other adverse effects.

On the contrary, U.S. EPA/OPP is entirely focused on ensuring that the use of pesticide products will pose ***no risk*** to humans. If U.S. EPA/OPP perceives a ***risk*** that a pesticide ***might*** cause an adverse effect in humans (or other non-target organisms, which EPA may also wish to protect), then U.S. EPA will regulate the uses of that pesticide so that the perceived potential ***risk*** will be safely avoided. In regulating the use of these compounds, ***U.S. EPA does not need to conclude that the evidence clearly establishes that the pesticide causes the particular harm in humans, and it has not done so in the case of the chlorotriazines.***

We have attached statements from five experts whose experience makes them highly qualified to discuss how U.S. EPA's Office of Pesticide Programs performs its function in assessing the potential risks of pesticides and regulating them to protect against such risks. *See* letters from Debra Edwards (Attachment C), Tina Levine (Attachment D), Edwin F. Tinsworth (Attachment E), Jack Fowle (Attachment F), and Gary Burin (Attachment G). As explained in their statements, each of these individuals has extensive experience in U.S. EPA's Office of Pesticide Programs, including working directly in the review of pesticides under the applicable guidelines for developmental and reproductive toxicity risk assessment, and in the management of the U.S. EPA human and ecological risk assessment, risk characterization and analysis, and registration and reregistration programs.

Individually and collectively, these statements demonstrate convincingly that U.S. EPA's Office of Pesticide Programs does not "list" chemicals "as causing reproductive toxicity" and does not otherwise "formally identify" the pesticides it regulates as reproductive or developmental toxicants. The calculations of reference doses and statements regarding reproductive and developmental effects in animal studies of the chlorotriazines cited in the NOIL do not constitute a "formal identification" by U.S. EPA that any chlorotriazine is a reproductive or developmental toxicant. Rather, those reference doses and quoted statements simply reflect U.S. EPA's risk-based approach to ensuring that human exposures to the regulated chemicals will always be below the levels at which any animal study has indicated that there is even a ***potential*** risk of developmental or reproductive harm. By proceeding in this manner, U.S. EPA can be confident that no human being or any other protected organism will be exposed to doses of chlorotriazines that even might, conceivably, cause any adverse effect. ***That*** is U.S. EPA's concern and the endpoint of the agency's analysis. The agency's concern obviously is ***not*** to reach a formal conclusion whether the chlorotriazines have been clearly shown to cause reproductive toxicity.

All of the U.S. EPA statements quoted in OEHHA's NOIL are consistent with the foregoing assessment of how U.S. EPA has approached and continues to approach the regulation of the chlorotriazines. Most of the quotes are simply descriptions of particular effects seen in animal studies that were the basis for U.S. EPA to select certain NOAELs to use in its four-step risk assessment process. None is a statement that U.S. EPA has concluded that the chlorotriazines will produce these effects in humans.

Indeed, one of the quotes in the NOIL has been excerpted from a longer passage which explicitly states that U.S. EPA's view is that the chlorotriazines ***might*** cause adverse human effects, rather than that they ***do*** cause such effects. Specifically, in the NOIL at page 2, OEHHA quotes U.S. EPA as follows:

> "EPA has determined that the triazine pesticides ... have common mechanism of suppression of LH surge and consequent developmental and reproductive effects."

This statement, misleading by itself, is truncated and excerpted from a longer passage, which reads as follows:

> "As summarized by the FIFRA Scientific Panel (SAP), 'there are considerable differences between the hypothalamic-pituitary-ovarian function in rats and humans, and the effects of aging on the function of the axis is also quite dissimilar. Therefore it is unlikely that the mechanism by which atrazine induces mammary gland tumors in female SD rats could be operational in humans. Nevertheless, it is ***not unreasonable to expect*** that atrazine ***might*** cause adverse hypothalamic-pituitary function in humans (SAP 2000)." Although the cancer mode of action may not be operative in humans, the SAP further to state [sic] that the same endocrine perturbations that induce tumors also ***appear to play a role*** in at least some developmental reproductive effects (not associated with reproductive aging) which ***may be relevant to humans***...
>
> "As indicated above, the cascade of events triggered by atrazine leading to mammary gland tumors in female SD rats are not expected to occur in humans given the species difference in reproductive aging. However, the ***potential for disruption*** of the hypothalamic pituitary axis and consequent attenuation of the LH surge leading to other health consequences not associated with reproductive aging (e.g., delay in prepubertal development) ***cannot be dismissed***. Thus, [the sentence fragment excerpted by OEHHA].

Interim Reregistration Decision for Atrazine (U.S. EPA, January 2003) at 16-17 (emphasis added).

This statement by U.S. EPA clearly shows that the Agency is regulating the chlorotriazines based not on a firm or clear conclusion that they cause adverse reproductive effects in humans, but rather on the basis that such effects are ***possible*** and that any risk of such ***possible*** effects can be prevented through regulatory measures based on those ***possibilities***. This precautionary approach is consistent with the U.S. EPA Risk Assessment Guidelines for developmental and reproductive toxicity. Therefore, contrary to OEHHA's legal conclusion in the NOIL, U.S. EPA has not "formally identified" the chlorotriazines "as causing reproductive toxicity."

B. U.S. EPA Is Currently Re-Evaluating the Potential Human Health Effects of the Chlorotriazines

As discussed in Attachment A at pages 4-5, U.S. EPA since 2009 has been engaged in a "comprehensive scientific reevaluation of the potential human health impacts of atrazine." 74 Fed. Reg. 51595, October 7, 2009. That reevaluation process, which is ongoing, includes consideration of all the animal data considered in the 2002-2006 U. S. EPA documents cited in the NOIL, as well as voluminous additional data developed since 2006. Until U.S. EPA's "comprehensive scientific

reevaluation of the potential human health effects" of the chlorotriazines has been completed, statements made by U.S. EPA prior to 2007 regarding those potential health effects should not be considered "final action" by U.S. EPA within the meaning of 27 CCR Section 25306(d)(1). Simply as a matter of sound policy, if OEHHA is considering whether to list the chlorotriazines based on U.S. EPA's assessment of those compounds, OEHHA should take no action until the U.S. EPA's ongoing comprehensive reassessment has been concluded.

II. The Animal Studies Referenced in the U.S. EPA Documents Cited in the NOIL Do Not Satisfy the Requirement of 27 CCR Section 25306(g) That Such Studies Be Sufficient Evidence to Indicate That Adverse Reproductive Effects in Humans Are Biologically Plausible

Section 25306(g) requires OEHHA to assess the animal studies that are the basis for U.S. EPA's purported "conclusions" about the adverse reproductive effects of chlorotriazines to determine whether those studies constitute "sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of exposure, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible." OEHHA states that it "has reviewed the studies or study descriptions cited by the U.S. EPA . . . relative to the criteria in Section 25306(g)" and that "The criteria for listing . . . have been met." NOIL at 3.

First, as discussed above and in the statements of the former EPA experts (Attachments C-G), it is clear that U.S. EPA, the authoritative body, did not ***itself*** review the animal studies cited in the NOIL to determine whether they were sufficient evidence to conclude that the chlorotriazines will cause the same effects in humans. Rather, consistent with its risk-based approach to pesticide regulation, the Agency simply ***assumed*** that the effects observed were ***potentially*** relevant to humans, and then proceeded to apply its risk-based methodology to ensure that humans would never be exposed to levels of the chemicals that could ***possibly*** cause any adverse effect, even in the hypothetical worst-case that humans are equally or more susceptible to the adverse effects in question. Under these circumstances and on the basis of the documents referred to in the NOIL, it simply is not possible for OEHHA to conclude that U.S. EPA, ***the authoritative body***, reached a conclusion that the animal data satisfy the criteria of 27 CCR Section 25306(g). The record shows that such a determination was not even on the agency's mind.

Second, to the extent that OEHHA believes that it has the authority to make that determination regarding the sufficiency of the animal evidence in the absence of a determination by the authoritative body, which we dispute as a matter of law, it is clear that the criteria set forth in Section 25306(g) have ***not*** been met for either developmental or female reproductive toxicity. The reasons for this conclusion are discussed in detail in the October 4, 2013 letter (Attachment A) at pages 6-10, and in the Syngenta Science Paper (Attachment B) at pages 11-30. Those discussions are hereby incorporated by reference.

In addition, recent studies by highly qualified experts, also attached to this letter and incorporated by reference, further demonstrate that the effects observed in the animal studies in question are not sufficient evidence that similar effects in humans are biologically plausible:

1. Abstract of a peer-reviewed article by Anthony R. Scialli, M.D. (Tetra Tech Sciences, Inc.) (Attachment H): Chlorotriazines do not cause birth defects in rats or rabbits; ossification delays observed in rat studies are transitory and secondary to maternal toxicity; the NOAELs for even such transitory effects are 10,000 times higher than the doses pregnant women would be exposed to at the atrazine MCL of 3 ppb in water.

2. Abstract of a peer-reviewed article by Chad. D. Foradori, Ph.D., *et al.* (Attachment I): Atrazine has no effect on LH surge even in rodents at maximum tolerated doses administered as temporally distributed doses in diet; temporally distributed doses in diet mimic the manner in which humans would potentially be exposed to the chlorotriazines in water.

3. Abstract of peer-reviewed article by John DeSesso, Ph. D. (Exponent), *et al.* (Attachment J): Atrazine has no adverse reproductive effects in rodents at maximum tolerated doses of ~40 mg/kg/day in studies following U.S. EPA guidelines.

4. A letter dated March 24, 2014 from Charles B. Breckenridge, Ph. D. (Syngenta LLC), *et al.* (Attachment K), describing several animal studies (including dietary studies, life-stage studies, and pharmacokinetic studies) that compel the conclusion that the adverse effects observed in the animal studies cited in the NOIL are not biologically plausible in humans.

5. A letter dated March 21, 2014 from James C. Lamb, Ph.D. (Center for Toxicology and Mechanistic Biology) (Attachment L) describing several reasons why the animal data cited in the NOIL do not satisfy the criteria of Section 25306(g), including issues related to route of administration, maternal toxicity, and interspecies differences.

For the reasons set forth in detail in the referenced abstracts and in the letters and Syngenta Science Paper, OEHHA should conclude that the animal data referenced in the U.S. EPA documents do not satisfy the requirements of Section 25306(g) and that an association between the chlorotriazines and adverse reproductive effects in humans has not been shown to be biologically plausible.

III. Significant New Animal Studies Not Considered by the Authoritative Body Clearly Establish That Adverse Reproductive Effects in Humans Associated with the Chlorotriazines Are Not Biologically Plausible

Finally, pursuant to 27 CCR Section 25306(h), OEHHA must determine that the chlorotriazines have ***not*** been shown to cause reproductive toxicity because "scientifically valid data which were not considered by the authoritative body clearly establish that the chemical

[chlorotriazines] does not satisfy the criteria of [27 CCR Section 25306(g)(2)]," *i.e.,* establish that adverse reproductive effects in humans due to chlorotriazine exposures are not biologically plausible.

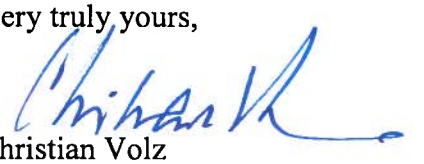
As noted above, U.S. EPA is in the process of performing a "comprehensive scientific reevaluation of the potential human health effects of [the chlorotriazines]," and atrazine, propazine and simazine are engaged in another reregistration process to renew, extend and modify their current U.S. EPA registrations. Syngenta has performed and commissioned numerous important studies on the chlorotriazines in the course of the reevaluation and reregistration processes, addressing subjects directly relevant to the potential developmental and reproductive effects of chlorotriazines. These significant new studies, not considered by U.S. EPA in reaching any "conclusions" expressed in the documents cited in the NOIL, are listed and discussed in detail in the October 4, 2013 letter (Attachment A) at pages 10-11 and Table 1, in the Syngenta Science Paper (Attachment B) throughout the document, and in Attachments H-L. Those discussions, which are hereby incorporated by reference, demonstrate that "scientifically valid data which were not considered by the authoritative body clearly establish" that adverse reproductive effects in humans due to chlorotriazine exposures are not biologically plausible.

IV. Conclusion

In summary, the attached statements from former U.S. EPA officials demonstrate that OEHHA is misapplying EPA's various statements and actions in regulating chlorotriazines to prevent the ***possibility*** of adverse effects to draw inferences of a "formal identification" of those chemicals as reproductive toxicants in ways that the authoritative body's regulatory process does not intend, and the underlying toxicological data would not support. By their own terms, moreover, whatever "conclusions" that U.S. EPA did intend cannot be deemed "final" for purposes of Proposition 65, because the ***Re***-evaluation process for these compounds is in progress now. Finally, by the terms of OEHHA's regulations, the new studies that U.S. EPA is considering ***now***, which were not before the agency at the time it made the statements on which OEHHA currently relies, demonstrate that the chlorotriazines should not be listed.

For all of these reasons, these compounds should not, and lawfully may not, be listed as reproductive toxicants under Proposition 65.

Very truly yours,



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Attachments

ATTACHMENT A

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October 4, 2013

Lauren Zeise, Ph.D.
Deputy Director
Office of Environmental
Health Hazard Assessment
1001 I Street
Sacramento, California 95812-4010

RE: COMMENTS OF SYNGENTA CROP PROTECTION LLC IN OPPOSITION TO POTENTIAL LISTING OF ATRAZINE, SIMAZINE, PROPAZINE, AND ASSOCIATED METABOLITES AS REPRODUCTIVE OR DEVELOPMENTAL TOXICANTS UNDER PROPOSITION 65'S AUTHORITATIVE BODIES LISTING MECHANISM

Dear Dr. Zeise:

As discussed in our meeting with representatives of the Office of Environmental Health Hazard Assessment ("OEHHA") in your Sacramento offices on August 30, 2013, we are submitting this letter and the attached science paper[1] on behalf of Syngenta Crop Protection LLC ("Syngenta") in opposition to the potential listing of atrazine, simazine, propazine or their associated metabolites deethylatrazine, deisopropylatrazine and diaminochloroatrazine (referred to collectively as the "chlorotriazines") as reproductive or developmental toxicants under Proposition 65's "authoritative bodies listing mechanism." As explained in this letter and the Syngenta science paper, none of the chlorotriazines meets the legal and scientific requirements for listing under that mechanism, as defined in the pertinent regulations at California Code of Regulations Title 27, Section 25306.

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[1] "Rationale for Not Listing Atrazine, Simazine, Propazine, Deethylatrazine, Deisopropylatrazine or Diaminochloroatrazine as Developmental or Reproductive Toxicant in Humans Under the Provisions of Proposition 65 — Final Report," authored by Charles B. Breckenridge, Ph.D. (Syngenta Crop Protection, LLC), Anthony R. Scialli, M.D. (Tetratech Science, Inc.) and James W. Simpkins, Ph.D. (West Virginia University) (October 2, 2013).

I. INTRODUCTION

The chlorotriazines should not be listed by OEHHA as developmental or reproductive toxicants pursuant to Proposition 65's "authoritative bodies" mechanism for three separate, independent reasons:

1. The authoritative body at issue in this case, the United States Environmental Protection Agency ("USEPA"), and more particularly, USEPA's Office of Prevention, Pesticides and Toxic Substances ("OPPTS") has not "formally identified" any chlorotriazine "as causing reproductive toxicity" as required by California Code of Regulations Title 27, Section 25306(d).

2. The animal studies referenced in the relevant USEPA documents as the basis for statements by USEPA that adverse developmental or reproductive effects have been observed in rats and rabbits exposed to chlorotriazines do not satisfy the requirement of 27 CCR Section 25306(g) that such animal studies, considering numerous factors, are sufficient to indicate that adverse developmental or reproductive effects in humans exposed to chlorotriazines are biologically plausible.

3. Numerous studies performed more recently than the dates of the USEPA documents in the OEHHA file relating to the potential authoritative bodies listing of the chlorotriazines, and therefore not considered by USEPA in making the statements cited by OEHHA as "conclusions" regarding the adverse effects of chlorotriazines, constitute "scientifically valid data which were not considered by the authoritative body" which "clearly establish that the chemical [chlorotriazines] does not satisfy the criteria of [27 CCR Section 25306(g)(2)]."

II. USEPA HAS NOT FORMALLY IDENTIFIED ANY CHLOROTRIAZINE "AS CAUSING REPRODUCTIVE TOXICITY" IN HUMANS

USEPA has not "formally identified" any chlorotriazine "as causing reproductive toxicity" in humans. First, the statements in the several USEPA documents in the OEHHA file that OEHHA has tentatively identified as definite scientific conclusions by USEPA that the existing animal data clearly show that the chlorotriazines cause developmental or reproductive toxicity in humans do not, upon close examination and when considered in context, in fact definite conclusions by the authoritative body. Second, even if those statements in the USEPA documents dated from 2002 to 2006 were definite conclusions, which Syngenta disputes, USEPA since 2009 has been engaged in a "comprehensive scientific reevaluation of the potential human health impacts of atrazine [and the related chlorotriazines]." This comprehensive reevaluation is expected to conclude in or around 2016. Until this "comprehensive reevaluation" by the authoritative body has been completed, any "conclusions" (if such they were) previously reached by USEPA should not be considered "final" and should not serve as a basis for listing the chlorotriazines.

1. *EPA's statements prior to 2007 do not "formally identify" any chlorotriazine as causing reproductive toxicity.*

USEPA/OPPTS's institutional focus is on risk assessment, prevention and mitigation, not hazard identification. USEPA's regulatory function in many cases does not require it to make formal determinations that a particular pesticide or other toxic compound is a reproductive or developmental toxicant in humans, and USEPA did not do so in the case of any of the chlorotriazines. Consistent with its regulatory role and focus, USEPA concluded that based on certain animal data (almost entirely rat data), it perceived a potential risk of reproductive harm to humans from chlorotriazine exposures. USEPA then calculated the conservative worst case potential extent of such possible risk given chlorotriazine usage patterns and human exposures, and imposed label requirements and use restrictions calculated to eliminate such possible risk. USEPA could, and did, pursue this risk assessment and mitigation objective without reaching a firm conclusion that any chlorotriazine is "known" to cause adverse developmental or reproductive effects in humans; it sufficed that USEPA believed such adverse effects were possible. A conclusion by the authoritative body that adverse effects in humans are possible, and that such a possibility justifies taking precautionary measures, is not a "formal identification" that the compound in question causes reproductive toxicity as required by 27 CCR Section 25306(d).

Syngenta acknowledges that there are statements in several of the USEPA documents in the OEHHA file that, read alone and taken out of context, appear to be conclusions that the chlorotriazines cause reproductive effects. When understood in the context of OPPTS' function and focus on risk mitigation, and how that focus affects the evaluation of the chlorotriazines being considered for registration, these statements clearly do not represent clear, formal identifications of the compounds as "known" to cause reproductive toxicity, which is the standard for listing under Proposition 65.

For example, in the Interim Reregistration Decision for Atrazine (January 2003), USEPA states that "EPA has determined that the triazine pesticides (with a common mechanism group of atrazine, propazine, simazine and their chlorometabolites) have common mechanism of suppression of LH surge and consequent developmental and reproductive effects." Id. at 17. On the face of it, that could be read as "formal identification" by USEPA that there is clear evidence that the chlorotriazines cause developmental and reproductive effects in humans. A review of the context of this sentence, however, shows clearly that USEPA has reached no such firm conclusion with regard to human effects:

> "As summarized by the FIFRA Scientific Panel (SAP), 'there are considerable differences between hypothalamic-pituitary-ovarian function in rats and humans, and the effects of aging on the function of the axis also is quite dissimilar. Therefore, it is unlikely that the mechanism by which atrazine induces mammary gland tumors in female SD rats could be operational in humans. Nevertheless, it is ***not unreasonable to expect*** that atrazine ***might*** cause adverse effects on hypothalamic-pituitary function in humans (SAR 2000).' Although the cancer mode of action may not be

> operative in humans, the SAP further to state [sic] that the same endocrine perturbations that induce tumors also ***appear to play a role*** in at least some developmental reproductive effects (not associated with reproductive aging) which ***may be relevant*** to humans....
>
> "As indicated above, the cascade of events triggered by atrazine leading to mammary gland tumors in female SD rats are not expected to occur in humans given the species difference in reproductive aging. However, the ***potential for disruption*** of the hypothalamic pituitary axis and consequent attenuation of the LH surge leading to other health consequences not associated with reproductive aging (e.g., delay in pubertal development) ***cannot be dismissed***. Thus, EPA has determined that the Triazine pesticides (with a common mechanism group of atrazine, propazine, simazine and their chlorometabolites) have common mechanism of suppression of LH surge and consequent developmental and reproductive effects."
>
> *Id.* at 16-17 [emphasis added].

The foregoing passage makes it quite clear that USEPA decided to regulate chlorotriazines based not on a finding that the animal data were conclusive evidence of reproductive or developmental effects in humans, but rather on the basis that in USEPA's opinion, such effects in rats "may be relevant to humans" and that "the potential [for such effects in humans] cannot be dismissed." That conditional and "cautionary" assessment of the potential for adverse effects in humans was sufficient for USEPA's purposes to impose use restrictions, label language, etc. calculated to eliminate even any potential risks. Under FIFRA, USEPA has the authority to regulate conservatively in this manner. Listing a chemical as "known to the state of California" to cause reproductive harm, however, requires a much greater degree of scientific evidence and certainty that the chemical ***does*** cause such harm, not only that it ***might*** cause such harm. USEPA's pre-2007 statements with regard to the chlorotriazines do not meet the stringent standard for listing under Proposition 65.

2. *USEPA is currently engaged in a comprehensive scientific reevaluation of the potential human health impacts of the chlorotriazines.*

Atrazine has been under review by USEPA in recent times through four programs: Special Review (initiated in 1994); reregistration concluded on April 6, 2006; a re-evaluation initiated in November 2009; and registration review initiated in June 2013.

In 1994, USEPA initiated the Special Review for the triazines to evaluate potential cancer risks and the potential exposure of persons to triazines through drinking water and other exposure pathways (59 FR 6014, November 23, 1994). The Special Review is still ongoing and will remain so until USEPA issues a Notice of Preliminary Determination or a Notice of Final Determination. Though this review is still open, USEPA concluded in 2000 that atrazine is not likely to cause cancer

in humans, and has recently convened Scientific Advisory Panels (SAP) to review all data related to cancer since 1985.

As part of a one-time "reregistration" program of all pesticides required by FIFRA and FFDCA, USEPA completed reregistration of atrazine and the other chlorotriazines in April 2006. USEPA concluded that "there is a reasonable certainty that no harm will result to the general U.S. population, infants, children, or other major identifiable subgroups of consumers from aggregate exposure (from food, drinking water, and non-occupational sources) to cumulative residues of atrazine and the other chlorinated triazine pesticides." D. Sherman, "Atrazine: Finalization of Interim Reregistration Eligibility Decision and Completion of Tolerance Reassessment and Reregistration Eligibility Process," April 6, 2006.

On October 7, 2009, USEPA announced in the Federal Register a "comprehensive scientific reevaluation of the potential human health impacts of atrazine," involving a series of scientific advisory panels that were conducted from 2009 - 2012. 74 Fed. Reg. 51595. As stated on their "Atrazine Updates" website, "EPA plans to take the recommendations from ... all previous SAPs into account as it updates the state of the science on the health effects of atrazine. The scientific information will be thoroughly considered in registration review of atrazine, scheduled to begin in 2013."

On June 26, 2013, USEPA initiated the "registration review" of atrazine (see docket EPA-HQ-OPP-2013-0266) as well as the other triazines, simazine (EPA-HQ-OPP-2013-0251) and propazine (EPA-HQ-OPP-2013-0250). Registration review, required by the Food Quality Protection Act of 1996, is an ongoing 15 year cyclic program that replaces the earlier reregistration and tolerance evaluation programs. USEPA will be considering the scientific data and evaluations conducted through previous actions, including the reregistration concluded in 2006 and the recommendations of the SAPs made as part of the re-evaluation of 2009-2012 (Atrazine Preliminary Work Plan, Registration Review Initial Docket Case Number 0062). Registration reviews for the triazines are scheduled to conclude starting in 2016.

Until USEPA has completed the ongoing "comprehensive scientific reevaluation of the potential human health effects" of the chlorotriazines, the agency cannot be said to have reached any firm or final conclusions concerning such potential effects. Any statements made by USEPA prior to the initiation of the reevaluation process in 2009 are clearly subject to potential revision or negation in the course of this reevaluation. For this reason alone, OEHHA should conclude that the pre-2009 statements by USEPA do not represent a "final action" by USEPA within the meaning of 27 CCR Section 25306(d)(1). Given the ongoing review of potential human reproductive and developmental effects of chlorotriazines and the extensive amount of new data to be considered in that review, previous USEPA statements are not a valid basis for listing the chlorotriazines under the authoritative bodies mechanism.

III. THE ANIMAL STUDIES CITED IN THE USEPA DOCUMENTS AS THE BASIS FOR ITS CONCERNS THAT ADVERSE REPRODUCTIVE EFFECTS IN HUMANS ARE POSSIBLE DO NOT SATISFY THE CRITERIA OF 27 CCR SECTION 25306(G).

Section 25306(g) requires OEHHA, as the lead agency, to determine whether the animal studies on which any purported USEPA "conclusions" regarding the adverse reproductive effects of chlorotriazines are based constitute "sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of exposure, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible."

Even if the statements in the USEPA documents regarding the potential adverse reproductive effects of chlorotriazines constitute "formal identifications" that the compounds cause adverse reproductive effects in humans, which Syngenta disputes as stated in Section II, the animal studies on which the USEPA statements are based are not sufficient data to indicate that adverse reproductive effects in humans as a result of exposure to chlorotriazines are biologically plausible. Much of the scientific evidence demonstrating that adverse effects in humans are not biologically plausible is new evidence not previously considered by USEPA.

1. *Developmental Effects*

The developmental effects in animals cited in the USEPA documents are based on three rat studies and one rabbit study in which the test animals were administered doses of technical grade atrazine by gastric intubation or gavage. In these studies, slight developmental delays were observed in the pups from the dams treated at the highest dose levels. The observed effects in the pups were delayed and/or incomplete ossification of certain bones, and the dams in each case also exhibited significant maternal toxicity.

These studies are not sufficient evidence that adverse developmental effects in humans are biologically plausible because (1) the slight developmental delays observed in the pups were transitory and of a type to be expected given the maternal toxicity observed in the dams at the doses in question; and (2) pharmacokinetic studies clearly demonstrate that adverse effects would never occur in humans because chlorotriazines are so quickly eliminated from the bloodstream following ingestion, by dermal contact, and/or by inhalation that serum concentrations would never, in any plausible exposure scenario, reach the levels at which maternal toxicity and developmental delays were observed in the rats and rabbits.

a. Maternal toxicity

"Consideration of maternal toxicity" is one of the factors related to the "adequacy of the experimental design and other factors [regarding particular animal studies]" that must be considered in determining whether the animal studies constitute "sufficient data ... indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible." 27 CCR Section 25306(g). USEPA, in its discussion of the rat and rabbit studies in question in the documents in OEHHA's file, noted that in every case where developmental delays were observed in the offspring, maternal toxicity was observed in the dams at the same dose levels. Given USEPA's focus on risk mitigation as opposed to hazard characterization, USEPA did not find it necessary to determine whether the maternal toxicity was the effective cause of the developmental delays, concluding that regulating atrazine exposures based on a dose level that affects both the dams and the fetuses is an appropriate risk mitigation approach. USEPA 2006. Given that a Proposition 65 listing is specifically a statement of hazard identification and not risk mitigation, however, OEHHA has an obligation to assess the role of maternal toxicity in these studies much more closely. As discussed in Syngenta's science paper in Section 6.2, the slight developmental effects observed in the offspring in these rat and rabbit studies – in all cases, delayed bone development – were of a type to be expected as a result of the type and degree of maternal toxicity observed in the dams. No malformations were observed, and the delayed ossification effects were transitory and would soon have been made up as the offspring matured. These limited and transitory effects were therefore "secondary" to the maternal toxicity in each case, and are not a sufficient basis for a conclusion that chlorotriazines would plausibly cause adverse developmental effects in humans.

b. Route of administration

"Route of administration" is another factor that must be considered in determining whether these studies are sufficient data to support a conclusion that adverse developmental effects in humans are biologically plausible. In this case, the key factor is that the route of administration was by bolus dose, either gastric intubation or gavage, such that each test animal's entire daily dose of atrazine was administered as a single, instantaneous dose. That route of administration might be realistic to model the potential harmful effects of, e.g., a drug that would be swallowed once daily; alternatively, if the test chemical in question is one that bioaccumulates or is absorbed and eliminated very slowly, it might not matter whether it is administered as a bolus dose or in feed. In the case of chlorotriazines, however, the bolus route of administration matters greatly and produces a completely artificial effect on the test animals that would not occur in the real world to animals or humans.

Pharmacokinetic data presented in Syngenta's science paper in Sections 5.0 and 7.0, much of which is new data not previously considered by USEPA, demonstrate clearly the radical differences in the plasma concentrations produced in rodents when administered atrazine by bolus dose, versus the same doses in feed over a typical daily cycle. These data show clearly that when

administered in feed, neither atrazine nor any other chlorotriazine ever approach the "biologically effective dose level" that is artificially produced, for a short time, by bolus dosing. Animals ingesting the same amounts of the test compounds in feed would be expected to show no adverse effects because the dosing would be spread out over the day. As discussed further in Section IV, Syngenta has performed and submitted significant new pharmacokinetic studies since 2006 that further demonstrate that metabolic elimination of chlorotriazines is so swift and efficient that the occurrence of adverse effects in humans is simply not biologically plausible. See Syngenta science paper, Section 7.

2. *Male Reproductive Effects*

The adverse male reproductive effect in animals cited in the USEPA documents is delayed male puberty (preputial separation) in rats, based primarily if not entirely on a single short-term study in which young male rats were administered doses of technical grade atrazine via gavage. The delayed preputial separation effect was observed in the high dose group. Stoker, et al., 2000.

This study is not sufficient evidence that the delayed puberty effect is plausible in humans because, as discussed above and in Syngenta's science paper, the effect was produced in the test animals only as a result of the gavage form of administration which temporarily (and unrealistically) overwhelms the very rapid metabolism of atrazine to produce short-term serum concentrations high enough to produce any adverse effect. Rodents fed the same daily doses of atrazine in feed or water eliminate the compound so rapidly that serum concentrations would never reach a level sufficient to produce an adverse effect. See discussion in Section IV, and in Syngenta science paper, Section 5.0 (discussing the comparative effect of dosing in feed or by gavage on LH surge). Potential exposures of human male children to chlorotriazines would be spread out over time due to slow dermal absorption of contacted residues, and ingestion or inhalation of low concentrations of chlorotriazines over the course of the day. As a result, their serum concentrations could never approach potentially harmful levels.

3. *Female reproductive effects*

The USEPA documents in OEHHA's file refer to two potential female reproductive effects: delayed female puberty and "estrous cycle alterations and LH surge suppression." The LH surge is not in itself a reproductive effect, and the delayed puberty effect was caused by bolus dosing. As a result, neither effect indicates that an adverse reproductive effect is biologically plausible in humans.

As was the case for the developmental effects and delayed male puberty reproductive effect discussed above, the female reproductive effect of delayed puberty was observed only in studies in which atrazine and propazine were administered by gavage. As discussed above and in Syngenta's science paper, bolus dosing by gavage or gastric intubation produces short-term elevations in serum levels of the administered chlorotriazines in the test animals that would never occur in any real world exposure scenario because all potential exposures of humans would be via ingestion of food or

water, or occupational exposure, and studies demonstrate that chlorotriazines are rapidly and efficiently eliminated, and do not bioaccumulate. See Syngenta science paper, Sections 5.0 and 7.0. Therefore, these animal studies that produce adverse effects only due to bolus dosing are not sufficient evidence that delayed female puberty is biologically plausible in humans exposed to chlorotriazines.

The female reproductive effect of "estrous cycle alterations and LH surge suppression," which is widely discussed in the several USEPA documents in OEHHA's file, is based on observations in a single six-month feeding study in female SD rats, MRID 44152102. Although USEPA recognizes that the phenomenon of LH surge suppression is not, in and of itself, an adverse reproductive effect, OPPTS in regulating atrazine, simazine and propazine regarded the LH surge effect as having a potential to affect reproduction in humans, and therefore chose to use the LOAEL and NOAEL derived from this six-month rat study as conservative figures from which to calculate human reference doses that would certainly be protective of humans. See Syngenta science paper, Figure 3 and page 9. In doing so, as noted in Section II, above, USEPA was not making a determination that chlorotriazines are known to affect human reproduction or even that the LH surge effect observed in the rats was even, conclusively, relevant to human females.

Pursuant to 27 CCR Section 25306(g)(2), OEHHA as the lead agency is required to make a determination whether the LH surge and other effects observed in this rat study are "sufficient evidence" to indicate that adverse effects on human reproduction from chlorotriazine exposure is biologically plausible. As explained in detail in Syngenta's science paper, there are several compelling reasons, supported by new scientific evidence, to conclude that this study does not meet that standard and that adverse effects on human reproduction are not plausible. Briefly, these include the following:

- *LH surge suppression is not an adverse reproductive effect.* The suppression of the LH surge in SD rats is not, in itself, an adverse reproductive outcome. USEPA concurs with this assessment. Syngenta science paper at Section 3.3.

- *Chlorotriazines do not affect reproductive outcomes.* Actual reproduction studies on rats show that chlorotriazines have no adverse effect on reproduction, fertility, or the ability of the next generation to reproduce. Syngenta science paper at Section 5.0, Tables 2 and 3. See also Atrazine IRED (April 2002) at 10, MRID 40431303, two-generation reproduction study on atrazine.

- *Human and rodent LH surge mechanisms are different.* The biological mechanisms controlling the LH surge in rodents are so different from those controlling the LH surge in humans that the effects of chlorotriazines on the LH surge in rodents are not biologically relevant to humans. Syngenta science paper at Section 3.0.

- *Human and rodent reproductive aging differences result in different chlorotriazine effects.* The female rat ages reproductively in a manner that is fundamentally different from human

female reproductive aging, and therefore the effects of chlorotriazines on reproductive aging in rats is not biologically relevant to humans. Syngenta science paper at Section 3.3 and Table 1.

- *Reproductive effects in rodents are the result of bolus dosing.* Animal studies show that in the case of young female rats not affected by reproductive aging, LH surge suppression does not occur in rats fed chlorotriazines in feed or water, but only in rats treated by bolus dosing. Syngenta science paper at Section 5.0 and Figures 8 and 9.

For all these reasons, the six-month rat feeding study is not "sufficient data" to conclude that adverse reproductive effects in human females exposed to chlorotriazines are biologically plausible.

IV. RECENT ANIMAL STUDIES NOT CONSIDERED BY THE AUTHORITATIVE BODY CLEARLY ESTABLISH THAT CHLOROTRIAZINES DO NOT SATISFY THE CRITERIA OF 27 CCR SECTION 25306(G)

Finally, pursuant to 27 CCR Section 25306(h), OEHHA must conclude that chlorotriazines do "not satisfy the definition of 'as causing reproductive toxicity' if scientifically valid data which were not considered by the authoritative body clearly establish that the chemical [chlorotriazines] does not satisfy the criteria of [27 CCR Section 25306(g)(2)]." As noted above, USEPA is in the process of performing a "comprehensive scientific reevaluation of the potential human health effects of [the chlorotriazines]," and atrazine, simazine and propazine are engaged in the early stages of another registration process to renew, extend and modify their USEPA registrations. Syngenta has performed and commissioned numerous important studies on chlorotriazines in the course of the scientific reevaluation and registration processes, addressing subjects directly relevant to the potential developmental and reproductive effects of chlorotriazines. Several of these studies have been submitted to USEPA and are under current review and discussion between USEPA and Syngenta; others are pending submission to USEPA or other agencies.

Many of these relevant studies are discussed in the Syngenta science paper, and links to each of the full new studies is provided in Section 9.0 of the Syngenta science paper to enable OEHHA staff to review the studies themselves. In addition, printed copies of the significant post-2006 studies are included as an attachment to this letter and the Syngenta science paper for OEHHA's convenience.

Table 1 lists the numerous significant studies (or papers) on the chlorotriazines that were initiated, completed and/or published during the period from 2006 to 2013 that are relevant to human health effects. Most of these studies were performed or commissioned by Syngenta or affiliated researchers; some were performed by EPA scientists or other independent researchers. As reflected in the left-hand column of Table 1, these significant new studies address all of the issues related to potential human reproductive or developmental effects that are discussed in this letter and in the Syngenta science paper, including:

1. LH surge or pulsatile LH: fourteen new studies.
2. Interaction between the hypothalamus-pituitary-adrenal axis and the hypothalamus-pituitary-gonadal axis: two new studies.
3. Adrenal hormones: one new study.
4. Gonadal hormones: one new study.
5. Immunotoxicity: two new studies.
6. Developmental toxicity: three new studies.
7. Fertility/reproductive toxicity: four new studies.
8. Pharmacokinetics: five new studies.
9. PBPK models: two new studies.
10. Quantitative risk assessment: two new studies.

None of these studies were considered by USEPA in issuing the documents between 2002 and 2006 that contain the statements identified by OEHHA as potentially forming a basis for concluding that USEPA "formally identified" one or more of chlorotriazines as causing developmental or reproductive toxicity. Most if not all of these studies will be reviewed and considered by USEPA in the course of its comprehensive scientific reevaluation of the human health effects of the chlorotriazines and related registration reviews. Syngenta respectfully submits that these studies, collectively, clearly demonstrate that an association between adverse reproductive effects in humans and exposure to chlorotriazines is not biologically plausible. Syngenta requests that after OEHHA has completed its review of these new data pursuant to 27 CCR § 25306(h), a meeting be scheduled at which OEHHA and Syngenta can discuss their findings and significance.

V. CONCLUSION

For the reasons set forth above and in Syngenta's science paper, Syngenta submits that the chlorotriazines should not be listed as reproductive or developmental toxicants pursuant to the authoritative bodies listing mechanism. The authoritative body, USEPA, has not formally identified any chlorotriazine "as causing reproductive toxicity" as required for listing pursuant to 27 CCR Section 25306(d). The animal studies in the USEPA documents that were the basis for the statements cited by OEHHA as potential bases for listing do not satisfy the requirement of 27 CCR Section 25306(g)(2) that such animal studies constitute "sufficient data ... indicating that an association between adverse reproductive effects in humans and [the chlorotriazines] is biologically plausible," based in part on the weight of evidence of numerous new studies not considered by

USEPA. Finally, those significant new studies not previously considered by USEPA clearly establish, pursuant to 27 CCR Section 25306(h), that the chlorotriazines do not satisfy the criteria of Section 25306(g)(2).

Respectfully submitted,

Christian Volz
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CV/gmp
Enclosures

cc: George Alexeeff, Ph.D., Director
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Poorni Iyer

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TABLE 1

Referenced New Studies Relevant to Human Safety or Risk Assessment That were Initiated Completed and/or Published by Syngenta -Affiliated Researchers or Other Independent Researchers During the Period from 2006 to 2013 (Exceptions Noted with one Asterisk)

Studies on the Chlorotriazines: General Topic Area	Listed in Breckenridge et al., (2013)	Studies Published by EPA Scientists** and Other Researchers
LH surge or pulsatile LH	**Coder (2010b), Coder (2011a); Coder (2011c); Coder (2011d); Coder (2011e); Coder (2011f); Coder (2011g); Coder (2012); Foradori (2009a); Foradori (2009b); Foradori (2013a); Handa (2010); Handa (2013); Plant (2012); Simpkins (2011)**	**Goldman (2013**); Ottowitz (2008); Stoker *(1999**)**
Interaction between the HPA and the HPG axis	**Handa (2010); Foradori (2011)**	
Adrenal hormones	**Handa (2010)**	**Fraites (2009**); Laws (2009**); Goldman (2013**)**
Gonadal hormones	**Handa (2010)**	Freeman (2006); Hall (2009); Oakley (2009); Zeleznik (2006)
Immunotoxicity	**Coder (2010c); Coder (2011a)**	
Sexual maturation		Laws *(2000**); Stoker* (2000; 2002**); Rosenberg (2008); Zeleznik (2006)
Developmental toxicity	**Coder (2010a); Scialli (2013); Fuchs (2008a,b)**	**Carney (2007); Davis (2011**); Fraites (2011**)**
Fertility/Reproductive toxicity	**Coder (2011d); Epstein, (1991*); Foradori (2013b); Fuchs (2008a,b); Mainiero (1987*)**	**Rosenberg (2008)**
Pharmacokinetics	**Breckenridge (2011); Coder (2011b); Hui (2011); Press (2012); Stuhler (2011)**	
PBPK Models	**Campbell (2011); Clewell (2011)**	
Quantitative Risk Assessment	**Breckenridge (2011); Sielken (2011)**	

HPA = Hypothalamus-Pituitary-Adrenal axis
HPG = Hypothalamus-Pituitary-Gonadal axis
Bold means that the study was included in the OEHHA Proposition 65 Syngenta Position
* Study conducted prior to 2006
** Studies conducted by EPA (Office of Research and Development) Scientists

ATTACHMENT B

Rationale for Not Listing Atrazine, Simazine, Propazine, Deethylatrazine, Deisopropylatrazine or Diaminochlorotriazine as Developmental or Reproductive Toxicant in Humans Under the Provisions of Proposition 65

Final Report

DATA REQUIREMENT(S): Not Applicable

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1.0 EXECUTIVE SUMMARY

Officials from the California's Office of Environmental Health Hazard Assessment (OEHHA) have indicated that their interpretation of the statements in USEPA documents dating back to 2006 and earlier, may provide a basis for the listing of the chlorotriazines, [atrazine (ATZ), propazine (PPZ), simazine (SMZ), deethylatrazine (DEA), deisopropylatrazine (DIA) and diaminochlorotriazine (DACT)] as developmental and/or reproductive toxicants under the Authoritative Body (AB) listing mechanism of California's Safe Drinking Water & Toxic Enforcement Act of 1986, California Health & Safety Code § 25249.2 et. Seq. (Proposition 65).

This document provides scientific evidence, much of which has been collected since 2006, indicating that:

1) The endocrine response, the suppression of the luteinizing hormone (LH) surge in rats exposed to high doses of the chlorotriazines is not in itself an adverse outcome. The United States Environmental Protection Agency (USEPA), the OEHHA designated AB, used the effect of the chlorotriazines on LH as a conservative surrogate for potential developmental and reproductive effects in humans.

2) The biological mechanisms controlling the LH surge in rodents are significantly different than those controlling the LH surge in humans.

3) The effect of the chlorotriazines on the LH surge mechanism in rodents is not relevant to humans.

4) Female rats age reproductively in a manner that is significantly different from that of women and therefore effects of the chlorotriazines on reproductive aging in female rats are not relevant to humans.

5) Because the chlorotriazines have a low rate of dermal absorption (Hui, 1996b), do not bio-accumulate and are rapidly eliminated from plasma, urine and feces, the biologically effective dose observed in rodent studies will never be achieved in humans exposed to the chlorotriazines in their diet, drinking water or as a result of occupational use of the chemicals.

6) Reproduction studies in rodents do not show any adverse effect on reproduction, fertility, development or the ability of next generations to successfully reproduce when the animals are exposed to the chlorotriazines in their diet, as a dose distributed throughout the entire day.

7) In contrast, developmental delay, LH surge suppression and reproductive effects are observed in rodents when the animals are administered their entire daily dose within a few minutes (bolus dose).

8) The bolus dosing scenario does not occur in humans exposed to the chlorotriazines in diet, drinking water or as a result of occupational or residential exposure and therefore, the effects observed following such dosing are not relevant to humans.

2.0 INTRODUCTION

California's Office of Environmental Health Hazard Assessment (OEHHA) is considering whether to list the chlorotriazine herbicides, atrazine, simazine, propazine and their common chlorotriazine metabolites (DEA, DIA, DACT) as developmental and male and female reproductive toxicants based on the Authoritative Body Listing mechanism of Proposition 65 (http://oehha.ca.gov/prop65/CRNR_notices/admin_listing/abtracking.html). OEHHA has indicated that its decision to list the chlorotriazines will depend on the following documents written by the United States Environmental Protection Agency (USEPA) through to the end of 2006: Report of the FQPA Tolerance TRED for Propazine (2006); Triazine Cumulative Risk Assessment (2006); Simazine RED (2006); Atrazine. Toxicology Chapter for the RED (2002); Atrazine/DACT- Fourth Report of the Hazard Identification Assessment Review Committee (2002); Propazine: Revised HED Risk Assessment for the TRED which includes a New Use on Grain Sorghum (2005); Decision Documents for Atrazine (2006).

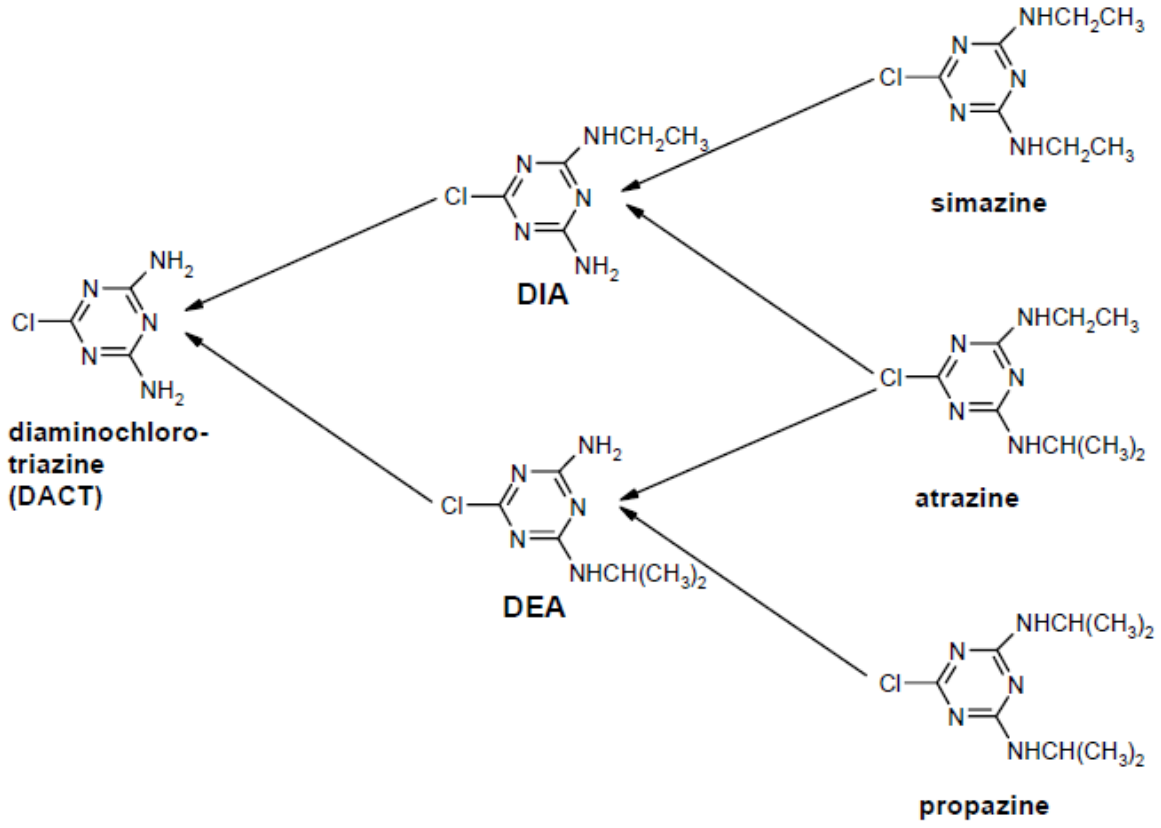
However, new scientific information generated during the period from 2006 through July, 2011 was evaluated by EPA and discussed during five Scientific Advisory Panel meetings held by the USEPA from November 2009 through July, 2011. Syngenta submitted new hazard identification studies, pharmacokinetic and mode of action studies, and exposure characterization and risk assessments to USEPA during this period. Syngenta presented its conclusions from these studies at each of the five SAP meetings. These materials can be found at the USEPA FIFRA Science Advisory Panel web site (http://www.epa.gov/scipoly/sap/) and in the USEPA docket for atrazine (http://www.epa.gov/opp00001/reregistration/atrazine/). This new information is relevant to the review being conducted by OEHHA.

2.1 Chlorotriazine Mode of Action

USEPA (2002) proposed that the chlorotriazines comprise a common mechanism group (Figure 1) based upon the neuroendocrinological mode of action (Figure 3). In the 2006 cumulative risk assessment of the chlorotriazines, USEPA used atrazine studies as surrogates for simazine, propazine and their chlorotriazine metabolites (DEA, DIA, DACT). The results from these studies provide the basis for establishing short, intermediate and long term exposure standards for the chlorotriazines (USEPA, 2000a; USEPA, 2003; USEPA 2013). Hence, information on atrazine including its pharmacokinetics is pertinent for all chlorotriazines belonging to the common mechanism group.

Since 2006, a large number of studies have been conducted to further characterize effects of chlorotriazines in rodents (Coder, 2010a, c; Coder 2011a-f; Coder, 2012) and the mode of action underlying these effects (Foradori, 2009a, b, 2011, 2013a), including an evaluation of the pharmacokinetic parameters associated with absorption, distribution, metabolism and elimination in rodents (Coder, 2010b) and non-human primates (Stuhler, 2011; Hui, 2011; Press, 2012). Key studies are bolded in blue in the reference section (Section 9).

Figure 1 Common Mechanism Group for the Chlorotriazines (USEPA, 2002; Figure 4, p 24)



Atrazine suppresses the luteinizing hormone (LH) surge in the Sprague-Dawley (SD) but not Fischer-344 rat (Figure 2). LH surge suppression, itself does not constitute an adverse effect. In Figure 3, USEPA (2006) postulated that the cascade of effects of atrazine on the LH surge is initiated in the hypothalamus as a decrease in levels of the neurotransmitter, norepinephrine followed in succession by decreased release of gonadotrophic releasing hormone (GnRH) and LH. Only when the reduction in LH reaches a critical level are adverse effects, such as pregnancy loss, delayed puberty and altered cyclicity observed.

The USEPA extended its interpretation of the neuroendocrine effects of the chlorotriazines on LH in subsequent reviews (USEPA, 2010; Figure 4). In the refined model, LH suppression, while identified as a precursor event in the neuroendocrine mode of action for the chlorotriazines, again was not designated as an adverse effect *per se*. Furthermore, the USEPA postulated that there were effects of atrazine, DIA, and DEA but not DACT (Fraites, 2009) on the hypothamalus-pituitary-adrenal axis (HPG) resulting in a modulating effect of the chlorotriazines on the HPG axis (Figure 5). Recently it has been shown by USEPA scientists (Goldman, 2013) that LH level may be either **increased or decreased, depending on the timing of the atrazine dose with respect to the occurrence of the LH surge (Goldman, 2013).**

Figure 2 Effect of 6 months of 400 ppm Atrazine in the Diet on the Estrogen-Induced LH Surge of Sprague-Dawley or Fischer-344 Rat (Simpkins, 2011)

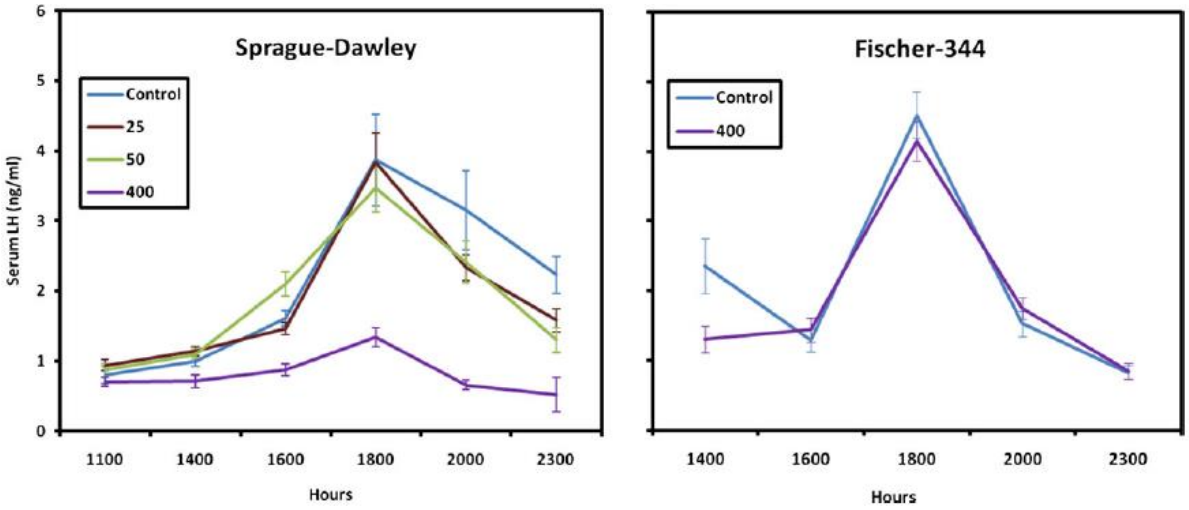


Figure 3 Atrazine Neuroendocrine Mode of Action and Associated Effects Found in Rats (USEPA, 2006, Figure 2, page 18)

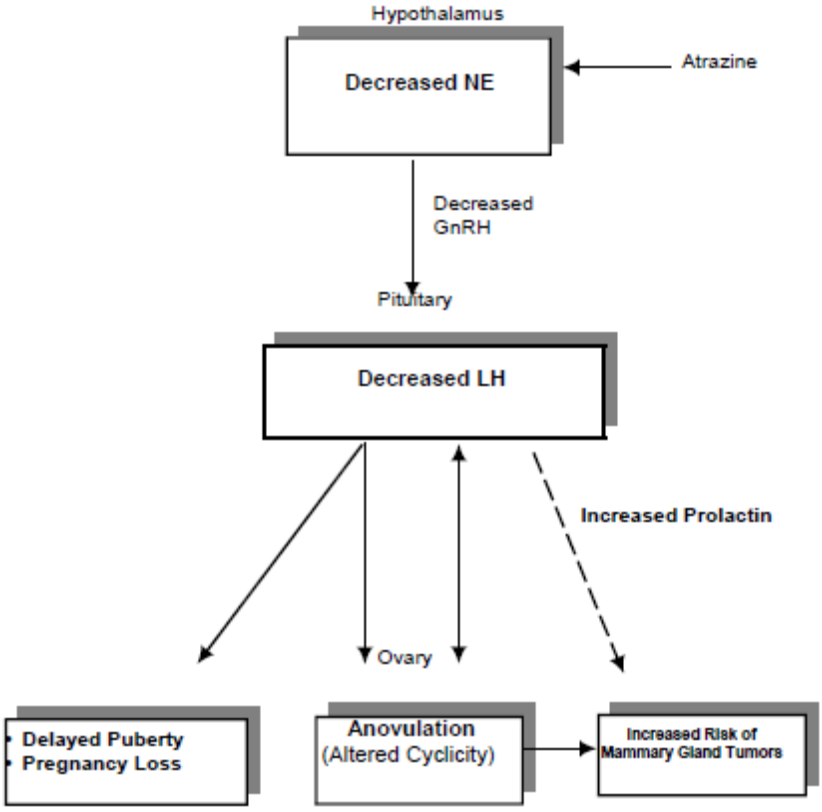


Figure 4 LH Suppression and Adverse Outcomes (USEPA, 2011a, p 14)

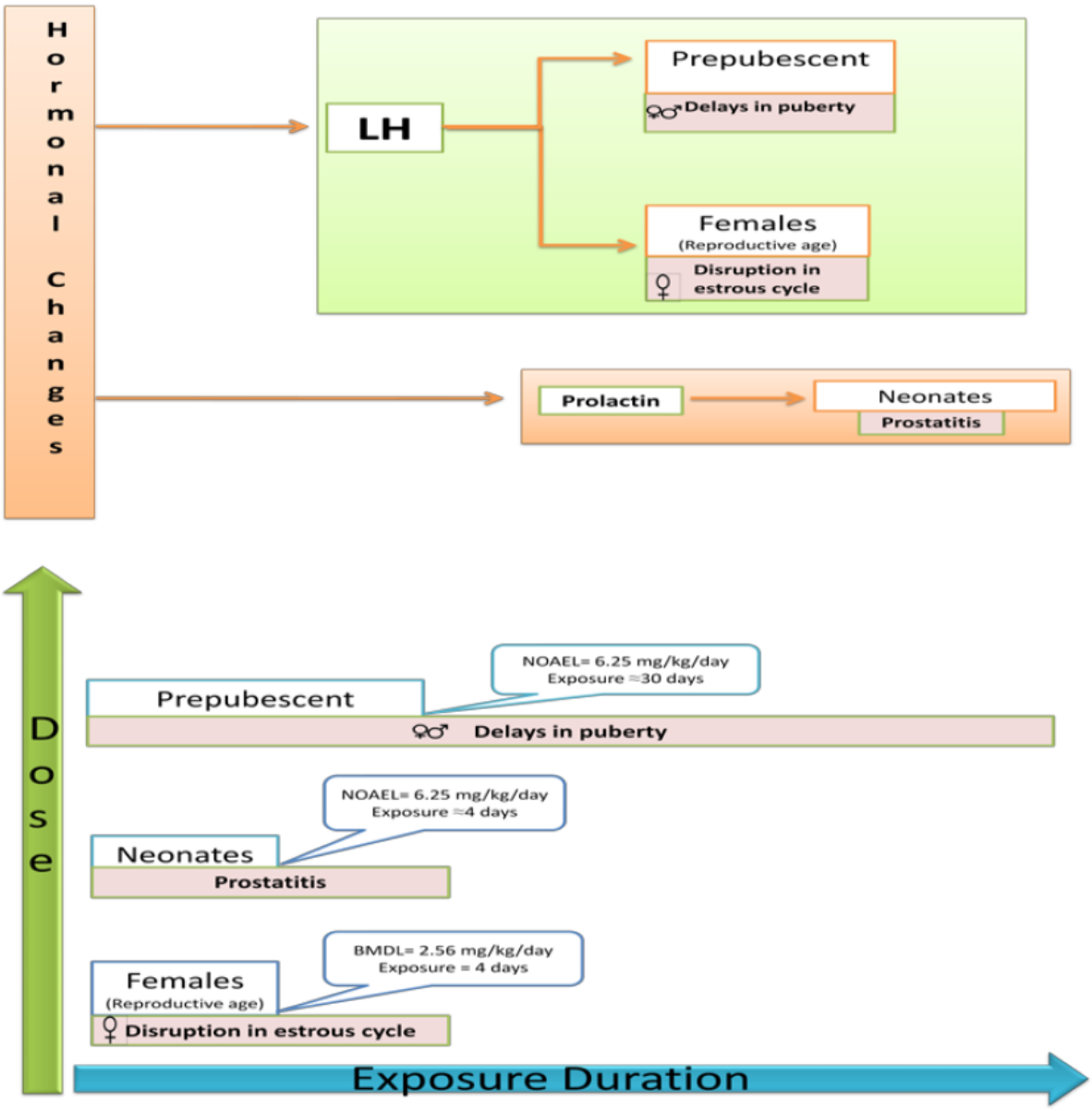
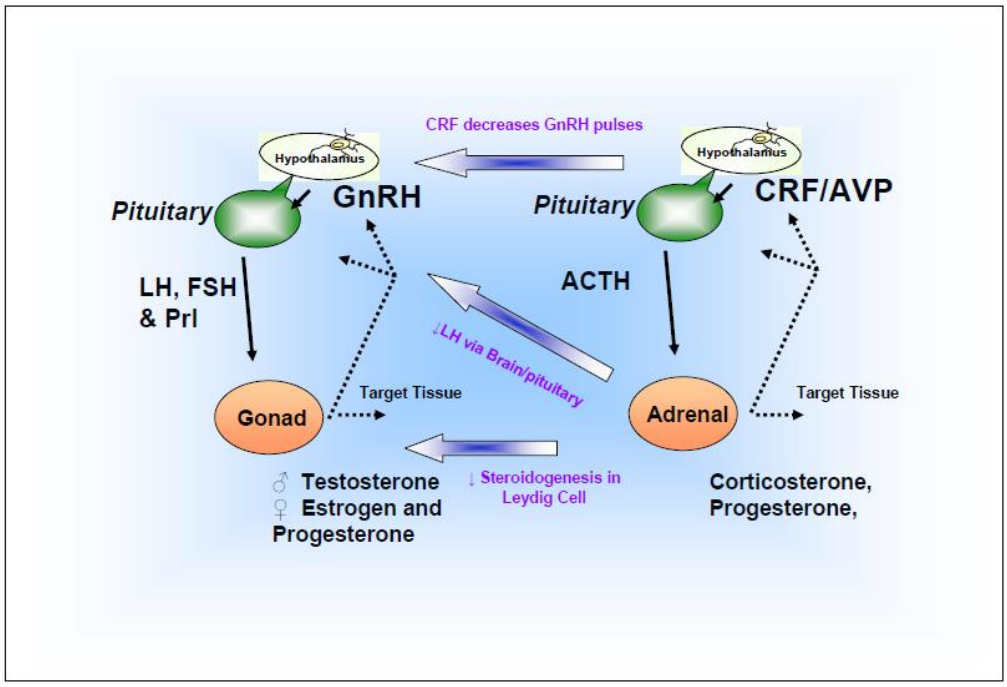


Figure 5 Proposed Effect of Atrazine on the Hypothalamus-Pituitary-Adrenal Axis (USEPA: Ralph Cooper Presentation to the Scientific Advisory Panel, April, 2010)



In 2010, the USEPA (USEPA, 2010, Page 13, Paragraph 2,) stated that

"In the course of the current evaluation, the Agency identified an effect of atrazine on reproductive function in both male and female rats. These effects provide insight into evaluation (sic) the vulnerability of specific lifestages such as sexual development, puberty, and the perturbation of adult reproductive performance (including premature aging). These effects can be linked to atrazine-induced changes in LH secretion. Consequently, the Agency will continue to uses changes in LH secretion as a basis of the atrazine risk assessment. As such, any of the identified adverse outcomes would be protected since they occur at doses higher than those eliciting changes in LH."

Thus, the USEPA has opted to conservatively regulate the chlorotriazines, not based on the occurrence of adverse effects, but rather on no observed effect levels (NOELs) for neuroendocrine precursor events. These precursor events may or may not be coupled to *"the vulnerability of specific life stages such as sexual development, puberty and the perturbation of adult reproductive performance (including premature aging)."*

This document presents evidence indicating that OEHHA should not list the chlorotriazines as developmental or reproductive toxicants in humans because

1) LH surge suppression in the rat is not relevant to human (Simpkins, 2011; Plant, 2012).

2) There are no adverse effects from atrazine, simazine or propazine on male or female fertility of F0 or F1 generations of rats exposed to chlorotriazines as distributed doses in diet indicating the absence of adverse effects of potential LH surge suppression.

3) The process of reproductive aging in humans is not the same as in SD rats (Simpkins, 2011) and thus NOELs based upon effects on the LH surge in aged rats (Morseth, 1996) are not relevant to humans (USEPA, 2000b).

4) Suppression of pulsatile LH release by atrazine (Foradori, 2009b) but not DACT (Handa, 2013), which has been linked functionally to the onset of puberty in rodents (Sisk, 2001) and non-human primates (Terasawa, 2001), has only been observed when atrazine was administered using an artificial dosing methodology (bolus gavage dosing) (Stoker, 2000, 2002). This dosing method leads to artificially high plasma concentrations (Coder, 2011b) that cannot plausibly occur in humans exposed to the chlorotriazines in diet, water or as a result of residential or occupational use.

5) Effects of atrazine on maternal prolactin levels and their secondary effects on the neuronal control mechanism regulating prolactin release in the offspring (Stoker, 1999) are not relevant to humans because again, these effects were produced using an artificial gavage bolus dosing methodology that results in plasma chlorotriazine concentrations that cannot plausibly occur in humans exposed to the chlorotriazines in diet, water (Campbell, 2011) or as a result of residential or occupational use.

6) Effects of high bolus gavage doses of atrazine on plasma estrogen (Fraites, 2009), testosterone (Trentacoste, 2001) or sperm count (Kniewald, 2000; Fuchs 2008a, b; Rosenberg, 2008) in rats are not relevant to humans who may be exposed to distributed doses of the chlorotriazines in the diet, water or as a result of residential or occupational uses.

7) Effects of high bolus doses of atrazine, DEA, DIA but not DACT on the pituitary hypothalamic-adrenal (HPA) axis as reflected by increased plasma levels of adrenal corticotrophic hormone (ACTH), corticosterone and progesterone (Fraites, 2009; Laws, 2009; Foradori, 2011) are no longer observed after multiple doses (Handa, 2010; Coder, 2010c). These transient effects of bolus gavage doses of the chlorotriazines, which are not adverse effects *per se*, cannot plausibly occur in human

exposed to distributed doses of the chlorotriazines. Furthermore, no adverse effects of HPA activation were found in studies on the immune system function of adult male (Coder, 2010c) or female SD rats (Coder, 2011a) nor in the offspring of rats exposed to gavage bolus doses of atrazine *in utero* (Fraites, 2011; Davis, 2011).

3.0 THE EFFECT OF ATRAZINE ON THE LH SURGE IN RODENTS IS NOT RELEVANT TO HUMANS

Changes in pituitary responsiveness to GnRH drive the human LH surge (Simpkins et al., 2011; Plant, 2012), whereas increased GnRH pulse frequency and amplitude drive the rodent proestrus LH surge (Simpkins et al., 2011).

3.1 The Menstrual Cycle in Humans

The human menstrual cycle is long and exhibits a protracted pre-ovulatory LH surge spanning 2-3 days and ends with menses, due to the involution of the corpus luteum and the resulting decline in estrogens and progesterone (Zeleznik and Pohl, 2006; Hall, 2009). In contrast to the rodent, the role of the primate brain, although obligatory in driving the menstrual cycle, is permissive rather than deterministic. In the human female, the preovulatory LH surge occurs in the absence of a GnRH surge (Hall et al., 1994; Ottowitz et al., 2008; Martin et al., 1998; Santoro et al., 1986) and unfolds in the face of an unchanging frequency of the GnRH pulse generator, as reflected by pulsatile LH release (Martin et al., 1998; Adams et al., 1994).

The LH surge in women is timed and elicited by a positive feedback action of estradiol at the level of the pituitary to dramatically enhance responsiveness to pulsatile GnRH stimulation in women. Indeed, the spontaneous menstrual cycle can be recapitulated in women deficient in GnRH, simply by the exogenous administration of a series of identical pulses of GnRH (Hall, 2009; Martin et al., 1998; Filicori et al., 1986; Santoro et al., 1986). These findings indicate that the entire pattern of gonadotropin secretion throughout the human menstrual cycle is governed by the negative and positive feedback actions of ovarian estradiol at the level of the pituitary.

3.2 The Estrous Cycle in Rodents

The estrous cycle in rodents is short, and the pre-ovulatory LH surge is brief, governed by the light-dark cycle, with the hypothalamus playing a key role in timing the pre-ovulatory LH surge (Freeman, 2006). Every afternoon during a critical period spanning approximately two hours, the rodent brain generates a circadian signal, which in combination with the positive feedback action exerted by the elevated levels of circulating estradiol on proestrus, activates the GnRH surge generator that triggers the LH surge. Thus, the role of the rodent brain in controlling the timing of ovulation may be viewed as deterministic. The hypothalamic neurons synthesizing GnRH in the rodent brain are located primarily in the pre-optic area (POA), with few in the more caudal medial basal hypothalamus (Silverman et al., 1994). Release of GnRH into the portal circulation is dependent on increased activity of norepinephrine neurons located in the brainstem (Sawyer, 1995; Simpkins et al., 1979a, b;

Wise et al., 1997, 1999; Herbison, 1997) and on kisspeptin neurons located in the anteroventral periventricular nucleus of the POA (Oakley et al., 2009), the site of positive feedback of ovarian estradiol (Goodman, 1978). As such, inhibition of neural activity early in the afternoon of proestrus by administration of barbiturate or other centrally acting drugs blocks the pre-ovulatory LH surge in rats (Freeman, 2006; Goodman and Knobil, 1981).

3.3 Reproductive Aging in Rodents Is Different Than in Humans

USEPA accepted that reproductive aging in the rat is unlike reproductive aging in humans (Table 1) and therefore concluded that the cancer mode of action, resulting from the inhibition of the LH surge in aged rodents is not relevant for humans because suppression of the LH surge would not lead to cancer in humans (USEPA 2000b).

Table 1 Species Differences in Reproductive Senescence (Simpkins, 2011)

Parameter	SD Rat	Fischer-344 Rat	Women
• Start of Senescence (% of normal lifespan)	30-40 %	60-70 %	60-70%
• Principal cause of senescence	Hypothalamic failure to stimulate LH/FSH	Hypothalamic failure to control prolactin surges	Depletion of ovarian follicle content
• LH surge capability	Lost	Maintained	Maintained
• Predominant cycle pattern	Persistent estrus	Pseudopregnancy episodes	Menopause
• Estrogen/progesterone ratio	Elevated/prolonged	Reduced	Reduced
• Prolactin secretion	Persistently elevated	Episodically elevated	Reduced
• Spontaneous mammary tumor incidence (lifetime)	30-40 %	2-5 %	8-10 %
• Principal known factors that increase MT Risk	Prolactin, estrogen, chemical mutagens	Prolactin, estrogen, chemical mutagens	Estrogen, nuliparity Family history
• Prolactin dependence	High	Medium	None

The no observed effect level used to set the chronic reference dose for ATZ and the chlorotriazines (RfD = 1.8 mg/kg/day ÷ 1000) is conservatively low because it is based upon suppression of the LH surge in reproductively aging female SD rats. In contrast to rats, women maintain normal LH surge capability throughout life and therefore would not display reproductive failure as a result of atrazine exposure to the chlorotriazines.

USEPA has accepted the neuroendocrine mode of action for atrazine and the chlorotriazines (Figure 1, USEPA, 2006) and recognizes that suppression of the LH surge *per se* does not indicate an adverse developmental or reproductive effect. Furthermore, USEPA recognizes that the chronic reference dose for the chlorotriazines, which is based upon a 6-month LH study in female SD rats, is conservatively low because of the enhanced sensitivity of aged SD rats.

4.0 DEVELOPING RATS ARE INSENSITIVE TO THE EFFECT OF ATRAZINE ON THE LH SURGE

Syngenta has conducted and submitted new studies (Coder, 2011c; Foradori, 2013b) to the EPA that compared the effects of atrazine administration on the LH surge in female Sprague-Dawley rats exposed daily by gavage from conception to approximately post-partum day 35, or from weaning to post-partum day 35 (Figure 6) or for 4 days as young adults (Figure 7). The results indicate that young animals are insensitive to the effect of atrazine on the LH surge (Figure 6) compared to older females (Figure 7).

The USEPA Scientific Advisory Panel (USEPA, 2011, page 14, Paragraph 1) in their review of the question of enhanced susceptibility of the young to the effects of atrazine on the LH surge state:

"The Panel agreed with the Agency's conclusion that exposure during the earlier life stages does not appear to lead to greater sensitivity, if one accepts the premise that the data on suppression of the LH surge is appropriate for use in making the comparisons. An extensive hazard database, spanning all life stages from conception to adulthood for atrazine, indicates no unique susceptibility in the developing organism."

Figure 6 Effects on the Estrogen-Induced LH Surge of Female Sprague-Dawley Rats Exposed to Atrazine Daily from Conception to Day 35 Post-Partum or Day 21 to Day 35 Post-Partum (Coder 2011c)

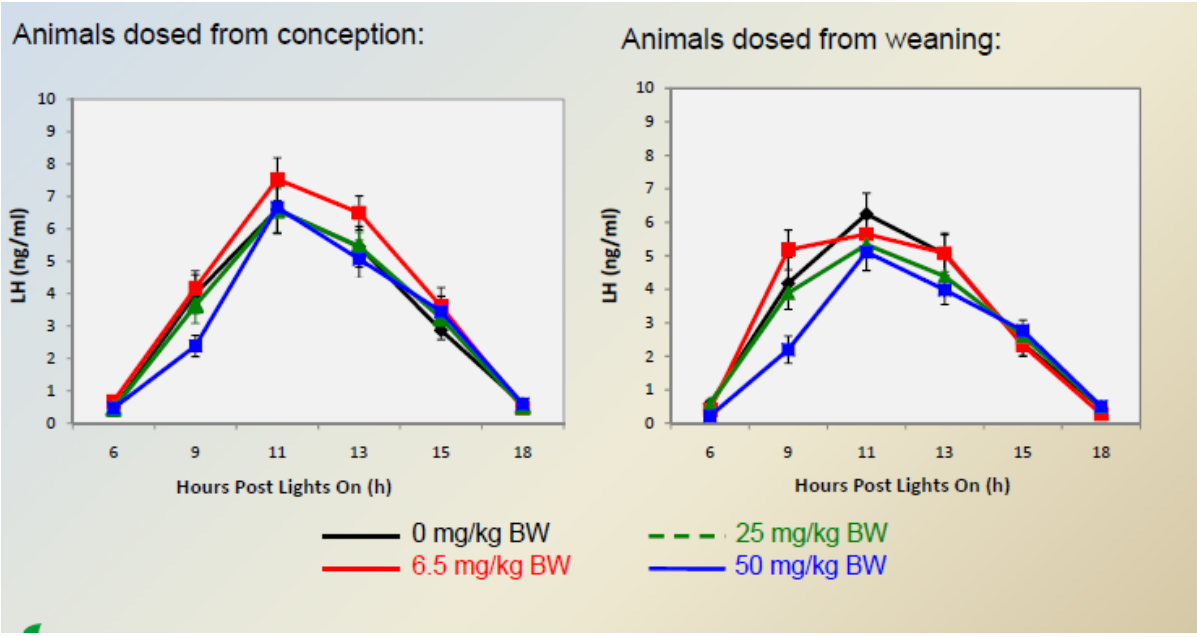
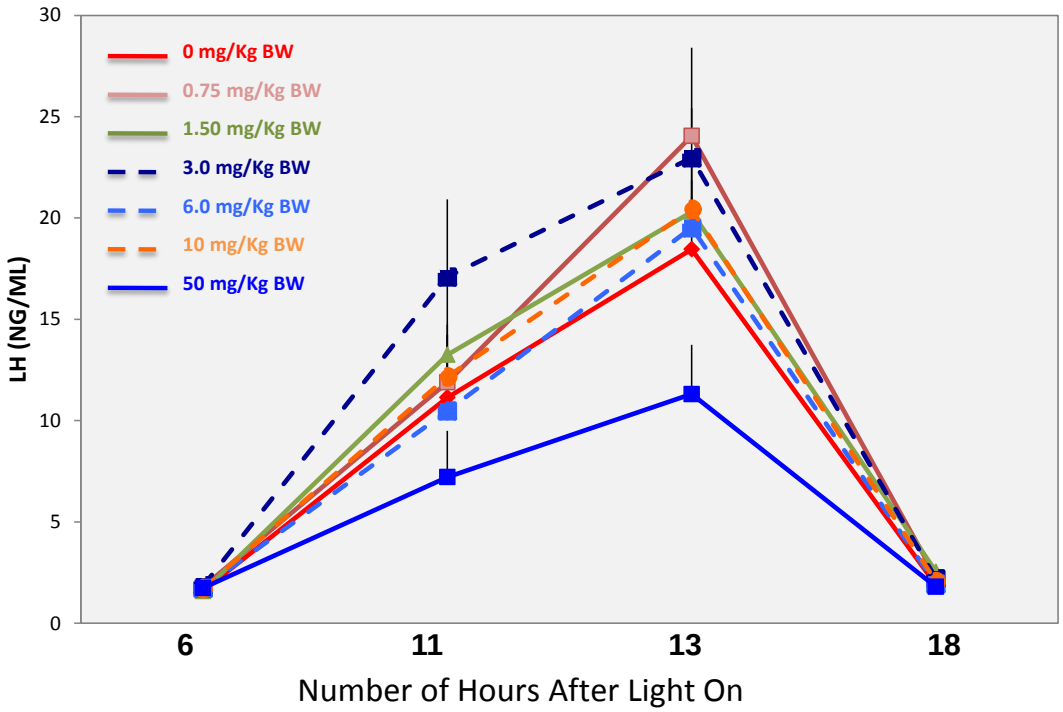


Figure 7 Effect of Atrazine on the LH Surge for 4-Days in Intact, Normally Cycling Young Adult (60 Days Post-Partum) Sprague-Dawley Rats (Foradori, 2013b)



5.0 REPRODUCTIVE EFFECTS ARE NOT OBSERVED IN RODENTS BECAUSE OF RAPID PHARMACOKINETICS

There are no effects on fertility or reproduction in rat multi-generation studies on atrazine (Table 2), simazine (Table 3) or propazine (USEPA, 2005; Section 4.2.4, page 25). Because LH surge triggers ovulation in rodents and the chlorotriazines suppress the LH surge in rats, an effect on fertility would be expected; however, no such effects are observed.

This lack of effect on fertility can be explained by pharmacokinetics and the artificial dosing method (gavage bolus dosing) utilized in studies where the LH surge was suppressed. The exception was the six month feeding study (Morseth, 1996) where the LH surge was suppressed in reproductively aged female SD rats, a model that was previously described as irrelevant to humans (Section 3.5). Coder (2011a) showed that peak plasma concentrations of atrazine, DEA, DIA and DACT are substantially greater when atrazine was administered as a bolus dose by gavage compared to the same dose distributed over 24 hours by administering the chemical in feed (Figure 8). Coder (2011b) showed that while the bolus dose of atrazine suppresses the LH surge, the distributed dose of atrazine has no effect on the LH surge in the rat (Figure 8 and Figure 9).

Figure 8 Comparison of the Effects of Atrazine on the LH Surge and Pharmacokinetics when Administered as Bolus Dose by Gavage or as Distributed Dose in Feed.

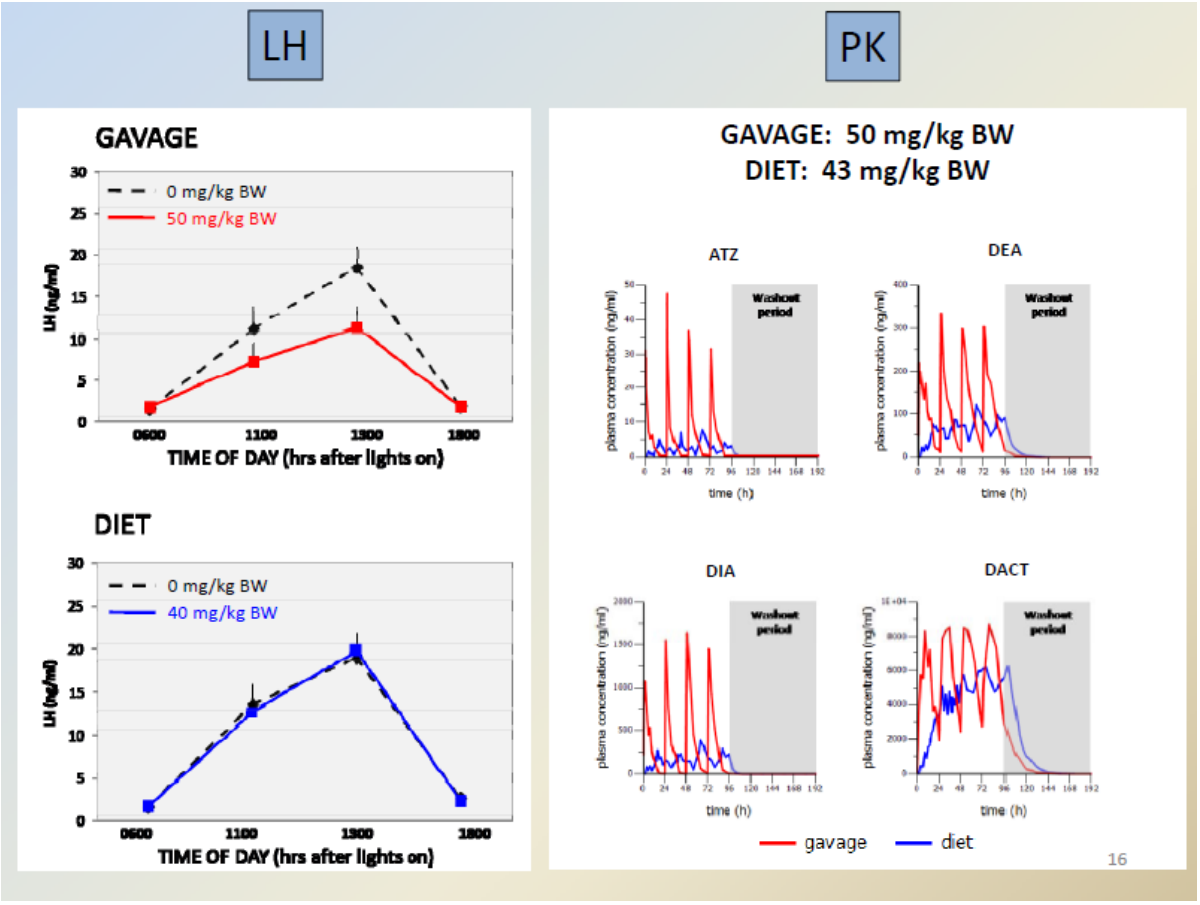
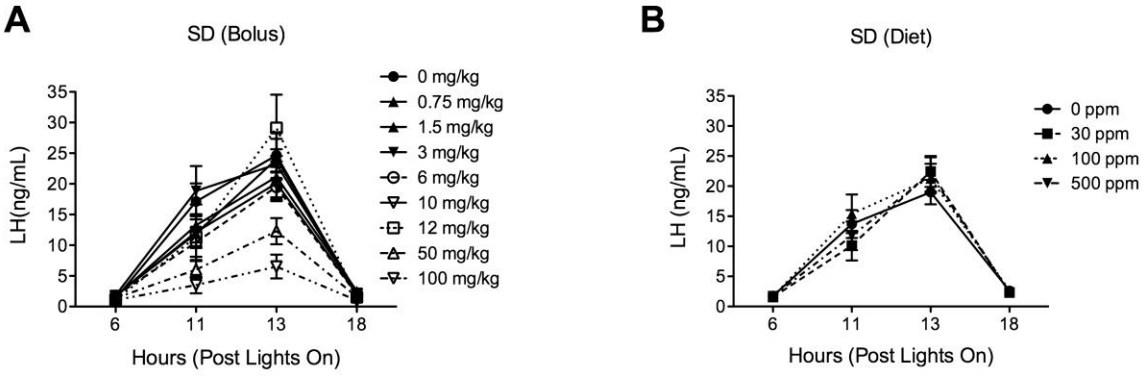


Figure 9 Comparison of the Effects of Atrazine on the LH Surge in Sprague-Dawley Rats When Administered as a Bolus Dose by Gavage (A) or as a Distributed Dose in the Diet (B)



In a subsequent experiment, Coder (2011c) showed that high bolus doses of atrazine administered to intact female Long Evans rats suppressed the LH surge and reduced the mean

number of follicles ovulated whereas equivalent distributed doses had no effect on these parameters (Table 4).

Collectively, these results explain the absence of effects of atrazine on fertility in the rat in the 2-generation reproduction study (Table 2). More importantly, they indicate that it is implausible that humans will experience adverse effects on LH surge, fertility or reproduction when exposed to atrazine in the diet, drinking water or as a result of occupational or residential use.

6.0 PUBERTAL AND OSSIFICATION DELAY ASSOCIATED WITH HIGH GAVAGE BOLUS DOSES

6.1 Delayed Sexual Maturation

Gavage doses of atrazine administered to rats during the peri-pubertal period delays the onset of puberty as reflected by a delayed vaginal opening (VO) in females (Ashby, 2002; Laws, 2000) and delayed preputial separation in males (Stoker, 2000, 2002). The lowest NOEL for delayed sexual maturation was a dose of 6.25 mg/kg/day based upon Vo delay in the study by Laws, 2000.

Rapid pharmacokinetics of the chlorotriazines makes it implausible that delayed sexual maturation will occur in humans because the effects have only been observed in rats following gavage doses. It is implausible that humans will be exposed to bolus doses of atrazine through diet, in drinking water or as a result of occupational exposure to atrazine.

6.2 Delayed Skeletal Ossification

High doses of atrazine and its metabolites, DEA, DIA and DACT, when administered by gavage, may result in decreased fetal weight and delayed ossification of certain bones in the skeleton (Scialli et al., 2013). These effects are consistent with maternal toxicity at the maximum tolerated dose (MTD) and are not evidence of a direct effect of the chlorotriazines on developmental processes. There was evidence of maternal toxicity in animals administered high doses of the chlorotriazines by gavage. Maternal toxicity was evidenced by reduced maternal body weight gain that was corrected for fetal body weight effects (Table 5).

Ossification delay occurs with deficits in fetal body weight and represents a transient effect of maternal toxicity (Carney and Kimmel, 2007). Most of the fetal bones are initially modelled in cartilage. Cartilage is a specialized tissue that differentiates from the embryonic mesenchyme and forms a template for bone. As the fetus matures, the cartilage is invaded by bone-forming cells called osteoblasts and by capillaries. The osteoblasts lay down a matrix of calcium and phosphate, beginning in ossification centers and extending ultimately to involve the entire cartilaginous template. The ossification process is highly dependent on the maturity of the fetus, and small mammal fetuses are actively ossifying their skeletons in the last three days of pregnancy and the first days of postnatal life.

Chemicals may cause a reduction in fetal body weight through effects on maternal food intake or maternal physiology. Recovery of offspring body weight after delivery is common, and achievement of normal ossification under these circumstances is expected. For example, a study by Marr et al. (1992) involved the administration of ethylene glycol 2500 mg/kg bw/day to pregnant rats on GD 6–15. Fetuses were examined at intervals before and after natural parturition, which occurred on approximately GD 21. Fetal weight was reduced an average of 28% by ethylene glycol treatment during the last three days of pregnancy and recovered nearly to control levels within 2 weeks after birth. Ossification also improved after delivery and reached control levels by 63 days.

Carney and Kimmel (2007) write that, "...delayed ossification is generally a finding that denotes generalized growth delays with subsequent catch-up postnatally. It also does not seem to have general predictive value for teratogenicity." These authors suggest that the pattern of bones that are involved can be helpful; if the reductions in ossification are restricted to bones that normally ossify late in gestation, the interpretation of a transient delay is tenable. These bones include the phalanges, sternebrae 5 and 6, the centra of the thoracic, sacral, and caudal vertebrae, and the calvarium. Carney and Kimmel also suggested that the presence of maternal toxicity would be consistent with delayed ossification of no consequence.

In the developmental studies with atrazine and its metabolites, maternal toxicity at the MTD is a feature of the pharmacokinetics of gavage dosing. It is implausible that such effects could occur in humans for distributed doses resulting from exposure via diet, in drinking water or as a result of occupational or residential use of the chlorotriazines. For example, in the rat two-generation study, there were no deficits in birth weights in spite of a decrease in maternal weight gain at the MTD. Dosing in the two-generation study was distributed in the diet rather than by bolus gavage administration.

Table 2 Results from the Two Generation Reproduction Study on Atrazine (Mainiero, 1987)

	Atrazine Feeding Level ppm (mg/kg/day)							
	0	***10 (0.73)***	***50 (3.64)***	***500 (38.7)***	***0***	***10 (0.73)***	***50 (3.64)***	***500 (38.7)***
Parental Generation	***F0 Generation***				***F1 Generation***			
Number of mated females	30	30	30	30	30	30	30	30
Number of pregnant females	29	28	26	26	24	18	28	26
Fertility index (%)[a]	96.7	93.3	86.7	86.7	85.7	69.2	93.3	89.7
Mating index (%)[b]	100	100	100	100	93.3	86.7	100	96.7
Gestation index (%)[c]	96.6	100	100	96.2	95.8	100	100	96.2
Number of viable litters	28[d]	28	26	25	23	18	28	25
Mean litter size ± SD, day 0	13.2±3.6	15.0±2.1	15.0±2.1	13.7±4.6	11.0±5.0	13.3±2.8	13.4±3.3	12.4±4.1
Mean N° of still birth ± SD, day 0	0.26±0.53	0.25±0.44	0.23±0.51	0.35±0.69	0.50±0.83	0.17±0.51	0.07±0.26	0.31±0.74
Offspring Generation	***F1 Generation***				***F2 Generation***			
Number viable males, day 0	166	218	206	171	131	114	182	182
Number viable females, day 0	190	203	183	184	133	126	194	194
Sex ratio (% males) day 0	46.6	51.8	53.0	48.2	49.6	47.5	48.4	48.4
% pups alive on PND4[e]	96.6	96.9	97.7	95.7	89.6	98.7	97.1	97.1
% pups alive from PND4 to PND21	97.6	91.1	96.2	98.0	96.6	98.6	99.6	99.6
Mean pup weight (g), PND 0, Males ± SD	6.4±0.1	6.0±0.1	6.2±0.1	6.3±0.1	6.4±0.1	**6.0±0.1***	6.2±0.1	6.2±0.1
Females ± SD	6.0±0.1	5.7±0.1	5.7±0.1	6.0±0.1	6.0±0.1	5.8±0.1	5.8±0.1	5.8±0.1
Mean pup weight (g), PND 4, Males ± SD	9.1±0.2	**8.1±0.2***	8.6±0.2	8.7±0.2	9.3±0.3	8.8±0.3	9.0±0.2	9.0±0.2
Females ± SD	8.6±0.2	**7.7±0.2***	**7.9±0.2***	8.4±0.2	8.9±0.2	8.4±0.2	8.5±0.2	8.5±0.2
Mean pup weight (g), PND 7, Males ± SD	14.4±0.4	13.0±0.4	13.5±0.4	13.4±0.4	14.0±0.5	13.4±0.5	13.7±0.4	13.3±0.4
Females ± SD	13.4±0.4	12.2±0.4	12.4±0.4	12.7±0.4	13.4±0.4	12.7±0.4	12.8±0.3	12.8±0.3
Mean pup weight (g), PND 21, Males ± SD	49.9±1.1	45.1±1.1	47.2±1.1	46.2±1.2	47.8±1.3	44.6±1.4	43.8±1.1	43.0±1.2
Females ± SD	46.8±1.0	43.4±1.0	44.0±1.0	44.4±1.0	44.2±1.4	42.5±1.4	41.3±1.2	42.3±1.3

[a] Fertility index = (Number of pregnant females / number of females cohabited with males) X 100
[b] Mating Index = (Number of sperm-positive females / number of females cohabited with males) X 100
[c] Gestation Index = (Number of females with liveborn / number of sperm-positive females) X 100
[e]PND = postnatal day
* Statistically different from controls at P≤ 0.05, covariate analysis (litter size as covariate)

Table 3 Results from the Two Generation Reproduction Study on Simazine (Epstein, 1991)

	Simazine Feeding Level ppm (mg/kg/day)							
	0	***10 (0.73)***	***50 (3.64)***	***500 (38.7)***	***0***	***10 (0.73)***	***50 (3.64)***	***500 (38.7)***
Parental Generation	***F0 Generation***				***F1/F1+ Generation***			
Number of mated females	30	28	30	29	23	27	27	30
Number of pregnant females	24	25	27	28	20	22	22	28
Fertility index (%)[a]	80.0	89.3	90.0	96.6	87.0	81.5	81.5	93.3
Mating index (%)[b]	100.0	93.3	100.0	96.7	76.7	90.0	90.0	100.0
Gestation index (%)[c]	100.0	100.0	100.0	100.0	100.0	95.5	100.0	96.4
Number of viable litters	24	25	27	28	20	21[d]	22	27
Mean litter size, day 0 ± SD	13.3 ± 3.78	13.6 ± 4.09	12.3 ± 4.16	13.5 ± 3.79	13.1 ± 3.93	13.4 ± 3.57[d]	13.2 ± 3.24	12.7 ± 3.97
Mean N° of still birth, day 0 ± SD	0.21 ± 0.66	0.96 ± 2.82	0.96 ± 2.01	0.25 ± 0.52	0.20 ± 0.52	0.25 ± 0.55[d]	0.59 ± 1.01	0.70 ± 2.49
Offspring Generation	***F1 Generation***				***F2***			
Number viable males, day 0	168	166	172	175	143	133[f]	153	175
Number viable females, day 0	151	173	161	203	119	135[f]	138	168
Sex ratio (% males), day 0	52.7	49.0	51.7	46.3	54.6	49.6[f]	52.6	51.0
% pups alive on PND4[d]	98.7	94.5	93.2	94.3	97.4	98.7[f]	97.5	95.4
% pups alive from PND4 to PND21	99.0	99.0	96.2	99.5	100.0	93.8[f]	99.4	96.2
Mean pup weight (g), PND 0, Males ± SE	6.48 ± 0.16	6.43 ± 0.15	6.55 ± 0.15	6.41 ± 0.15	6.44 ± 0.15	6.24 ± 0.15	6.35 ± 0.14	6.51 ± 0.13
Females ± SE	6.14 ± 0.15	6.08 ± 0.15	6.14 ± 0.15	6.15 ± 0.14	5.97 ± 0.14	5.9 ± 0.13	6.04 ± 0.12	6.22 ± 0.11
Mean pup weight (g), PND 4, Males ± SE[e]	9.45 ± 0.30	9.86 ± 0.29	9.92 ± 0.29	9.48 ± 0.28	9.44 ± 0.34	8.79 ± 0.33	9.52 ± 0.31	9.55 ± 0.29
Females ± SE[e]	9.07 ± 0.29	9.35 ± 0.29	9.46 ± 0.28	9.20 ± 0.27	9.10 ± 0.32	8.38 ± 0.30	9.00 ± 0.29	8.99 ± 0.26
Mean pup weight (g), PND 7, Males ± SE	14.75 ± 0.40	15.82 ± 0.40	15.74 ± 0.39	14.82 ± 0.37	14.93 ± 0.47	14.49 ± 0.48	15.28 ± 0.43	14.77 ± 0.40
Females ± SE	14.44 ± 0.41	14.83 ± 0.41	15.25 ± 0.40	14.34 ± 0.38	14.68 ± 0.43	13.42 ± 0.41	14.38 ± 0.38	14.06 ± 0.35
Mean pup weight (g), PND 21, Males ± SE	51.05 ± 1.13	**54.84 ± 1.12***	54.19 ± 1.10	49.39 ± 1.06	48.10 ± 1.11	48.12 ± 1.16	49.71 ± 1.05	46.33 ± 0.99
Females ± SE	50.05 ± 1.08	52.04 ± 1.08	52.03 ± 1.06	47.68 ± 1.01	46.32 ± 1.03	44.18 ± 1.02	47.50 ± 0.95	43.90 ± 0.89

[a] Fertility index = (Number of pregnant females / number of females cohabited with males) X 100
[b] Mating Index = (Number of sperm-positive females / number of females cohabited with males) X 100
[c] Gestation Index = (Number of females with live born / number of sperm-positive females) X 100
[d] PND = postnatal day [e] Precull data; * Significantly different from controls at $p \leq 0.05$

Table 4 Comparison of the Effect of Atrazine on the LH surge and the Mean Number of Corpora Lutea and Ova When Administered by Gavage or in the Diet

Indices of Ovulation Affected by the LH Surge	Dose Level (mg/kg/day)				
Long Evans-Bolus	**0**	**6**	**50**	**100**	
No. of Females Evaluated	11	12	13	11	
No. of Females Displaying LH surge	8	9	9	5	
Mean No. of corpra lutea/animal	14.4±2.6	13.7±2.5	13.5±2.2	6.3±1.9	a
Mean No. of corpra lutea/animal displaying LH surge	18.1±1.9	17.3±2.0	18.3±0.8	9.4±3.7	*
Mean No. of ova/animal	11.5±2.4	11.7±2.4	11.8±2.3	3.9±2.1	a
Mean No. of ova/animal displaying LH surge	15.8±1.3	15.2±2.0	15.4±1.8	8.2±4.0	a
	Dietary Concentration (ppm)				
Long Evans-Distributed	**0**	**160**	**660**	**1460**	
No. of Females Evaluated	11	12	11	15	
No. of Females Displaying LH surge	11	12	8	14	
Mean No. of corpra lutea/animal	15.4±1.2	17.7±0.7	17.9±1.6	13.9±1.9	
Mean No. of corpra lutea/animal displaying LH surge	15.4±1.2	17.7±0.7	19.8±0.8	14.8±1.9	
Mean No. of ova/animal	14.6±1.1	16.6±0.7	14.6±2.2	12.9±1.7	
Mean No. of ova/animal displaying LH surge	14.6±1.1	16.6±0.7	17.8±0.7	13.9±1.5	
Data are presented as mean±SEM.					
* = p≤0.05 when compared control groups (0 ppm or 0 mg/kg)					
a = Reduced but not statistically significant					

Table 5 Mean Fetal Weight, Maternal Body Change and Incidence of Skeletal Variation

	Atrazine dose (mg/kg/day)				
Atrazine Rat Teratology (1984)	**0**	**10**	**70**	**700**	
Mean fetal body weight (g) ± SD, males	3.44±0.21	3.60±0.47	3.38±0.34	1.89±0.45**	
females	3.26±0.20	3.30±0.46	3.24±0.38	1.79±0.43**	
Mean ± SD maternal body weight change (g)	61±3	59±3	53±2	-25±8	
No. fetuses (litters) with skeletal variations	203(23)	205(23)	240(25)	NE	
Percentages fetuses (litters) with skeletal variations	100.0(100.0)	94.5(100.0)	98.4(100.0)	NE	
	Atrazine dose (mg/kg/day)				
Atrazine Rat Study (1989)	**0**	**5**	**25**	**100**	
Mean fetal body weight (g) ± SD, males	3.5±0.05	3.6±0.05	3.6±0.05	3.5±0.05	
females	3.3±0.04	3.4±0.04	3.4±0.04	3.3±0.05	
Mean maternal body weight change (% of control)	100.0	96.7	96.7	79.8*	
No. fetuses (litters) with skeletal variations	181(26)	177(25)	179(24)	166(21)	
Percentages fetuses (litters) with skeletal variations	100.0(100.0)	99.4(100.00)	100.0(100.0)	100.0(100.0)	
	Atrazine dose (mg/kg/day)				
Atrazine Rabbit Study	**0**	**1**	**5**	**75**	
Mean fetal body weight (g) ± SD, males	46.1±5.5	44.0±6.1	43.2±6.0	35.7±5.8**	
females	44.0±3.7	43.3±5.4	43.1±4.5	35.8±6.2**	
Mean maternal body weight change (% of control)	100.0	64.6	51.0	18.6	
No. fetuses (litters) with skeletal variations	94(16)	80(13)	99(15)	75(14)a	
Percentages fetuses (litters) with skeletal variations	67.1(100.0)	64.5(92.9)	72.8(100)	84.3(93.3)	
	DIA or (atrazine equivalent) dose (mg/kg/day)				
Deisopropylatrazine (DIA) Rat Study	**0**	**5 (4.2)**	**5 (20.8)**	**75 (80.3)**	
Mean fetal body weight (g) ± SD, males	5.6±0.3	5.6±0.3	5.7±0.4	5.5±0.3	
females	5.3±0.3	5.3±0.3	5.3±0.4	5.2±0.3	
Mean maternal body weight change (% of control)	100.0	80.5	80.2	55.4**	
No. fetuses (litters) with skeletal variations	160(22)	155(21)	164(22)	172(23)	
Percentages fetuses (litters) with skeletal variations	100.0(100.0)	100.00(100.0)	99.4(100.0)	100.0(100.0)	
	DEA or (atrazine equivalent) dose (mg/kg/day)				
Deethylatrazine (DEA) Rat Study	**0**	5 (4.3)	25 (21.7)	100 (86.8)	
Mean fetal body weight (g) ± SD, males	5.7±0.3	5.6±0.3	5.8±0.3	5.6±0.3	
females	5.3±0.3	5.3±0.3	5.4±0.3	5.3±0.3	
Mean maternal body weight change (% of control)	100.0	97.6	89.5*	68.8**	
No. fetuses (litters) with skeletal variations	168(23)	173(23)	163(22)	158(24)	
Percentages fetuses (litters) with skeletal variations	100.0(100.0)	99.4(100.0)	99.4(100.0)	100.0(100.0)	
	DACT or (atrazine equivalent) dose (mg/kg/day)				
Diaminochlorotriazine (DACT) Rat Study	**0**	2.5 (1.7)	25 (16.9)	75 (50.7)	150 (101.4)
Mean fetal body weight (g) ±SD, males	3.45±0.06	3.45±0.06	3.43±0.06	3.14±0.06*	2.79±0.06*
females	3.29±0.05	3.32±0.05	3.29±0.05	3.03±0.05*	2.68±0.05*
Mean maternal body weight change (% of control)	100.0	103.0	102.0	97.0	56.7*
No. fetuses (litters) with skeletal variations	148(22)	150(23)	170(25)	174(25)b	133(23)b
Percentages fetuses (litters) with skeletal variations	99.3(100.0)	100.0(100.0)	100.0(100.0)	100.00(100.00)	100.00(100.00)

* Different from the control group at $p \leq 0.05$;
** Different from the control group at $p \leq 0.01$
a Significantly increased incidence of delayed ossification of certain bones and an increased incidence of resorbed fetuses.
b Significantly increased incidence of partially ossified parietals, interparietals and unossified hyoids
NE = Not Evaluated

7.0 PHARMACOKINETIC STUDIES AND PBPK MODEL

7.1 Pharmacokinetic Studies in Rats

Coder (2011b) conducted a study to explicitly characterize the pharmacokinetics of atrazine and its chlorometabolites (DEA, DIA, DACT). The study compared the pharmacokinetics of bolus doses that have been shown to suppress the LH surge in rodents and feeding doses that are more representative of the distributed dose characteristic of potential human exposure.

The results indicate that following a single gavage dose of atrazine, maximum plasma concentrations of ATZ, DEA and DIA are achieved within 0.4 to 1.25 hours and within 1.25 to 8 hours for DACT depending on the ATZ dose administered (Figure 10, Table 6).

Figure 10 Pharmacokinetic Characterization of Atrazine in Female Sprague-Dawley Rat (Coder et al., 2011b)

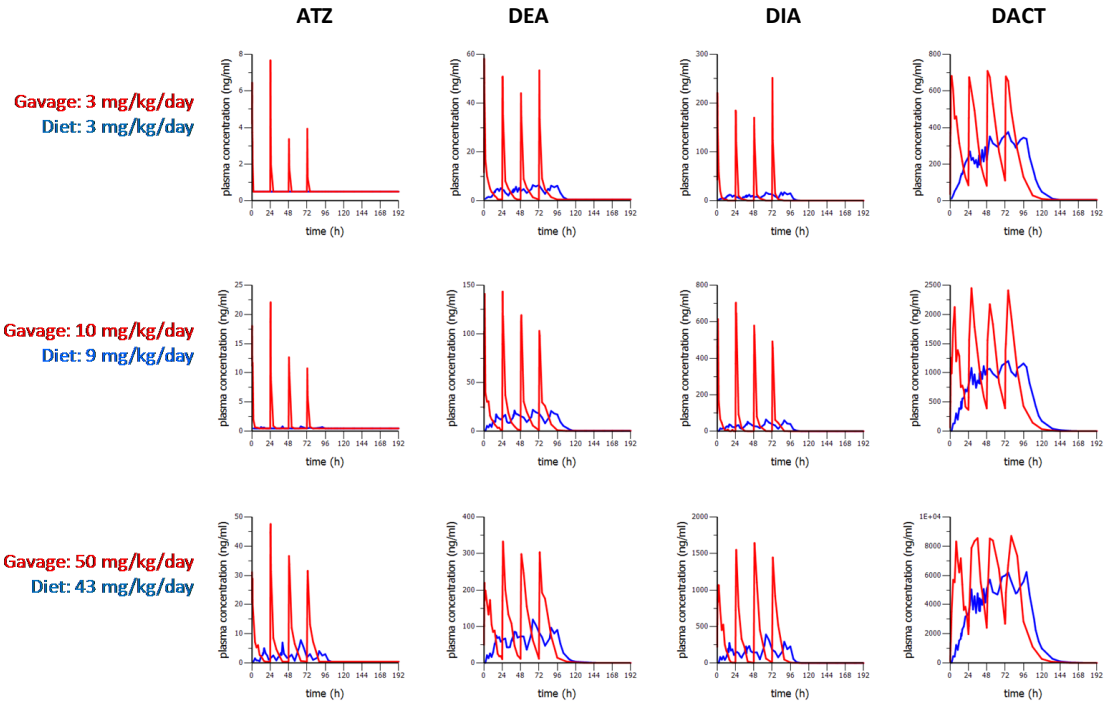


Table 6 Pharmacokinetic Parameters for ATZ, DEA, DIA and DACT in Female Sprague-Dawley Rats (Coder et al., 2011)

Parameter	ATZ			DEA			DIA			DACT		
Dose	3	10	50	3	10	50	3	10	50	3	10	50
Tmax (hrs)	0.4	0.5	0.5	0.46	0.75	0.94	0.4	0.63	1.25	1.25	4.5	8.0
Cmax(ng/ml)	5.4	15.9	36.7	51.5	126.5	288.5	207.0	597.3	1426	686.5	2290	8523
AUC(ng*h/ml)	5.9	26.3	144.3	157.5	527.3	2736	389.5	1609	8981	8840	29986	144245
Appearance (hrs)	0.17	0.17	0.08	0.17	0.50	0.38	0.17	0.50	1.00	1	3	4
Elimination (hrs)	0.4	0.7	2.3	1.3	1.8	7.0	0.9	1.2	3.9	9.7	8.3	11.5
Steady State Conc. (ng/ml)	--	--	--	--	--	138	--	--	546	395.5	1221	5516
Steady State Time(T90:hrs)	--	--	--	--	--	0.5	--	--	0.18	1.09	3.06	11.0

7.2 Pharmacokinetic Studies in Non-Human Primates

Hui et al. (2011) published the results of a pharmacokinetic study conducted for Syngenta (Hui, 1996a) that indicate that like the rodent, non-human primates display rapid clearance of ^{14}C atrazine from the plasma and rapid elimination in urine (Figure 11).

In addition to these studies, in 2011, Syngenta initiated two PK studies in cynomolgus females to characterize the kinetics of clearance of the chlorotriazine metabolites from plasma (Stuhler, 2011; Figure 12) and to identify metabolites greater than 1% of total radioactivity using exact mass spectroscopy procedures with ^{14}C labelled atrazine (Press, 2012; Figure 13). This research was commended by the USEPA Scientific Advisory Panel as state of the art and fit for characterizing potential human risk, including risks of developmental and reproductive toxicity potential based upon the neuroendocrine MOA for atrazine (USEPA, 2011b).

7.3 Pharmacokinetic Studies in Humans

Syngenta conducted a pharmacokinetic study in humans (Cheung, 1990) and submitted an updated report to EPA in 2011. The urinary elimination data for DEA, DIA and DACT was fitted with using an exponential decay function (Figure 14; Breckenridge, 2011). The concentration observed in humans was comparable to concentrations predicted based on the

rodent physiological based pharmacokinetic (PBPK) model scaled to humans as described in Section 7.4.

Figure 11 Kinetics of 14C Atrazine Plasma Clearance following an Intravenous Dose of 14C Atrazine Administered to Female Rhesus Monkey (Hui, 2011)

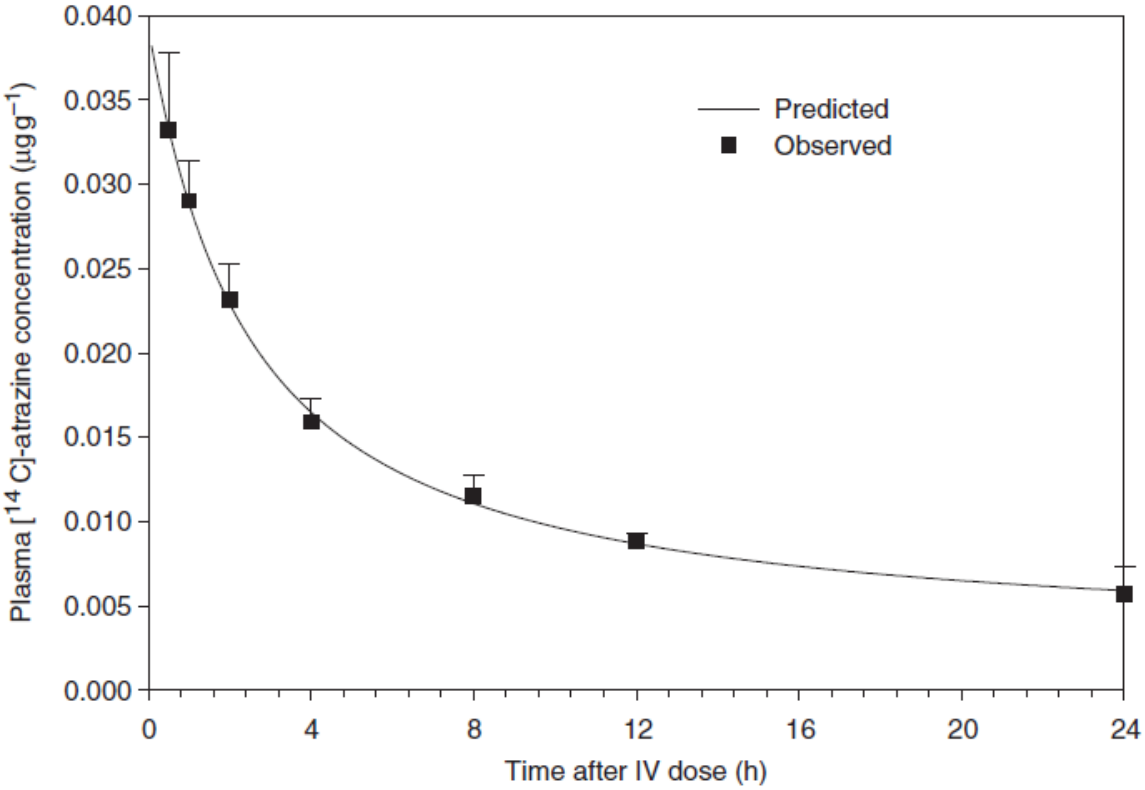


Figure 12 Plasma Clearance of Atrazine, DEA, DIA and DACT in female Cynomolgus Monkeys following a Gavage Dose of 0.125 mg/kg Atrazine in 2.5% Ethanol/Water

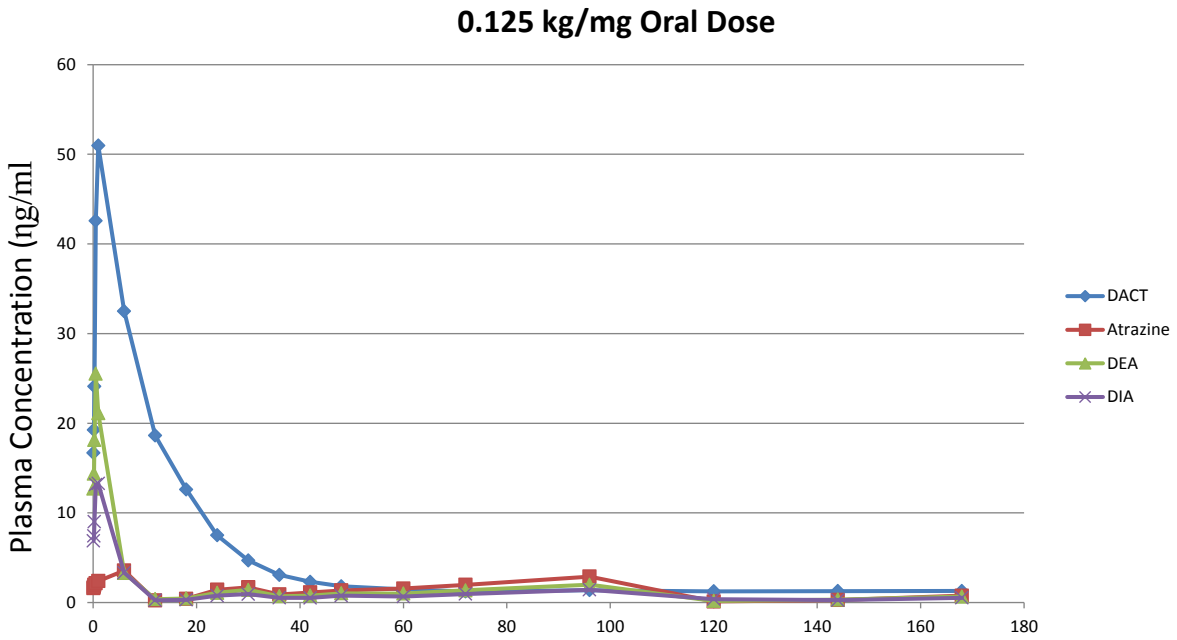


Figure 13 Clearance of Total Radioactivity from the Plasma of Female Cynomolgus Administered and Gavage Dose of 5 mg/kg Dose of 14C Atrazine

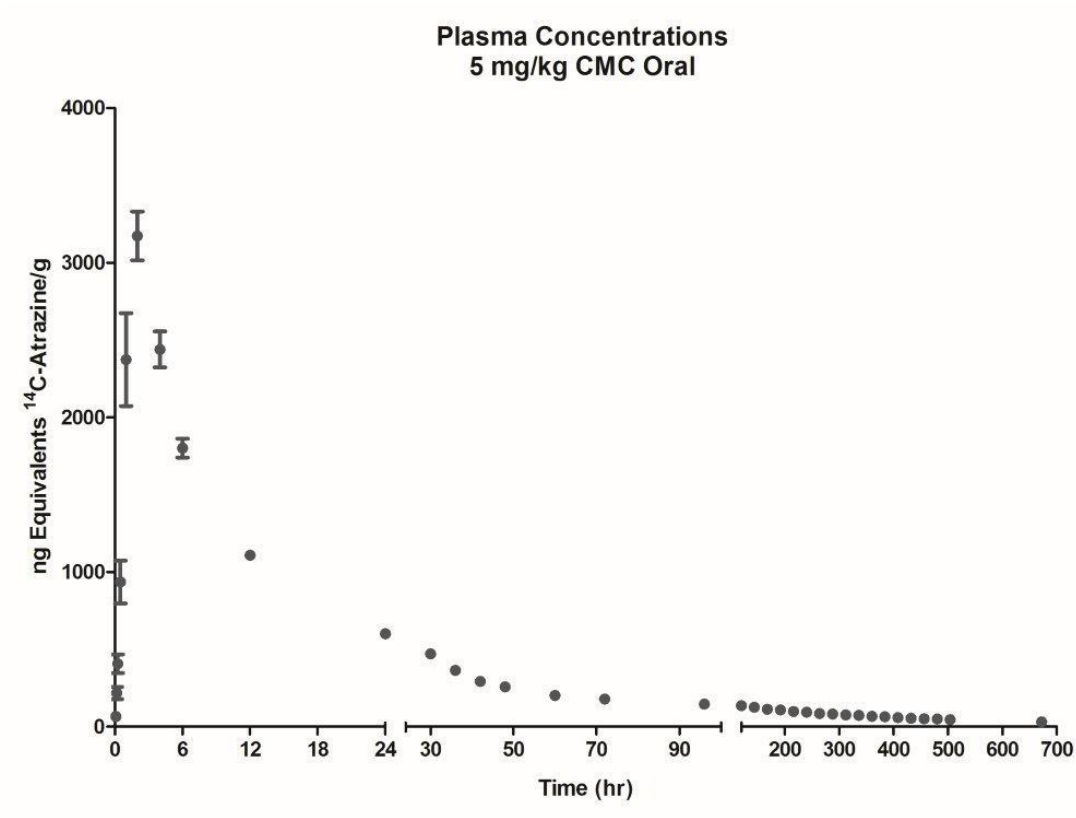
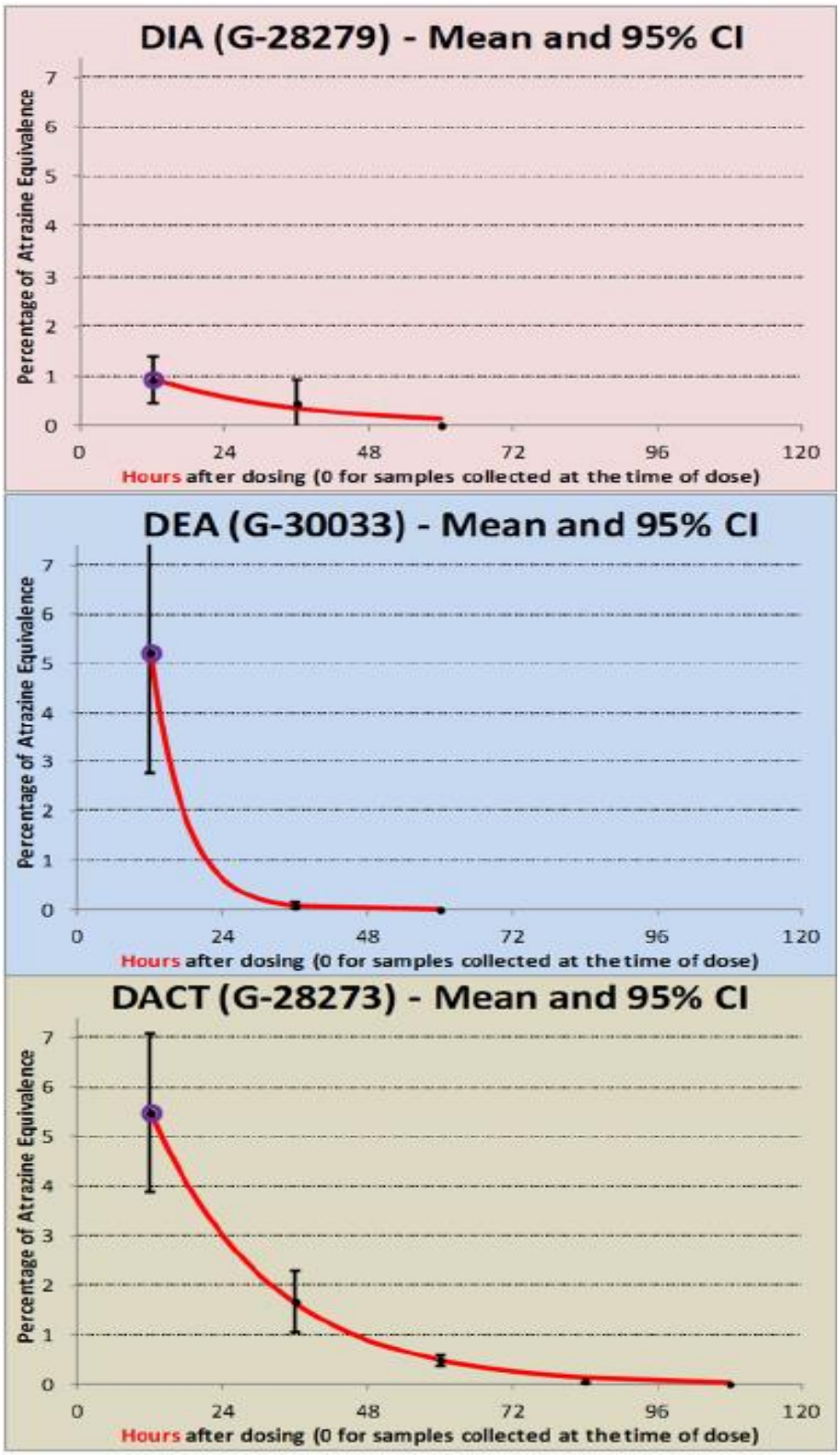


Figure 14 Average Human Urinary Elimination of DIA, DEA and DACT Following an Oral Capsule Dose of 0.1mg/kg Atrazine (From Cheung, 1990)



7.4 Physiologically Based Pharmacokinetic Model

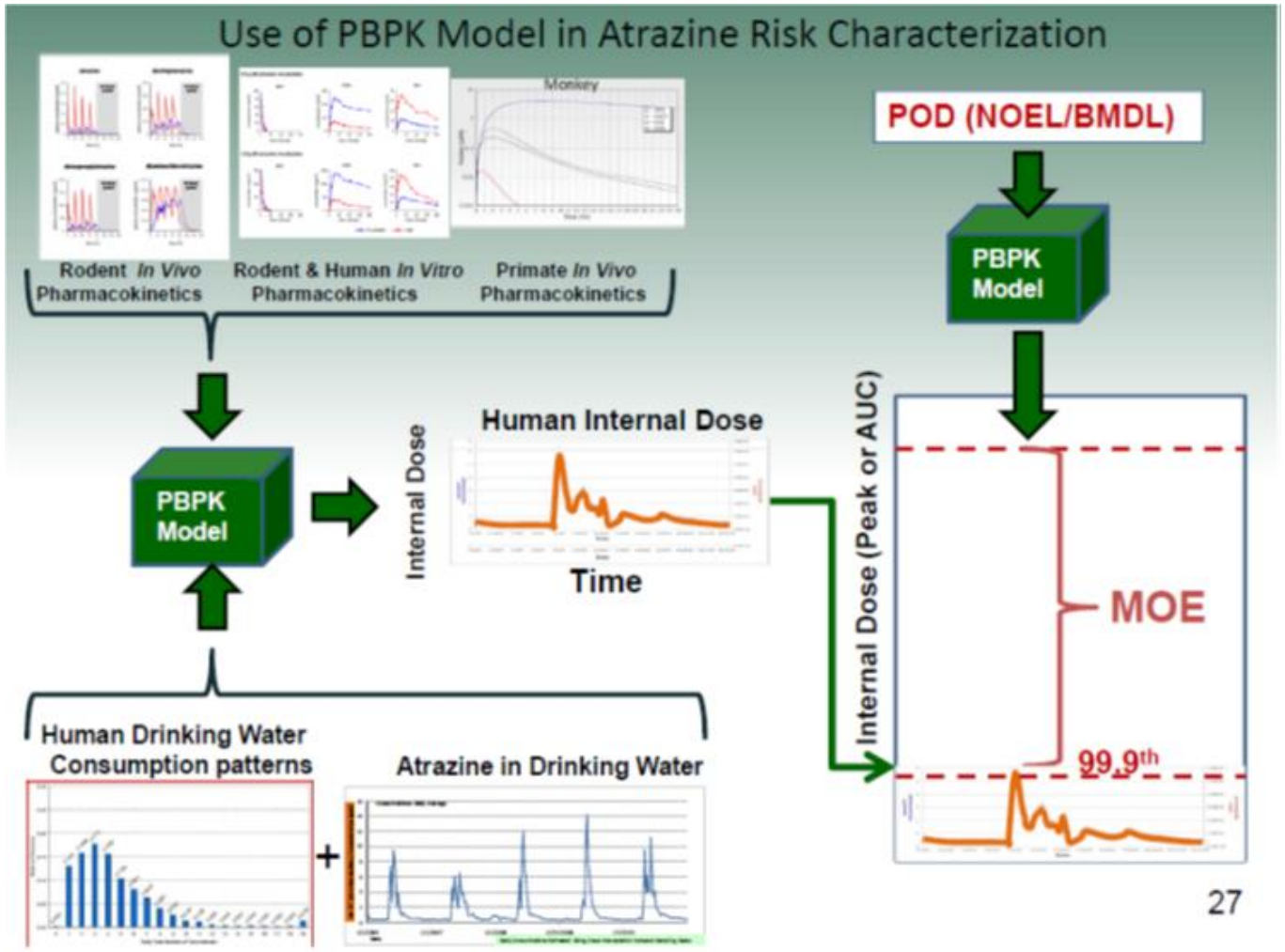
The rodent data described in Section 7.1 were used to develop a PBPK model which was scaled to humans. This model was submitted to the USEPA in 2011 (Campbell et al., 2011). The non-human primate data described in Section 7.2 will be used to recalibrate the model. The human urinary clearance data will be used to validate model predictions.

The utility of the PBPK model for the chlorotriazines in human hazard and risk characterization, which is recognized as a high tier assessment, is illustrated schematically in Figure 15 (Clewell, 2011). Using the PBPK model, a comprehensive risk assessment for the most vulnerable Community Water Systems (CWS's) in the United States, none of which were in California, was conducted (Sielken, 2011). Margins of safety were greater than 1000 at the 99.9th percentile of the risk distribution, for the most vulnerable CWS's.

To our knowledge, USEPA has not yet formally reviewed this information nor considered its implications for the assessment of human developmental or reproductive hazard or risk. However, the USEPA scientific advisory panel encouraged the EPA to utilize the model developed by Syngenta by stating:

"In general, the Panel supported the work of the Agency in pursuing a dose-response analysis based on an internal dose metric, as an alternative to administered dose in the interest of reducing uncertainty in inter-route, interspecies and intraspecies extrapolations. In the one compartment model, the Agency has attempted to maximize use of the data available to them, making mainly conservative choices in the absence of hard information and verifying estimates to the extent possible. However, it was noted that the one compartment model was proposed by EPA as an interim approach, given that a thorough review and evaluation of a recently submitted PBPK model by Syngenta has not been completed. It has also been noted by the Agency that a verified PBPK model would constitute the 'ideal approach'" (USEPA, 2011b, Paragraph 4, page 73).

Figure 15 Use of PBPK Model in Atrazine Risk Characterization (From Clewell, 2011)



8.0 CONCLUSIONS

OEHHA should not list chlorotriazines as developmental toxicants because

1) Developmental delay, as indicated by reduced fetal body weight and delayed ossification of certain bones in rodent or rabbit fetuses, only occurred at chlorotriazine doses that were toxic to the mother. The effects of maternal toxicity on developmental delay of fetuses has been described previously and is generally regarded as not reflecting a direct action of a chemical on the fetus. (Carney and Kimmel, 2007).

2) Developmental delay only occurred in fetuses whose mothers were administered bolus doses of the chlorotriazines.

3) There was no effect on fetal body weight when atrazine, simazine or propazine were administered as a distributed dose in the diet indicating that it is biologically implausible that the chlorotriazines will have developmental effects in humans exposed to the chlorotriazines in diet, drinking water or as a result of occupational or residential exposure.

OEHHA should not list the chlortriazines as reproductive toxicants because

1) Reproduction studies in rodents do not show any adverse effects on reproduction, fertility, development or the ability of next generations to successfully reproduce when the animals are exposed to the chlorotriazines in their diet, which distributes the dose throughout the entire day.

2) LH surge suppression is only observed in rodents when the animals are administered their entire daily dose within a few minutes (bolus dose) except in the 6-month study in reproductively aged SD rats. The bolus dosing scenario does not occur in humans exposed to the chlorotriazines in diet, drinking water or as a result of occupational or residential exposure and therefore, the effects observed following such dosing are not relevant to humans.

3) The chlorotriazines have a low rate of dermal absorption, do not bio-accumulate and are rapidly eliminated from plasma, urine and feces, therefore the biologically effective doses at which adverse effects were observed in rodent studies will never be achieved in humans exposed to the chlorotriazines in their diet, drinking water, or as a result of occupational use of the chemicals.

4) The endocrine response, the suppression of the luteinizing hormone (LH) surge, in rats exposed to high doses of the chlorotriazines is not in itself an adverse outcome.

5) The United States Environmental Protection Agency (USEPA) uses the effect of the chlorotriazines on LH as a conservative surrogate for potential reproductive effects in humans.

6) The biological mechanisms controlling the LH surge in rodents are significantly different than those controlling the LH surge in humans and thus the effect of the chlorotriazines on the LH surge mechanism in rodents is not relevant to humans.

7) The female rat ages reproductively in a manner that is significantly different from that of women and therefore effects of the chlorotriazines on reproductive aging in female rats are not relevant to humans.

OEHHA should not list the chlortriazines as reproductive toxicants that delay sexual maturation because

1) The effect has only been observed in rats following bolus doses of the chlorotriazines.

2) Rapid pharmacokinetics of the chlorotriazines makes it implausible that delayed sexual maturation will occur in humans.

3) Humans will not be exposed to bolus doses of atrazine through diet, in drinking water or as a result of occupational exposure to atrazine.

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ATTACHMENT C

March 21, 2014

Lauren Zeise, Ph.D.
Deputy Director
Office of Environmental Health Hazard Assessment
1001 I Street
Sacramento, California 95814

Re: *Notice of Intent to List Chlorotriazines as Reproductive Toxicants for Purposes of Proposition 65*

Dear Dr. Zeise:

This responds to a Notice of Intent to List (NOIL or Notice) atrazine, simazine, propazine and certain of their chlorometabolites (triazine compounds) as developmental and reproductive toxicants for purposes of Proposition 65, issued by OEHHA on February 7, 2014. According to the Notice, OEHHA has concluded that the United States Environmental Protection Agency (EPA), an authoritative body for purposes of Proposition 65, has "formally identified" these compounds as causing developmental and reproductive toxicity. The basis for this conclusion is several statements in certain EPA documents dated from 2002 to 2006, quoted in the NOIL. As explained below, I do not believe EPA has concluded that these compounds cause developmental or reproductive effects in humans. Rather, EPA scientists have taken certain dose-related effects noted in laboratory animal studies into account in developing precautionary and protective risk assessments for these pesticide active ingredients.

To provide context for my comments, I will provide a brief history of my professional background and experience. From 2007 to 2010 I was the Director of the Office of Pesticide Programs (OPP) at EPA. In that role, I supervised over 800 employees within Divisions with responsibility for assessing human and ecological risks and for making risk management decisions related to pesticide product registration, reregistration and compliance with the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) as well as the Federal Food, Drug and Cosmetic Act (FFDCA), both of which were amended in 1996 by the Food Quality Protection Act (FQPA).

I joined EPA's Office of Pesticide Programs in 1985 and was employed there for over 24 years, where I held several other senior level management and executive positions, including Director of the Risk Characterization and Analysis Branch, Associate Director of the Health Effects Division, Associate Director of the Antimicrobial Division, Director of the Registration Division and Director of the Special Review and Reregistration Division. Thus, I believe I am well-qualified to speak with authority on the subject of how EPA approaches the evaluation and regulation of pesticides.

As the basis for the opinions expressed in this letter, I have reviewed the NOIL and the EPA statements and documents referred to in the NOIL. I also have reviewed pertinent portions of the Proposition 65 regulations at Title 27 of the California Code of Regulations, in particular Section 25306, which provides for listing chemicals as

reproductive toxicants on the basis of their "formal identification" by authoritative bodies, such as EPA.

In the NOIL, OEHHA lists a number of OPP documents dated 2002 to 2006 that relate to tolerance reassessment and reregistration of the triazine compounds. OEHHA quotes statements from these documents, describing adverse reproductive and developmental effects observed in animals dosed with triazines, and notes that EPA has calculated reference doses on the basis of the animal studies in which these effects were observed. OEHHA appears to conclude from these statements and the fact that EPA calculated reference doses based on these observations that EPA "formally identified" the triazines as causing developmental and reproductive toxicity in humans.

OEHHA's conclusion that EPA has identified triazine pesticides as causing developmental and reproductive toxicity in humans is inaccurate and appears to be based on a fundamental misunderstanding of EPA/OPP's role and approach to the regulation of pesticides. To explain, EPA does not follow a strictly hazard-based approach to regulation, but rather uses the National Research Council's four-step ***risk assessment*** process, as follows:

- **Step 1 - Hazard Identification**
  Examination as to whether a substance has the *potential* to cause harm to humans and/or ecological systems and, if so, under what circumstances.
- **Step 2 - Dose Response Assessment**
  Examination of the numerical relationship between exposure and effects.
- **Step 3 - Exposure Assessment**
  Examination of what is known about the frequency, timing, and levels of contact with a substance.
- **Step 4 - Risk Characterization**
  Examination of how well the data support conclusions about the nature and extent of the risk from exposure to pesticides.

EPA's approach to risk assessment is highly protective. In fact, I can think of virtually no currently EPA-registered pesticide product for which it can be said that harm to humans is expected to occur. Simply put, EPA's routine risk assessment and regulatory process is intended to preclude any such outcome by extrapolating from levels and routes of exposure where adverse effects were observed in animals and restricting conditions of use by law to levels where exposure to humans will be far lower, *i.e.*, orders of magnitude lower, than the levels to which the test animals were dosed. Thus, barring gross negligence or illegal use, no harm to humans should occur.

It is important to emphasize that the first step of EPA's four-step risk assessment process is *not* the equivalent of the "hazard identification" process contemplated by Proposition 65. The Prop 65 hazard identification process is focused on reaching a conclusion whether the chemical in question is "known," or "clearly shown" to cause cancer or reproductive harm in humans, based on the weight of all available scientific evidence. Chemicals that meet that standard are published on a list as "known" to cause

the harm in question. Where such a potential listing is based solely on animal data, the animal data are to be carefully scrutinized to determine whether the effects seen in animals are sufficient evidence to conclude that the chemical would cause the same effects in humans. The factors to be considered in scrutinizing the animal data are summarized in Title 27 CCR Section 25306(g), which, I understand from reviewing the "Statement of Reasons" explaining the intent of the regulations, is intended to ensure that chemicals listed by the "authoritative bodies" mechanism meet the same standards of sufficiency of evidence that are applied by the "state's qualified experts" when they review chemicals for potential listing.

The "hazard identification" step of the EPA risk assessment process, as the first of four steps in risk assessment, is not intended to involve such a careful weighing of the animal data to determine whether the data support "listing" or "formally identifying" a chemical as causing reproductive harm in humans. It simply identifies adverse effects, observed in laboratory animals, which may have the ***potential*** to cause harm in humans and for which the risk of harm is to be assessed and mitigated by regulatory measures. In step two , EPA scientists examine the relationships between dosing levels, *i.e.,* exposure, and adverse effects observed. EPA then applies additional uncertainty factors to appropriately selected "No Observable Adverse Effects Levels" (NOAELs) in establishing benchmark values for risk assessment purposes. These uncertainty factors, intended to account protectively for potential increased sensitivity in humans and/or within a population, generally yield "acceptable" exposure values that are 2-3 orders of magnitude lower than the NOAELs selected for use in assessing risk. Step 3 then involves estimation of potential high-end, real-world exposures to the chemical for comparison to the acceptable levels identified in step 2. A characterization of risk then occurs in step 4, taking into account a number of factors including data quality, uncertainties, populations exposed, etc.

The objective of this entire process is to ensure that humans will experience *no harm* from use of the chemical. That end result of the four-step process, protection of humans based on multiple conservative assumptions, is EPA's focus.

My review of the EPA documents OEHHA has cited in the NOIL shows that they are consistent with the foregoing general discussion. The documents contain various statements indicating that the effects have been observed in animals, and that EPA is regulating the triazines on the basis of such effects on the assumption that similar effects in humans are possible. The documents nowhere state that EPA has concluded that the triazines *will* cause such effects in humans, only that EPA believes such effects are ***possible*** and as long as the possibility exists, EPA will ensure that human exposures are below the levels at which adverse effects are even possible. In taking such a conservative, protective approach, EPA has not "formally identified" the triazines as reproductive toxicants.

The EPA documents cited by OEHHA all were generated in the course of EPA's reregistration and tolerance reassessment programs, which were mandated by the FQPA in 1996 and essentially completed in 2006. The passages quoted from these EPA documents are taken out of context, as they relate solely to the first step of EPA's risk assessment process (Step 1) and are simply consistent with the fact that EPA considers

and evaluates pesticides and candidate pesticides for all ***potential*** adverse effects observed at doses tested in animal studies. It is a virtual truism that adverse effects will be observed in these studies, because EPA test guidelines specify that dosing regimens must elicit an adverse effect (or a "limit dose," in the absence of achieving a maximum tolerated dose). Thus, when adverse effects are observed, EPA does not then conclude that exposure to the chemical will "cause" adverse effects in humans, but rather completes the remaining steps of the routine risk assessment process and regulates accordingly to avoid any adverse effects or "harm." In the case at hand, to my knowledge, EPA has never stated that it expects reproductive or developmental effects to occur in humans under actual conditions of legal sale and use of triazine pesticide products.

In 2006, EPA completed decision-making processes for reassessing tolerance and reregistration decisions for all of the triazine pesticide active ingredients, based upon safety standards under both FIFRA and the FQPA. The FQPA is indisputably one of the most protective/precautionary environmental statutes in existence. The standard for safety is "reasonable certainty of no harm" and, in effect, does not even include a provision for balancing risks against benefits, as does FIFRA. In 2006, EPA concluded that for purposes of the FQPA, taking into account the estimated cumulative exposures of ***all*** triazine pesticides through diet, drinking water and any residential use, there existed a reasonable certainty of ***no harm.***

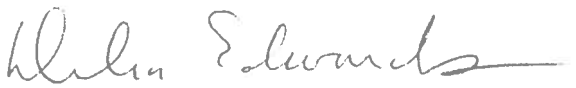
In my opinion, EPA/OPP's scientifically rigorous and highly protective risk-based approach to regulating pesticides runs counter to the simplistic approach of labeling chemicals as "known to cause cancer" or "known to cause reproductive toxicity" under Proposition 65. The two approaches are so dissimilar that it is inappropriate to use isolated statements from evaluations of animal studies in the absence of a firmly stated conclusion, as the basis for designating a chemical as a reproductive toxicant for purposes of Proposition 65.

Finally, I believe there is a compelling policy reason why EPA's statements and actions in 2006 should not be used as the basis for an "authoritative body" listing. Though a comprehensive reevaluation process for the triazines was concluded successfully in 2006, EPA has recently initiated its "Registration Review" process for the triazines. Registration Review is EPA's newest reevaluation program for pesticides and requires periodic reevaluation of the risks and risk management needs associated with all pesticide products. The legal mandate is for reevaluation at least every 15 years. For example, in December of 2013, EPA published its Final Work Plan for the Registration Review of atrazine. This work plan indicates that EPA intends to fully ***re***assess the human and ecological risks associated with ***all*** uses of these chemicals as active ingredients pesticides and will make those risk assessments available for public comment as early as June of 2015, ***i.e.,*** little more than one year from now.

This comprehensive reevaluation of the triazines, currently ongoing, also provides a compelling reason not to pursue any determination of whether these chemicals should be listed as reproductive toxicants for purposes of Proposition 65, on the basis of evaluations conducted in 2006. In my view, it would be highly prudent to carefully consider EPA's more recent risk assessments, based in current science, prior to assuming

any "known" or "causal" relationship between human exposure to triazines and reproductive or developmental effects. If EPA's new risk assessments indicate ***any*** concern whatsoever that these compounds might result in adverse effects in humans, the Agency will certainly require changes in the registered use patterns to preclude that possibility.

Sincerely yours,



Debra Edwards, Ph.D.
Pesticide Regulatory Consultant
Former Director, Office of Pesticide Programs/EPA

ATTACHMENT D

1206 North Jefferson Street
Arlington, VA 22205-2413
March 22, 2014

Lauren Zeise, Ph.D.
Deputy Director
Office of Environmental Health Hazard Assessment
1001 I Street
Sacramento, California 95814

Re: Comments in Opposition to Potential Listing of Triazine Compounds as Reproductive or Developmental Toxicants Under Proposition 65

Dear Dr. Zeise:

OEHHA has issued a Notice of Intent to List (NOIL) atrazine, simazine, propazine and certain of their chlorometabolites (triazine compounds) as developmental and reproductive toxicants on the basis that the United States Environmental Protection Agency (EPA), an authoritative body for purposes of Proposition 65, has "formally identified" these compounds as causing developmental and reproductive toxicity in certain EPA documents dated from 2002 to 2006, which OEHHA has listed and selectively quoted in the NOIL. I do not believe EPA has concluded that these compounds cause developmental or reproductive effects in humans.

I am well qualified to speak with authority on the subject of how EPA evaluates the human health effects of pesticides. I spent 31 years working as a toxicologist at the Environmental Protection Agency, the last 26 in the Office of Pesticide Programs. From 2005-2011, I was the Director of the Health Effects Division (HED), responsible for human heath risk assessments for all conventional pesticides. Therefore, I oversaw, at the executive level, the development of many of the triazine documents referenced in the NOIL. In addition, for several years before becoming the Director of HED, I served on the Hazard Identification Assessment Review Committee, HIARC, which was responsible for overseeing endpoint selection for HED's risk assessments.

EPA/OPP is not required to "formally identify" hazards as part of its regulatory process. Rather, it must make a finding of "reasonable certainty of no harm" in order to establish tolerances for residues of pesticides on food. To do so, a highly protective risk-based approach to regulating pesticides has been developed, very different from a simple

identification of hazard. The routine approach to pesticide risk assessments involves the evaluation of animal toxicity studies. There is an assumption that these studies indicate what could possibly happen in humans. Without this assumption, there would be no way to do the risk assessment and make the finding of "reasonable certainty of no harm." However, the risk assessment only evaluates a potential risk. No final determination of risk or hazard is implied by the process.

Hazard identification has long been considered the first step in risk assessment, hence the name of the HIARC committee. But as practiced in HED, hazard identification is really endpoint selection, as opposed to a definitive identification of hazard. The use of a NOAEL from a study that found an effect at some higher dose does not constitute a determination that the chemical poses a hazard of a particular type to humans. Many pesticides show little mammalian toxicity in their database, but endpoints are chosen and a risk assessment is done based on NOAELs.

The risk assessment process follows a classic series of steps: all the toxicity studies are reviewed, exposure pathways are articulated, the endpoints from the various studies that fit the exposure scenarios are evaluated and the most protective endpoints are chosen to form the basis of the risk assessment. The exposures are calculated and compared to the doses determined to be acceptable. Frequently, expected exposures are acceptable despite protective endpoints and exposure assumptions, and no further work is needed. If problems are identified, there can be refinement of the risk assessment and this is where there are sometimes considerations of Modes or Mechanisms of Action and relevance to humans. But on a routine basis, the process is protective and without deep judgment as to whether the study is relevant to humans, is truly adverse, etc. This was certainly true during the heavy workload leading to meeting the deadline for reregistration under the Food Quality Protection Act of 1996 (FQPA), when the cited documents were developed. While sometimes frustrating to registrants, this process is highly protective of human health and is generally considered the best use of Agency resources.

The language EPA uses in its regulatory documents is assertive. The documents are written as if the effects seen in animals will occur in humans. That is the nature of regulatory language. Taken at face value they appear to denote a certainty that is not necessary for the regulatory process to go forward. For EPA, it is enough that there is potential risk for the risk assessment and regulatory action to be justified. No definitive formal assessment of the hazard is required.

The documents cited in the OEHHA listing are relatively old. The HIARC document on atrazine/DACT was written in 2002. Unlike most pesticide risk assessments, the triazine assessments looked at much non-standard laboratory data on purported precursor endocrine disrupting events as the basis for the risk assessment. There continues to be

much data generation and review activity surrounding these data. While I was the HED Division Director there were several Scientific Advisory Panel meetings to discuss these data. At that time, the conclusion of these meetings was that the current risk assessment was protective. However, the review of the triazines is continuing through the Registration Review process, the periodic reevaluation of pesticides every 15 years mandated by FQPA. The triazines are scheduled for registration review in 2015. Clearly, no final determination of hazard or risk around these chemicals has been made.

Sincerely yours,

Tina E. Levine

Tina E. Levine, Ph.D.

ATTACHMENT E

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March 21, 2014

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Subject: Comments in Opposition to Potential Listing of Atrazine, Simazine, Propazine, and Associated Metabolites as Reproductive or Developmental Toxicants under Proposition 65's Authoritative Bodies Listing Mechanism

Dear Dr. Zcise:

On February 7, 2014, California's Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Intent to List (NOIL) atrazine, simazine, propazine, and their associated chlorometabolites (triazine compounds) as developmental and reproductive toxicants on the basis that the United States Environmental Protection Agency (EPA or the Agency), an authoritative body for purposes of Proposition 65, has "formally identified" these compounds as causing developmental and reproductive toxicity in certain EPA documents dated between 2002 and 2006, which OEHHA references and selectively quotes from in thc NOIL. As discussed below, **these compounds should not be listed under Proposition 65.**

PERSONAL BACKGROUND

I am a principal at Exponent and the Director of its Washington, DC office. Exponent is an engineering, scientific and regulatory consulting firm. I have more than 45 years of government and consulting experience dealing with hazard and risk assessment, and the regulation of pesticides, chemicals, foods, drugs, and consumer products. I recognize and understand the importance of using sound science to regulate risk and the need to effectively communicate potential hazards to a variety of audiences including consumers.

I spent 22 years working for three Federal agencies: The US Food and Drug Administration (FDA), the US Consumcr Product Safety Commission (CPSC), and the US Environmental Protection Agency (EPA). I began my government career as a food and drug inspector with FDA. I also served as a program analyst writing compliance programs for FDA field and compliance personnel. Following my FDA experience, I worked at the CPSC in a variety of senior positions that focused primarily on injury investigation and regulatory and compliance activities related to consumer products.

At EPA, I served in three different positions. I began my EPA career as the Deputy Director of the Office of Toxic Substances. In that position, I was responsible for the implementation and management of the Toxic Substances Control Act and its supporting regulations.

Subsequently, I moved to EPA's Office of Pesticide Programs (OPP). I spent several years as the director of OPP's Registration Division. At that time, the Registration Division was responsible for three major programs: The registration of pesticide products, the reregistration (now called registration review) of pesticides, and the special review activity. I completed my time at EPA by then becoming the Director of OPP's newly created Special Review and Reregistration Division, which was responsible for those two named activities.

As a Division Director in EPA's Office of Pesticide Programs, I was responsible for making or recommending risk management (regulatory) decisions. Based on substantial amounts of data and information, OPP science divisions developed hazard and exposure assessments which were combined into risk assessments. Such risk assessments evaluated potential human, ecological and environmental risks. Risk and benefit information was then considered in order to weigh possible risks and potential benefits associated with the use of pesticides. Based on the entire body of data and assessments of those data, regulatory decisions were made. These decisions focused on whether or not to register a pesticide, whether or not to continue (reregister) a pesticide, and whether or not to conduct a special review and/or cancellation proceeding that could lead to the cancellation of a pesticide registration. As discussed below, the comprehensive assessment and decision making process was, and is, based on the consideration of potential risk rather than the formal designation of a pesticide as any sort of toxicant.

REASONS WHY THE TRIAZINE COMPOUNDS SHOULD NOT BE LISTED UNDER PROPOSITION 65

The triazine compounds should not be listed under Proposition 65 as developmental or reproductive toxicants for the following reasons:

1. EPA has no statutory or regulatory mandate or authority to formally identify pesticides as toxicants.

2. OEHHA cannot rely on EPA's hazard identification and risk assessment process.

3. OEHHA cannot rely on EPA registration review (reregistration) documents.

Each of these reasons is discussed below.

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1) EPA Has No Statutory or Regulatory Mandate or Authority to Formally Identify Pesticides as Toxicants.

EPA's Office of Pesticide Programs regulates pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA). The Agency has issued regulations under each of those statutes (40 CFR 150-189). In addition, EPA provides guidance and policy documents that are available on the Agency's website.

FIFRA is a licensing statute. A registrant (holder of a pesticide registration) cannot sell or distribute a pesticide unless the product has been registered by EPA.

EPA requires that substantial amounts of data be submitted to support an application for registration. Studies include toxicology, residue and product chemistry, environmental fate, ecotoxicology, and exposure studies. Agency scientists review submitted studies and other available information, and conduct risk assessments that consider possible risk issues. If risks are acceptable, EPA grants the registration.

In addition, under the FFDCA, the Agency must establish a tolerance for any food use of a pesticide. A tolerance is the allowable level of a pesticide in or on food. EPA reviews residue data and considers potential dietary risk from the use of a pesticide. EPA cannot establish the tolerance and thus cannot grant the registration unless the use of the pesticide meets the **FFDCA statutory safety standard of a reasonable certainty of no harm.**

There are statutory mandates that require registrations and tolerances for pesticides. EPA has issued regulations covering both of these activities through notice and comment rulemaking as required by the Administrative Procedure Act. Thus, there are formal requirements, procedures and policies that govern the granting of registrations and the establishment of tolerances.

There is no statutory mandate that requires or authorizes the Agency to develop and issue a list of developmental or reproductive toxicants. There is no process for formally identifying pesticides as developmental or reproductive toxicants. Such designations are not the role of the EPA.

The EPA pesticide program is focused on the assessment of possible risk, coupled with the mitigation of such potential risk by use restrictions and safety requirements. When EPA grants a food use registration and establishes a tolerance for that use, the Agency is making a finding that, within a reasonable certainty, humans will be exposed to essentially no risk. This statutory and regulatory framework does not involve a formal and definitive identification of a pesticide as a particular kind of toxicant known to cause toxicity in humans.

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2) OEHHA Cannot Rely on EPA's Hazard Identification and Risk Assessment Process.

The typical EPA pesticide risk assessment process includes hazard identification, dose-response, exposure assessment, and risk characterization phases. EPA's hazard identification process is far different than OEHHA's hazard identification activity.

OEHHA's Proposition 65 hazard identification activity involves a weight of the evidence review of available information and data targeted toward a determination of whether or not a chemical has been clearly shown to cause cancer or reproductive effects in humans. That is, is there enough evidence to determine that the chemical is known to cause such effects and should therefore be formally listed by OEHHA as a known toxicant.

EPA's hazard identification step in its risk assessment process stands in sharp contrast to the OEHHA system. EPA is not attempting to determine whether a pesticide should be listed or formally identified as being known to cause effects in humans. Rather, EPA uses the hazard identification step to review available animal toxicity studies and identify adverse effects which may present potential or possible risk in humans. Based on that review, the Agency selects an appropriate no observed adverse effect level (NOAEL) for risk assessment purposes. EPA then proceeds from the hazard identification phase through the next three phases of its risk assessment process which it must do to determine whether anticipated exposures of a food use pesticide meet the required reasonable certainty of no harm safety standard.

To determine whether or not a pesticide use meets that safety standard, the Agency utilizes each of the four steps in its risk assessment process, but is focused on the end result of the last risk characterization phase. Rather than formally identifying a pesticide as a particular kind of toxicant, EPA looks at a variety of toxicology endpoints. The Agency selects the lowest available NOAEL from the suite of NOAELs in animal toxicology studies, and uses that number for risk assessment purposes. For EPA, a risk is acceptable if potential exposure is less than a calculated reference dose (RfD), where the RfD is determined by dividing the selected NOAEL (i.e., a dose with no observed toxicity) by whatever safety or uncertainty factors (usually 100 to 1,000) are considered adequate by the Agency. Thus, the reasonable certainty of no harm standard is met if anticipated exposures are 100 to 1,000 times (two to three orders of magnitude) less than the most sensitive NOAEL in a suite of toxicology studies. If the safety standard is met, the Agency has determined there is a reasonable certainty of no risk to humans. EPA can then grant or continue a registration and can establish or continue a tolerance. If the standard is not met, the food use cannot be approved unless risk can be mitigated (e.g., reduce the application rate of the pesticide) so that the safety standard is met.

OEHHA's mandate is to use hazard identification information as the basis for providing hazard information to consumers and other stakeholders. EPA's pesticide program uses information from each of the four risk assessment steps to evaluate and respond to possible or potential risks that may be presented by pesticide products.
Different mandates and responsibilities lead OEHHA and EPA to act differently. Both OEHHA and EPA have important but very different public health roles. The focus of EPA is on risk

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assessment and risk mitigation whereas OEHHA is focused on formally identifying and communicating hazards. EPA does not formally identify or list toxicants.

3) OEHHA Cannot Rely on EPA Registration Review (Reregistration) Documents.

EPA's pesticide registration review program (formerly called reregistration) has been ongoing since the 1970's. The current registration review program requires that each pesticide be reviewed every 15 years. As science evolves, new data requirements are put in place, and older studies may no longer meet current scientific standards. As a result the database supporting the use of a pesticide needs to be upgraded periodically. Once again, the focus of the Agency's registration review program is not on hazard identification and hazard communication related to the formal identification of pesticides as toxicants that are known to cause toxicity in humans. Rather, EPA requires new studies, conducts new risk assessments, and determines whether the uses of a pesticide meet the reasonable certainty of no harm standard or whether possible risks must be mitigated through cancellation or adjustments of some or all of the uses of the pesticide to achieve a reasonable certainty of no human risk.

As in the case of registration and tolerance setting, EPA conducts a registration review to ensure that the uses of a pesticide meet that safety standard. The Agency is not formally identifying any pesticide as a particular kind of toxicant known to cause toxicity to humans. EPA did not formally identify the triazine compounds as developmental or reproductive toxicants in the registration review and tolerance reassessment documents referenced by OEHHA.

CONCLUSIONS

EPA's Office of Pesticide Programs is a technically competent authoritative body that bases regulatory decisions on a rigorous assessment of possible risks. The Agency focuses on whether or not food use pesticides such as the triazine compounds meet the FFDCA safety standard of a reasonable certainty of no harm. EPA's OPP does not formally identify pesticides as developmental or reproductive toxicants. Formally identifying pesticides as particular types of toxicants is neither the mandate nor the function of EPA under either the FFDCA or FIFRA. The statutory responsibility of EPA's OPP is to make regulatory decisions based on the conservative assessment of potential risk; it is not to develop lists of toxicant pesticides.

For the reasons discussed, OEHHA cannot rely on EPA statements concerning the triazine compounds as developmental or reproductive toxicants. **While EPA is an "authoritative body", it does not formally identify pesticides as developmental or reproductive toxicants.**

Sincerely,

Edwin F. (Rick) Tinsworth

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ATTACHMENT F

SCIENCE TO INFORM, L.L.C.
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March 21, 2014

Lauren Zeise, Ph.D.
Deputy Director
Office of Environmental Health Hazard Assessment
1001 I Street
Sacramento, California 95814

Re: *Notice of Intent to List Chlorotriazines as Reproductive Toxicants for Purposes of Proposition 65*

Dear Dr. Zeise:

I write in response to the February 7, 2014 Office of Environmental Health Hazard Assessment (OEHHA) Notice of Intent to List (NOIL or Notice) atrazine, simazine, propazine and certain of their chlorometabolites (triazine compounds) as developmental and reproductive toxicants for purposes of Proposition 65. In the Notice, OEHHA concludes that the United States Environmental Protection Agency (EPA), an authoritative body for purposes of Proposition 65, has "formally identified" these compounds as causing developmental and reproductive toxicity based on material from EPA documents dated from 2002 to 2006, quoted in the NOIL.

In my opinion as a former Deputy Director of the Health Effects Division of EPA's Office of Pesticide Programs (OPP), these documents do not show that EPA has concluded that these compounds cause developmental or reproductive effects in humans. Rather, they show that OPP has taken a precautionary approach in noting certain dose-related biological responses observed in laboratory animal studies, and used this information as reference points in imposing regulatory requirements to protect against the risk of potential adverse effects that might be caused in human populations by these pesticide active ingredients.

By way of background I was Deputy Director of OPP's Health Effects Division from 2009-2011, with responsibility for the efforts of the OPP health scientists preparing the risk assessments and other related evaluations conducted to inform decisions about the registration review of pesticides. During this time, OPP undertook a re-evaluation of the human health effects of atrazine. This review included three Scientific Advisory Panel (SAP) meetings in 2010 and one in 2011.

During the course of my 33 year career at EPA I served in a variety of other positions, including Acting Division Director of the Neurotoxicology Division (2007-2009) and Assistant Lab Director for Toxics & Pesticides (2002-2007) within the National Health and Environmental Effects Research Laboratory in the Office of Research and Development, as Deputy Staff Director of the Science Advisory Board (1995-2002) among other positions. I also served as Science Advisor to Senator Daniel Patrick Moynihan (1992-1994).

During the preparation of this letter, I reviewed the pertinent portions of the Proposition 65 regulations under Title 27 of the California Code of Regulations. In particular, I have reviewed Section 25306 of that Title, which provides for listing chemicals as carcinogens or reproductive toxicants on the basis of their "formal identification" by authoritative bodies, such as EPA. Of course, I also reviewed the NOIL and the EPA statements and documents that it refers to. In addition, I have read the statements by Debra Edwards, a past Director of the OPP, and Rick Tinsworth, a former Director OPP's Special Review and Reregistration Division.

Based on this information, I agree with the opinions expressed in the statements by Drs. Edwards and Tinsworth: OEHHA's conclusion that EPA identified triazine pesticides as causing developmental and reproductive toxicity in humans is inaccurate, and is based on a misunderstanding of OPP's approach to the regulation of pesticides; given the FQPA safety standard of "reasonable certainty of no harm," OPP's approach to regulating chemicals to ensure the safety of humans runs counter to the simplistic approach of labeling chemicals as "known to cause reproductive toxicity."

I also have noted, as Dr. Edwards observed, that the Final Workplan for the Registration Review of atrazine, published on December 31, 2013, calls for the review of atrazine to be conducted during 2014 and completed in 2015. In light of this, I believe that EPA statements and actions in 2006 should not be treated as "final." Rather, they are under re-evaluation at this very time. Accordingly, it appears inappropriate to use EPA statements and actions in 2006 as the basis for an "authoritative body" listing. As Dr. Edwards states: "...it would be highly prudent to carefully consider EPA's more recent risk assessments, based in current science, prior to assuming any "known" or "causal" relationship between exposure to triazines and reproductive or developmental effects."

These professional experiences that I referred to above have provided me with an understanding of how EPA uses data, including data from tests on laboratory animals to conduct risk evaluations to inform regulatory and other decisions, and I understand the uncertainties and other limits of such data used when assessing potential hazard and potential risk. EPA has developed policies on planning and scoping and risk characterization because environmental legislation at both the federal and state level has been drafted at different times and for different purposes. Experience has shown that risk assessments conducted for one purpose are not necessarily appropriate for other purposes.

Here, for reasons explained above, statements and observations from EPA during the EPA risk assessment process for regulating pesticides, and in particular the triazine compounds, appear to an inappropriate basis for determining that these pesticides have been "formally identified" as reproductive toxicants for purposes of Proposition 65.

Sincerely,

John R. Fowle III, Ph.D., DABT
Principal
Science to Inform, LLC

ATTACHMENT G

Technology Sciences Group Inc.
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20036

Gary J. Burin, Ph.D., DABT
Senior Managing Toxicologist

March 21, 2014

Lauren Zeise, Ph.D.
Deputy Director
Office of Environmental Health Hazard Assessment (OEHHA)
1001 I Street
Sacramento CA
95812-4010

Re: **Comments of Gary Burin, Ph.D., MPH, DABT in Opposition to Potential Listing of Atrazine as a Reproductive or Developmental Toxicant under Proposition 65's Authoritative Body Listing Mechanism**

Dear Dr. Zeise,

OEHHA proposes to list atrazine as a developmental and reproductive toxicant because it concludes that the US Environmental Protection Agency (US EPA), an authoritative body for purposes of Proposition 65, has formally identified atrazine as causing reproductive toxicity under the California Code of Regulations Title 27, Section 25306(d). There are compelling reasons why this listing should not occur at the present time and I discuss these reasons below.

By way of background I am familiar with the US Environmental Protection Agency evaluation of reproductive and developmental toxicity because I worked at the US EPA for 13 years and during my employment I served as the Chairman of the Developmental and Reproductive Toxicity Peer Review Committee for the US EPA Office of Pesticide Programs. I also served as a member of the US EPA working groups that authored the 1991 Guidelines for Developmental Toxicity Risk Assessment (Federal Register 56(234): 63798-63826) and the 1996 Guidelines for Reproductive Toxicity Risk Assessment (Federal Register 61(212): 56274-56322).

First, it should be recognized that the US EPA Office of Pesticide Programs does not formally identify a chemical as a developmental or reproductive toxicant. Many natural and synthetic chemicals induce manifestations of developmental or reproductive toxicity at sufficiently high dose levels in sensitive species of laboratory animals and test guidelines for developmental and reproductive toxicity require that the highest dose level induce toxicity (or that the chemical be tested at a limit dose of 1,000 mg/kg/day). Recognizing this, the US EPA guidelines require the US EPA to identify the most sensitive endpoints of developmental or reproductive toxicity to compare the dose-response patterns for the endpoints with the expected human exposure to determine the acceptability of these exposures. Neither of these EPA guidelines contains a definition for "developmental toxicant" or "reproductive toxicant" because such classification of chemicals is discouraged by the EPA guidelines and is unnecessary in the risk assessment process used by the US EPA.

The 2002-2006 statements regarding atrazine cited by OEHHA in the Notice of Intent to List are consistent with these EPA guidelines. The EPA notes reproductive and developmental effects that were observed under certain conditions in laboratory animals but the Agency does not go so far as to classify the pesticide as a developmental or reproductive toxicant. This distinction follows the admonition of the US EPA developmental toxicity guidelines: "Judging that the health-related database is sufficient to indicate a <u>potential</u> developmental hazard does not mean that the agent will be a hazard at every exposure level (because the assumption of a threshold) or in every situation (e.g., hazard may vary significantly depending on the route and timing of exposure)." (emphasis added). The US EPA Office of Pesticide Programs evaluations of developmental and reproductive toxicity data therefore must be used with caution for purposes of Proposition 65.

The second reason that atrazine should not be identified as a developmental or reproductive toxicant under Proposition 65 is that the EPA position documents that are cited as the basis for the authoritative body determination are outdated and no longer reflect the knowledge that is available regarding the reproductive and developmental toxicity of atrazine. Of critical importance is recent research which casts doubt upon the human relevance of atrazine-associated perturbations of the hypothalamic-pituitary ovarian axis in rats. The route of administration for the atrazine studies showing the suppression of the Luteinizing Hormone (LH) surge is bolus dosing by oral gavage. This dosing method results in artificially high atrazine plasma concentrations (C_{max}) which have been demonstrated to result in developmental and reproductive effects that are not observed using more relevant dosing methods.[1] It is clear that the C_{max} rather than Area Under the Curve (AUC) is critical in the case of an effect such as the suppression of the LH surge following the dosing of rats

[1] See Coder et al., (2011). Atrazine: An oral (gavage and dietary) study of the effects of atrazine on the spontaneous luteinizing hormone surge in female Sprague-Dawley rats. WIL Laboratories, April 7, 2011.

with atrazine. 27 CCR Section 25306(G) requires OEHHA to determine whether animal studies cited by the authoritative body constitute sufficient evidence taking into account a number of factors including the route of administration. It appears that recent research shows that the bolus route of administration in the studies supporting a listing is less relevant than dietary administration studies which show no evidence of developmental or reproductive toxicity.

Finally, consideration should be given to the fact that the authoritative body for atrazine, the US EPA, is actively re-evaluating this herbicide and their conclusions regarding the developmental and reproductive toxicity of atrazine will be issued in the near future (the Registration Review of atrazine began in mid-2013). The body of knowledge concerning mechanism of action and the human relevance of atrazine-related toxicity has grown significantly since the US EPA evaluated atrazine in the period of 2002 to 2006. In fact, atrazine has since become one of the most thoroughly researched pesticides. The US EPA is carefully reviewing this new evidence and weighing the advice and conclusions of several FIFRA Scientific Advisory Panel meetings that have evaluated new atrazine research. It would be prudent to allow the authoritative body to complete the review which is now taking place before a decision whether to list atrazine as a developmental or reproductive toxicant is made by the State of California.

Sincerely,

Gary Burin

Gary Burin, Ph.D., MPH, DABT

ATTACHMENT H

Developmental effects of atrazine and its metabolites in rats and rabbits

Anthony R. Scialli, M.D.

Atrazine, a chlorotriazines herbicide used to control broadleaf weeds predominantly in corn, sorghum, and sugar cane, has been evaluated in standard developmental toxicity studies in rats and rabbits (Infurna et al., 1988; Scialli et al., 2014). Developmental toxicity testing in rats has also been conducted with the main animal (including human) metabolites of atrazine, deethylatrazine (DEA), deisopropylatrazine (DIA), and diamniochlorotoluene (DACT) and with hydroxyatrazine (OH-ATR), which is a major plant metabolite of atrazine (Scialli et al., 2014).

All dosing in these studies was performed by gavage approximately from implantation (gestational day [GD] 6 in rats, GD 7 in rabbits) until closure of the hard palate (GD 15 in rats, GD 19 in rabbits). There were 24–27 treated rat dams and 19 treated rabbit does per dose group in these studies. Pregnant animals were killed just prior to natural delivery, and fetuses were evaluated using standard protocols.

Two atrazine developmental toxicity studies were performed in rats. In the first study, atrazine dose levels were 0, 10, 70, and 700 mg/kg bw/day. The high dose level was excessively toxic to the dams, resulting in 78% maternal mortality. Only 5 litters in the high-dose group produced evaluable, though small, fetuses. There were no increases in external or visceral malformations in any dose group. There were no increases in skeletal malformations in the low- and mid-dose group; the high-dose group was not evaluated for skeletal malformations due to extreme reductions in fetal body weight in this dose group.

A second rat developmental toxicity study was performed with dose groups of 0, 5, 25, or 100 mg/kg bw/day. Maternal toxicity in the high-dose group consisted of decreases in food consumption and body weight gain. There were no decreases in litter size or fetal body weight and no increases in external, visceral, or skeletal malformations in any dose group. A rabbit developmental toxicity study used atrazine dose levels of 0, 1, 5, or 75 mg/kg bw/day. Maternal food consumption during the dosing interval, body weight gain, and body weight were decreased in the high-dose group. There were sporadic decreases in food consumption on some days in the mid-dose group. There were increases in post-implantation losses, including resorptions, and decreases in number of live fetuses and fetal body weight in the high-dose group. There were no increases in external, visceral, or skeletal malformations. Skeletal variations consisting predominantly of delayed ossification were identified in the high-dose group.

Rat developmental toxicity studies were performed with DEA, DIA, DACT, and OH-ATR at dose levels up to 100 mg/kg bw/day (DEA, DIA), 150 mg/kg bw/day (DACT), and 120 mg/kg bw/day (OH-ATR) based on previous dose-ranging studies. The high-dose levels were appropriate, because they produced the requisite maternal toxicity consisting of decreased weight gain during all or part of the treatment period, often associated with decreased food consumption. Decreases in fetal body weight in the mid- and high-dose groups were observed for DACT and in the high-dose group for OH-ATR. There were no increases in external, visceral, or skeletal malformations in any dose group for any of the metabolites. There were isolated increases in skeletal variations in the high and, for DIA and DACT, mid-dose groups. These variations included findings often associated with maternal toxicity and fetal weight reductions, including

ossification delays, fused sternebrae, and short ribs. Ossification delays and minor skeletal variations are not indicators of malformation; they are due to impairments of maternal nutritive function and are reversible after birth (Carney & Kimmel, 2007).

These studies demonstrate that atrazine (rat, rabbit) and its major metabolites (rat) do not increase malformations in rats at maternally toxic dose levels. Changes in fetal weight and skeletal variations at the high-dose levels were consistent with maternal toxicity. The lowest effect level in these studies was seen after treatment with DIA 25 mg/kg bw/day, a dose level at which the developmental findings included an increase in fused sternebrae 1 and 2 and shortened rib 13 compared to control. This dose level is equivalent on a molar basis to atrazine 20.1 mg/kg bw/day. The EPA maximum contaminant level (MCL) for atrazine in drinking water is 3 ppb, which is 3 μg/L. A 60-kg woman who drinks 2 L/day of water with the MCL for atrazine would consume atrazine 0.1 μg/kg bw/day, more than 5 orders of magnitude lower than the lowest experimental animal effect level for atrazine or its metabolites. Based on these studies, atrazine is not expected to produce adverse developmental effects in humans.

References

Carney EW, Kimmel CA. 2007. Interpretation of skeletal variations for human risk assessment: Delayed ossification and wavy ribs. Birth Defects Res (Part B) 80:473–496.

Infurna R, Levy B, Meng C, Yau E, Traina V, Rolofson G, Stevens J, Barnett J. Teratological evaluations of atrazine technical, a triazine herbicide, in rats and rabbits. J Toxicol Environ Health 1988;24:307–319.

Scialli AR, DeSesso JM, Breckenridge CB. Developmental toxicity studies with atrazine and its major metabolites in rats and rabbits. Birth Defects Res (Part B) 2014;in press doi:10.1002/bdrb.21099

ATTACHMENT I

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

Chad D. Foradori, Prägati Sawhney Coder, Merrill Tisdel, Kun Don Yi, James W. Simpkins, Robert J. Handa, Charles B. Breckenridge

Atrazine, a chlorotriazines herbicide used to control broadleaf weeds, was administered daily to intact female Sprague Dawley (SD) or Long Evans (LE) rats by gavage (0, 0.75 1.5, 3, 6, 10, 12, 50 or 100 mg/kg/day) or diet (0, 30, 100, 160, 500, 660 or 1460 ppm) during one complete 4-day estrous cycle, starting on day of estrus. Estrous status, corpora lutea, ova and LH plasma concentrations were evaluated after the 4th treatment day. A second cohort of animals was mated on the 4th treatment day. Fertility metrics were assessed on gestational day 20.

Bolus doses of ATR ($\geq$ 50mg/kg) inhibited the peak and AUC for the pre-ovulatory LH surge in SD but not LE animals. Likewise, only bolus treated SD, not LE, rats displayed reduced mean number of corpora lutea and ova. There were no effects of atrazine administered by gavage on mating, gravid number or fetus number. Dietary administration had no effect on the estrous cycle, LH surge or any reproductive parameter measured. These findings indicate that short duration, high bolus doses of ATR can inhibit the LH surge and reduce the number of follicles ovulated; however, dietary administration has no effect on any endocrine or reproductive outcomes.

Taken together, the results in this study suggest that the cellular mechanisms within the endocrine system responsible for fertility are robust and that marked reduction in the LH surge have little effect on overall reproductive performance in rodents. In addition, atrazine effects on the rat LH surge are dependent on bolus delivery, most likely resulting from achieving critical plasma concentration of atrazine and/or its chlorometabolites. Equivalent daily doses of atrazine distributed over a 24-hour period had no effect, likely because critical plasma and target tissue concentrations were not achieved. Thus, the effects of atrazine on the LH surge and ovulation following bolus doses are highly unlikely to occur in humans exposed at low, temporally distributed, concentrations of atrazine in drinking water.

References

Foradori, CD, Sawhney-Coder, P, Tisdel, M, Yi, KD, Simpkins, JW, Handa, RJ, Breckenridge, CB. 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. Submitted to Birth Defects Res (Part B) 2014.

ATTACHMENT J

Multigeneration Reproduction and Developmental Toxicity Studies on Atrazine

John M. DeSesso, Anthony R. Scialli, Tacey EK White and Charles B. Breckenridge

Atrazine (ATR), a chlorotriazine herbicide used to control broadleaf weeds predominantly in corn, sorghum, and sugar cane, was evaluated for potential reproductive toxicity in Sprague Dawley rats in 2- or 3-generation studies at dietary concentrations of 0, 10, 50, 100 or 500 ppm. Parental systemic toxicity occurred only at 500 ppm (38.7 mg/kg/day); there were no effects on male or female reproductive endpoints (Reproductive Toxicity NOEL 38.7 mg/kg/day).

The potential effect of ATR on the development of male offspring was assessed after bolus gavage at doses of 1, 5, 25 or 125 mg/kg to female Wistar rats either during gestation (from gestation day 6 to 21), or during lactation, from postnatal day (PND) 2 to 21. Following gestational exposure, fetal mortality was observed in the 125 mg/kg/day dose group; among surviving male offspring the percentage of abnormal sperm was increased in this group on PND70. The percentage of abnormal sperm was increased in the 25 mg/kg/day dose group on PND170. However, there were no effects on testicular/epididymal weights or sperm counts, and no effects on plasma testosterone concentrations at any dose. The no observed effect level (NOEL) was 5 mg/kg/day.

Lactational exposure to ATR on PND 2-21 resulted in significantly reduced body weight gain in male offspring whose dams received a 125 mg/kg/day oral gavage dose. These pups also presented with a 6-7% reduction in testis weight on both PND 70 and PND170; a 10% reduction in epididymis weight on PND70; and increased numbers of abnormal sperm on both PND70 and PND170. The NOEL was 25 mg/kg/day for all these parameters. There were no effects of treatment on plasma testosterone or sperm count at any dose.

In summary, the data from these studies indicate there were no effects of ATR on rat reproduction when ATR was administered as a temporally distributed dose in the diet up to a NOEL dose of 38.7 mg/kg/day. Although there were effects on male offspring development after high bolus doses to dams, the NOELs following prenatal (5 mg/kg/day) and post-natal (25 mg/kg/day) exposures were 50,000 to 400,000 fold greater than the dose that would be received by a 60-kg woman who drank 2 liters per day of water containing ATR at the maximum contaminant level (MCL) of 3 µg/L (U.S Environmental Protection Agency, 2012),

References

DeSesso JM, Scialli, AR, White, TEK, Breckenridge CB. Developmental toxicity studies with atrazine and its major metabolites in rats and rabbits. Birth Defects Res (Part B) 2014;In press doi:10.1002/bdrb.21099.

USEPA (2012). Basic Information about Atrazine in Drinking Water. Available at http://water.epa.gov/drink/contaminants/basicinformation/atrazine.cfm#four. Accessed August 7, 2013.

ATTACHMENT K

March 24, 2014

Lauren Zeise, Ph.D.
Deputy Director, Office of Environmental Health Hazard Assessment (OEHHA)
1001 I Street
Sacramento CA 95812-4010

Comments in Opposition to Potential Listing of Atrazine as a Reproductive or Developmental Toxicant under Proposition 65's Authoritative Body Listing Mechanism

Dear Dr. Zeise,

OEHHA has proposed to list atrazine, propazine, simazine and the chlorometabolites DEA, DIA and DACT (chlorotriazines) as developmental and reproductive toxicants because it concludes that the US Environmental Protection Agency (USEPA), an authoritative body for purposes of Proposition 65, has formally identified the chlorotriazines as causing reproductive toxicity under the California Code of Regulations Title 27, Section 25306(d).

We oppose OEHHA listing the chlorotriazines as developmental and reproductive toxicants because

1) **The USEPA did not formally conclude** that the chlorotriazines are human developmental and reproductive toxicants.

2) In 2011, the Scientific Advisory Panel of the USEPA advised EPA that "**a causal association between changes in LH surge peak and adverse fertility measures has not been made.**"

3) OEHHA did not exercise due diligence in evaluating the scientific record because it relied on statements made by the USEPA originating during or prior to 2006, whereas substantial new **"scientifically valid data"** were presented to the USEPA after 2006.

4) This new scientific data demonstrated that, based upon what is known about the indicators of reproductive or development effects in animals, and new information on pharmacokinetics, **it is not biologically plausible** that humans exposed to the chlorotriazines will display developmental or reproductive toxicity.

Title 27, of the California Code of Regulations, Section §25306 states that

> **(g) For purposes of this section, "as causing reproductive toxicity" means that either of the following criteria have been satisfied:**
>
> **(1) Studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity, or**
>
> **(2) Studies in experimental animals indicate that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible.**
>
> **(h) The lead agency shall find that a chemical does not satisfy the definition of "as causing reproductive toxicity" if scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria of subsection (g), paragraph (1) or subsection (g), paragraph (2).**

OEHHA relied only on authoritative body statements that were no more recent than the year 2006. We submit that contrary to Title 27, (Section §25306, Subpart h), the **USEPA had not considered "scientifically valid data" submitted to the agency after 2006 showing that adverse reproductive effects could not plausibly occur in humans.**

In 2010, the USEPA displayed its own uncertainty about the interpretation of the potential effects of atrazine on a key indicator of potential reproductive effects, the luteinizing hormone (LH) surge, by asking its own Scientific Advisory Panel for scientific advice in interpreting the data.

We submit that as late as 2010, neither the EPA, nor its advisory panel, concluded that atrazine and the chlorotriazines would have adverse reproductive effects in humans.

USEPA's Scientific Advisory Panel Comment #1

The Scientific Advisory Panel (SAP) convened by the USEPA from September 14th to September 17th, 2011 reported to the EPA[1] that

> **"...while attenuation of the LH surge over one estrous cycle represents a sensitive biological response, a causal association between the observed modest, yet statistically significant, changes in LH surge peak and adverse fertility measures has not been made." (p 11)**

Response

The reproduction studies on atrazine, simazine and propazine, which were not reviewed by the SAP but have been summarized for OEHHA,[2,3] clearly show that the chlorotriazines do not have any effect on reproduction. The absence of effects of the chlorotriazines in reproduction studies is explained by rapid

clearance of the chlorotriazines from plasma[4] thereby preventing an effect on the LH surge following distributed dosing (See Response to SAP Recommendation #2 and #4).

USEPA's Scientific Advisory Panel Comment #2

The SAP recommended to the USEPA that data generated from dietary administration should be considered, since it

> **"... provides a smoother plateau, is less stressful and disruptive than gavage, and is more realistic representation of human exposure through drinking water, depending on the presence of food in the digestive tract." (p48)**

Response

Syngenta submitted a dietary study[5] to USEPA on April 29, 2011 and the results of this study were accepted for publication in Birth Defects Research Part B, Development and Reproductive Toxicology[6] on March 17, 2014. The study, which to our knowledge has yet to be taken into account by the USEPA, showed that dietary exposure to atrazine had no effect on the LH surge in the rat (Figure 1, Panel A).

SAP Comment #3

The SAP expressed the need to determine the potential for sensitivity to LH suppression across the reproductive lifespan. The Panel stated,

> **"Specific data which examine long-term diminution of the LH surge over the reproductive lifespan and resultant effects on fertility have not been studied with atrazine... Studies specifically addressing the effects of atrazine during all key phases of the reproductive lifespan are lacking." (p 56-57).**

Response

Syngenta submitted a life-stage study[7] to the USEPA in February, 2011. The effect of atrazine on the LH surge was evaluated in young adult female rats that had just attained sexual maturity and in approximately 4-month old female rats. The results when compared to those obtained in reproductively senescent rats indicate that

1) Young adult female rats, irrespective of whether they were exposed to atrazine *in utero* and/or post-natally, are insensitive to the effect of atrazine on the LH surge.

2) The reproductively senescent female rat is more sensitive to the effects of atrazine than is the mid-aged rat.

3) Reproductive senescence in humans is unlike reproductive senescence in rodents.[8]

4) The neuroendocrinologic mechanisms underlying the "LH surge" in rodents are unlike those in humans, and are not relevant to the LH surge mechanisms in non-human primates and humans.[9]

5) The short- and long-term reference doses for the chlorotriazines, which are based upon LH surge effects of atrazine in reproductively senescent female rats, are conservative, hazard based doses that are not predictive of adverse reproductive effects in humans.

SAP Comment #4

The Panel stated these data

> **"...need to be taken into account when, for example, selecting the appropriate uncertainty factors, along with the adequacy of the toxicokinetic and toxicodynamic data that will inform the inter- and intra-species extrapolations." (p 53).**

Response

On April 9th, 2011, Syngenta submitted to the USEPA a comprehensive pharmacokinetic study[4] on atrazine administered to rats either as bolus gavage doses or as temporally distributed doses in feed. The data were scaled to humans using a PBPK model[10] (See Figure 2, Panel B). The USEPA was also provided a protocol for a similar study in the cynomolgus monkey[11]. This study has been completed and a revised PBPK model based on this data will be finished in 2014.

In the report of another Scientific Advisory Panel meeting (USEPA, 2011b)[12], the SAP encouraged the EPA to use the PBPK modeling approach for risk assessment purposes and complimented Syngenta for advancing the science.

> **"In general, the Panel supported the work of the Agency in pursuing a dose-response analysis based on an internal dose metric, as an alternative to administered dose in the interest of reducing uncertainty in inter-route, interspecies and intraspecies extrapolations. In the one compartment model, the Agency has attempted to maximize use of the data available to them, making mainly conservative choices in the absence of hard information and verifying estimates to the extent possible. However, it was noted that the one compartment model was proposed by EPA as an interim approach, given that a thorough review and evaluation of a recently submitted PBPK model by Syngenta has not been completed. It has also been noted by the Agency that a verified PBPK model would constitute the 'ideal approach'" (USEPA, 2011b, Paragraph 4, page 73).**

Response

As a follow up to SAP recommendation cited above, Syngenta submitted a comprehensive risk assessment for the chlorotriazines[13] using the PBPK model. The analyses demonstrated that effects on reproduction cannot plausibly occur in humans exposed to the chlorotriazines in their drinking water because bolus gavage doses of atrazine result in peak plasma concentrations of atrazine and its metabolites, which do not occur following distributed dosing. To our knowledge the USEPA has not taken into account the results presented in those analyses.

Conclusions

1) **the chlorotriazines should not be listed as developmental or reproductive toxicants because such effects cannot plausibly occur in humans.**

2) **The EPA did not conclude that the chlorotriazines are developmental or reproductive toxicants in humans in the documents cited by OEHHA and dated prior to 2007.**

3) **OEHHA has failed to consider significant new data since 2006 indicating "that a chemical (the chlorotriazines) does not satisfy the definition of 'causing reproductive toxicity' if scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria of subsection (g), paragraph (1) or subsection (g), paragraph (2)."**

4) **This interpretation of the record is buttressed by statements of the Scientific Advisory Panel to the USEPA in 2011 that "while attenuation of the LH surge over one estrous cycle represents a sensitive biological response, a causal association between the observed modest, yet statistically significant, changes in LH surge peak and adverse fertility measures has not been made."**

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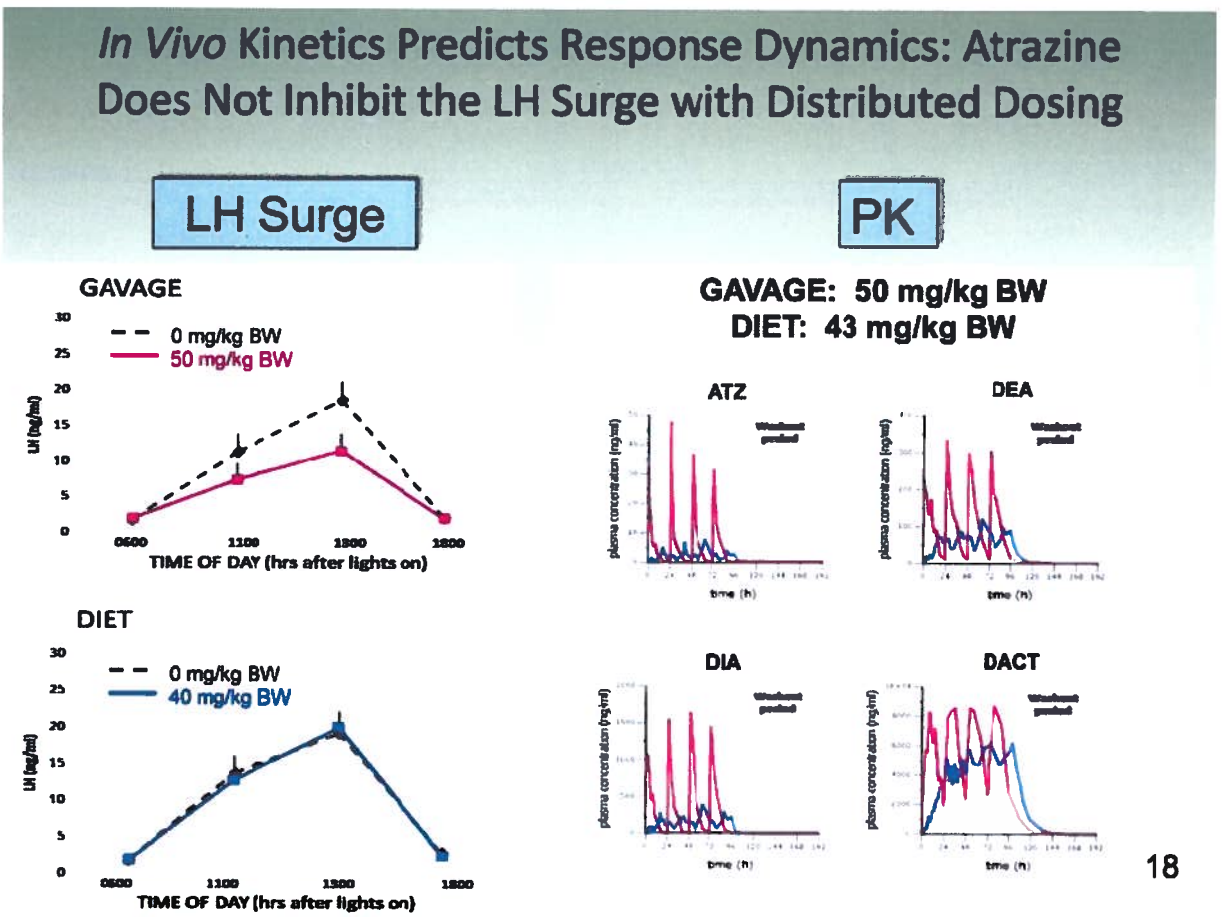
Figure 1*



*The top left panel displays the effect on the estrogen-induced luteinizing hormone (LH) surge in female Sprague-Dawley (SD) rats administered 50 mg/kg atrazine as a bolus gavage dose daily for 4 days. The corresponding plasma concentrations of atrazine and its metabolites (DEA, DIA, DACT) are displayed as red lines in the right panel. The data are analytical results derived from frequent blood samples collected after each atrazine as described by Coder et al.,(2011a)[4].

The bottom left panel demonstrates that atrazine had no effect on the LH surge when it was administered to female SD rats as a distributed dose (40 mg/kg/day) in feed over 4 days. Peak plasma concentrations of ATZ, DEA, DIA and DACT were substantially less following dietary administration (blue lines) compared to plasma concentrations following gavage dosing (red lines).

ATTACHMENT L

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March 21, 2014

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Re: Opposition to Notice of Intent to List: Atrazine, Propazine, Simazine, and the chlorometabolites DACT, DEA, and DIA

Dear Dr. Zeise:

California's Office of Environmental Health Hazard Assessment (OEHHA) has recently published a Notice of Intent to List: Atrazine Propazine, Simazine, and the chlorometabolites DACT, DEA, and DIA under California's Safe Drinking Water and Toxic Enforcement Act of 1986 (Prop 65) as "known to the state to cause reproductive toxicity." I have been asked by Syngenta, based upon my knowledge about the potential reproductive and developmental toxicology of atrazine and my experience at US EPA, to review and comment on the evidence presented in the Notice of Intent to List.

This letter expresses my opposition to the proposed listing of atrazine based on the lack of sufficient data to support the stated reproductive effects. The pertinent regulation requires that the determination of sufficiency take into account:

> *"the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible."*

OEHHA did not fully take into account these factors and the current state of knowledge regarding atrazine. In particular, when the reproductive effects reported in rats are considered in light of the mechanism of action (MOA) for atrazine and pharmacokinetics from the studies that compare gavage and dietary exposure to atrazine, it is clear that the

reproductive effects seen in rodents are not relevant to humans. These factors are described in greater detail below, and demonstrate that the potential for reproductive toxicity from atrazine exposure in humans lacks biological plausibility.

Mechanism of Action: Suppression of LH Surge in Sprague Dawley Rats

The Notice of Intent to List cites several US EPA documents from 2002 and 2006 that describe a common MOA for neuroendocrine effects in rats associated with the chlorotriazine herbicides, including atrazine. Although the US EPA has relied on this MOA as a point of departure in risk assessment, the hormonal alteration is not, in and of itself, an adverse effect and is described by the Agency as "a precursor event for the reproductive effects" in rats, not humans (US EPA 2011, p. 14). Furthermore, since the 2002 and 2006 reports, new data have been developed and are being actively considered by the Agency. The new data provide even more information on the MOA to show that the reproductive effects seen in rats are not relevant to humans because:

- Significant differences exist between the rat and human female reproductive hormone cycle;
- Reproductive effects are observed only in studies where atrazine is administered by gavage resulting in high plasma concentrations that could not occur in humans from dietary, drinking water or occupational exposure to atrazine.

The common MOA for chlorotriazine herbicides relied on by EPA for risk assessment is suppression of the luteinizing hormone (LH) surge that is part of the hormonal cascade that comprises the rat estrous cycle. This suppression of the LH surge has been observed in several animal models, but the Sprague Dawley (SD) strain of rat is the most sensitive. The observed differences in response to atrazine raise the question about whether this strain of rat is appropriate for assessing potential human health effects.

The estrous cycle in the rodent corresponds to the menstrual cycle in humans with ovulation or release of an egg for possible fertilization as the end result. The estrous cycle in the rat is only four days in length and is linked to circadian signals from the brain in conjunction with feedback from circulating levels of the hormone, estradiol. Normally, during the four day cycle the brain sends a signal that produces release of gonadotropin releasing hormone (GnRH), which in turn triggers the LH surge (Plant et al. 2012). The LH surge induces ovulation and if the animal does not become pregnant, the cycle repeats itself. SD rats begin to lose reproductive capability at 9 months or at one-third of their lifetime. This change is predominantly due to the reduced hypothalamic GnRH stimulation of the pituitary secretion of LH and follicle stimulating hormone. Estrogen levels remain elevated, resulting in a higher estrogen to progesterone ratio.

In humans, the menstrual cycle is approximately four weeks in duration with the LH surge occurring for two to three days prior to ovulation. Unlike the rat, the LH surge in humans

appears to occur independently from a GnRH signal and is primarily the result of positive feedback from estradiol (Simpkins et al. 2011). The timing and control of ovulation in humans is not linked with a circadian signal and the primary site for feedback from estradiol is the pituitary, not the preoptic area of the hypothalamus which is the feedback site in rats (Plant et al. 2012). The loss of reproductive capability of human females is related to the reduced number of eggs in the aging ovaries, not the reduction in GnRH levels seen in aging SD rats (Chapin et al. 1996). Menopause is also associated with lower estrogen production leading to a lower estrogen to progesterone ratio – the direct opposite of what is seen in SD rats. Thus, there are several significant differences in the induction of the LH surge between rats and humans.

When rats are administered certain doses of atrazine, the LH surge is suppressed and the animals exhibit a lengthened estrous cycle or remain in persistent estrus, one of the phases of the estrous cycle. Under these conditions ovulation does not occur and these rats exhibit an accelerated reproductive aging (described as senescence). The suppression of the LH surge by atrazine is very dependent on the timing, duration, and route of exposure. Although reproductively aged female SD rats have been shown to be sensitive to the effects of atrazine, younger animals are more resilient to the influences of atrazine on GnRH (Ashby et al. 2002), which was acknowledged by the US EPA Scientific Advisory Panel (SAP):

> *An extensive hazard database, spanning all life stages from conception to adulthood for atrazine, indicates no unique susceptibility in the developing organism. Additionally, the proposed point of departure, based upon attenuation of the LH surge, appears to be protective against adverse reproductive/developmental outcomes such as delays in onset of puberty, disruption of ovarian cyclicity and inhibition of suckling-induced prolactin release. (EPA SAP 2011, p 14)*

Recent studies have shown that multiple doses are required to suppress the LH surge and that a single, high dose just prior to the LH surge induces an increased (not decreased) response in plasma LH levels (Goldman et al. 2013). The route of exposure is particularly important since high bolus doses of atrazine are associated with suppression of the LH surge, but extremely high dietary exposures are required to produce a similar effect. Although all of the details of the cellular mechanism related to the suppression of LH surge are not known, several pieces of evidence suggest that the disruption of the LH surge is not relevant to humans.

First, alterations by the triazines and certain metabolites in the LH surge appear to be the result of an effect on the hypothalamus, reducing the release of GnRH (Cooper et al. 2007, Fraites et al. 2009). Because the signal for initiating the LH surge in humans is a feedback mechanism driven by estradiol released by the ovary, the reduction in GnRH is unlikely to impact the LH surge in humans. Second, atrazine does not directly affect LH secretion from the pituitary in the rat (Cooper et al. 2000). Given the fact that the ovary and pituitary play

a more central role in the hormonal control of the menstrual cycle in humans, this suggests that atrazine should not affect the LH surge in humans. Third, the causes of reproductive aging are different between rats and humans. Because exposure to atrazine suppresses the LH surge, leading to pre-mature reproductive aging in rats, this would not be relevant to human females since aging is not a consequence of changes in LH. Finally, in comparative studies of gavage and dietary exposure to atrazine, only the bolus doses from gavage have been demonstrated to alter the LH surge in rats. The direct administration by gavage allows for the rapid absorption and metabolism of atrazine, producing high plasma concentrations of atrazine and metabolites. As discussed in greater detail below, the pharmacokinetics of atrazine demonstrate that the gavage route of exposure is not appropriate for modeling the potential exposure to atrazine in humans.

OEHHA specifically identifies estrous cycle alterations as one of the endpoints indicative of reproductive toxicity. The estrous cycle alterations include persistent estrus, which leads to premature senescence in female rats. These changes are a direct result of the suppression of the LH surge, and as outlined above, cannot be considered relevant to humans.

Considering the current body of evidence on the MOA for atrazine, it is apparent that the suppression of the LH surge is not relevant or biologically plausible in humans. The US EPA SAP similarly concluded that:

> *It seems unlikely that humans would ever experience the sorts of internal exposures necessary in rats to produce suppression of the LH surge. (EPA SAP 2011, p. 84)*

Therefore, the sufficiency of the data presented by OEHHA as evidence for the biological plausibility of reproductive toxicity from exposure to atrazine in humans cannot be supported.

Reproductive Toxicity and Consideration of Experimental Study Design

OEHHA specifically identifies several male and female reproductive endpoints as the basis for the Notice of Intent to list atrazine as a reproductive toxicant. These endpoints include: prolonged estrus in the dams (as discussed above), delayed ossification of certain cranial bones of fetuses, delayed vaginal opening (VO) in female pups, and delayed preputial separation (PPS) in male pups. As acknowledged by EPA at the Scientific Advisory Panel in July 2011, all of these effects all of these effects occur at doses greater than that associated with suppression of the LH surge:

> *The Agency will continue to use changes in LH secretion as the basis of the atrazine risk assessment. As such, any of the identified adverse outcomes would be protected since they occur at doses higher than those eliciting changes in LH (US EPA 2011, p. 13)*

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The reproductive effects noted by OEHHA have been observed in gavage studies, but have not been reported in dietary studies at comparable doses. The precursor event, suppression of the LH surge, has been only been observed in dietary studies at doses greater than 400 ppm, which is considered higher than the maximum tolerated dose and is associated with significant effects on body weight and body weight gains (Chapin et al. 1996, Simpkins et al. 2011). The changes in body weight are considered signs of systemic toxicity and in a reproductive study would clearly represent maternal toxicity which, as stated in the Prop 65 regulations, should be considered in judging the biological plausibility for humans.

A number of recent studies have been conducted to better understand the pharmacokinetics (PK) of atrazine (Coder et al. 2011, Hui et al. 2011, Press et al. 2012, Stuhler et al. 2011). These studies have shown that administration by gavage results in rapid, high plasma concentrations of atrazine and its metabolites, while dietary intake at similar doses resulted in lower peak and total plasma concentrations of atrazine and its metabolites (see Figure 8 in the Syngenta Science paper, Breckenridge et al. 2013). The gavage route of exposure results in a bolus dose to the animal, which is immediately available for absorption and distribution. In contrast, animals exposed to atrazine in the diet have a slow steady exposure, resulting in a lower, more constant plasma levels. Given the rapid elimination of atrazine and metabolites, they do not build up in the body, so there is no opportunity for plasma concentrations to reach the levels achieved by gavage (Coder et al. 2011, Foradori et al. 2014, Hui et al. 2011, Press et al. 2012, Stuhler et al. 2011). As stated by the SAP, "[i]t is important to be cognizant that the toxicological doses of atrazine being discussed (e.g., 12.5 – 100 mg/kg/day) are not relevant to probable exposure levels in the "real" environment. (US EPA SAP 2011, p. 40). Thus, when one takes into account that the reproductive effects of atrazine are associated with gavage exposures and high plasma concentrations, it is not biologically plausible for these types of effects to be seen in humans, given the substantially lower exposures to atrazine for humans.

It is also important to note that in two- and three-generation reproductive studies, no effects on reproduction, including mating and fertility have been reported (DeSesso et al. 2014). Thus, long-term dietary exposures, which are more representative of potential human exposures, do not support reproductive effects from atrazine.

In addition to the consideration of the route of exposure, a couple of additional factors should be taken into account when evaluating the relevance of the developmental toxicity highlighted by OEHHA. First, the observation of delayed ossification of cranial bones is not considered an adverse effect, such as a malformation. Second, as noted by US EPA (2006), these developmental delays were seen in conjunction with a decreased body weight gain, which suggests maternal toxicity. Furthermore, in a recent review of all developmental toxicity studies, Scialli et al. (2014) concluded that "[o]verall, data show that neither

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[atrazine] or its metabolites statistically significantly affected rat or rabbit embryo-fetal development even at dose levels producing maternal toxicity."

I conclude that atrazine should not be listed by the State of California on the basis of reproductive toxicity. This conclusion is based on the study design parameters and other toxicological factors that are associated with the observation of reproductive effects in rats. When the route of administration, frequency and duration of exposure, and maternal toxicity are taken into consideration, the biological plausibility of these effects occurring in humans at typical or higher occupational exposures is not credible.

Sincerely,

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