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December 11, 2012

VIA HAND AND ELECTRONIC DELIVERY TO OEHHA

Ellen Gold, Ph.D., Chairperson, and Committee Members
Developmental and Reproductive Toxicant Identification Committee

RE: Critical Evaluation of Hazard Identification Document for Deltamethrin

Dear Dr. Gold and Committee Members:

On behalf of our client Bayer CropScience LP ("Bayer"), we are submitting the attached Critical Evaluation of Hazard Identification Document for Deltamethrin ("Critical Evaluation"), prepared by our client to assist the Committee in its evaluation of whether the chemical known as deltamethrin (CAS No. 52918-63-5) should be designated (or "listed") as a chemical "known to the State to cause reproductive toxicity" for purposes of the Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65").

We have requested that this letter and the attached materials be distributed to you, along with other documents that may be provided to you by the Office of Environmental Health Hazard Assessment ("OEHHA"). By this letter, Bayer also is requesting an opportunity to be heard on this issue if deltamethrin is considered by the Committee at a public meeting. We also identify below some critical points that the Committee should consider in its deliberations, and present a factual assessment of the complete body of available studies, demonstrating that deltamethrin should not be listed.

1. REFERRAL OF DELTAMETHRIN TO THE COMMITTEE FOR EVALUATION IS NOT AN INDICATION THAT THE CHEMICAL SHOULD BE LISTED

Deltamethrin has been referred to this Committee so that you may ***evaluate*** the scientific data and determine ***whether*** the chemical should be listed under Proposition 65. While this may be understood, we feel it is worth mentioning because the evaluation of deltamethrin will be the first for several new members of the Committee, and it may appear from the nature of this process and some of the documents referred to the Committee that the expected outcome of this proceeding is to list the chemical. In fact, the "Hazard Identification Document" or "HID" prepared by OEHHA that is a part of your package (entitled "Evidence on the Developmental and Reproductive Toxicity of Deltamethrin") and the descriptions of data from some of the

studies summarized therein could be read (incorrectly) to imply that the chemical has already been designated as a developmental or reproductive toxicant. That is decidedly ***not*** the case. But in case the document may leave that misimpression, we call to your attention the final sentence of the Preface (at page 3), which states as follows:

> "OEHHA developed this document to provide the DART IC with comprehensive information on the reproductive toxicity of deltamethrin for use in its ***deliberations*** on ***whether or not*** the chemical should be listed under Proposition 65." (Emphasis added).

2. *Listing a Chemical Requires a Determination by the Committee That the Substance Is "Clearly Shown" by the "Weight-of-Evidence" to Cause Reproductive Toxicity*

The determination ***whether*** deltamethrin should be designated as a reproductive toxicant requires the expert judgment of the Committee, collectively and as individuals. That judgment is not to be a subjective one, however. Rather, it requires an objective determination, in accordance with strict criteria established under Proposition 65 (the statute), its implementing regulations and a further set of guidance criteria established by the Committee itself in 1993.

The Statute. For purposes of this proceeding, a "chemical is known to the state to cause . . . reproductive toxicity if in the opinion of the state's qualified experts [*i.e.,* the Committee] it has been ***clearly shown*** through ***scientifically valid testing*** according to ***generally accepted scientific principles*** to cause . . . reproductive toxicity." California Health & Safety Code § 25249.8(b). (Emphasis added.)[1]

This determination thus will require the Committee to evaluate all of the data presented to it (and not just the Hazard Identification Document), taking due care to ensure that it considers only data that are "scientifically valid . . . according to generally accepted scientific principles."

The Regulations. The duties of this Committee in making its determination are set forth in Proposition 65 implementing regulations, which also have the force of law. In pertinent part,

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[1] Portions of the statute not included in the quote above relate to chemicals considered for listing because they are "known to the state to cause ***cancer***," or to chemicals that may be listed because an "authoritative body" such as the United States Environmental Protection Agency ("EPA") or Food & Drug Administration ("FDA") have designated them as reproductive toxicants (or carcinogens), or to chemicals that a state or federal agency has formally required a chemical to be labeled as causing cancer or as a reproductive toxicant. Those provisions of the statute are not directly relevant to the proceeding here, because it is the role of the Committee members in this proceeding to determine in their judgment whether deltamethrin is "known to cause reproductive toxicity." In this context, however, it is relevant for the Committee to consider that the US EPA exercises regulatory authority over the use of deltamethrin as a pesticide, and that FDA regulates the use of the substance as a "food additive" (to the extent that deltamethrin is applied to agricultural commodities). *See* 40 Code of Federal Regulations § 180.435. It further is relevant to the Committee's consideration that neither of these agencies, both of which are "authoritative bodies" under the statute, has designated deltamethrin as a reproductive toxicant. Nor has the California Department of Pesticide Regulation (DPR) done so. A decision by the Committee to list deltamethrin would be inconsistent with the actions of all three agencies (and other agencies), as discussed further herein.

these regulations provide that "the DART Identification Committee may . . . render an opinion . . . whether [deltamethrin] has been ***clearly shown***, through ***scientifically valid testing*** according to generally accepted principles, to cause reproductive toxicity."[2]

In addition, the regulations provide the Committee with authority to "[r]eview or propose standards and procedures for determining reproductive toxicity of chemicals."[3] The Committee exercised that authority in 1993 and published the document entitled "Criteria for Recommending Chemicals for Listing as Known to the State to Cause Reproductive Toxicity," referred to herein as the "DART Criteria," discussed below.

DART Criteria. Because this document is six pages long, we have included it as an attachment to this letter, and will address only the most critical passages below.

The document provides that:

> "***criteria included herein shall be utilized*** by the [DART IC] to identify chemicals as known to the State to cause reproductive toxicity."
>
> * * *
>
> "In evaluating the sufficiency of data, a ***"weight of evidence" approach shall be used*** to evaluate the body of information for a given chemical."

(Emphasis added.)

There are no human (epidemiological) studies on the developmental or reproductive effects of deltamethrin, so its potential designation as a developmental or reproductive toxicant must be based solely on animal studies. The DART Criteria specify that a listing can be based solely on "sufficient evidence in experimental animals (mammals), such that extrapolation to humans is appropriate," *id.* at 4, but set forth very detailed criteria for determining whether the "animal data" in any particular case are "sufficient."

The DART IC Criteria explain that:

> "Sufficient" animal data would, in most cases, be based on the adequacy of the following:
>
> (1) The experimental design, including overall protocol and numbers of animals, and presence of appropriate controls.
>
> (2) The exposure, in terms of route of administration, is relevant to expected human exposures, and in terms of timing, with regard to critical periods of development for developmental toxicity, sexual maturation, stage of pregnancy, or other critical periods for female reproductive toxicity, and sexual maturation, spermatogenesis, or other critical periods for male reproductive toxicity.

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2 22 Cal. Code Regs. § 25305(b)(2) (emphasis added).

3 22 Cal. Code Regs. § 25305(b)(4).

(3) Number of dose levels, so that the presence of dose-response relationship can be evaluated. It is desirable that the high dose level should elicit maternal toxicity in developmental studies, and systemic toxicity in female and male reproductive studies, and that the low dose should elicit no observable adverse effect for adult and offspring.

(4) Consideration of maternal and systemic toxicity.

Differentiating between (a) the effects of a toxic agent on the conceptus or reproduction and (b) the effects on the conceptus or reproduction that are secondary to the maternal or systemic toxic effects is sometimes difficult and may require special attention, on a case by case basis.

(5) Number of tests or experimental animal species.

a. In general, effects should occur in multiple studies or multiple species for a substance to be recommended for listing.

b. Weight of evidence considerations.

1. Data on a single species from a well-conducted developmental or reproduction study may be sufficient to classify an agent as a reproductive toxicant provided there are not equally well-conducted studies which do not show an effect and which have sufficient power to call into questions the repeatability of the observation in the positive study.

2. Data on more than one species or from more than a single study increase the confidence for classification of an agent as a reproductive toxicant.

(6) Other considerations, including, but not limited to those listed below, which can increase or decrease the confidence for classification of an agent as a reproductive toxicant.

a. Severity or consistency of findings.

b. Metabolic and pharmacokinetic data.

c. Time course of events.

DART Criteria at 4-5.

3. *THE HAZARD IDENTIFICATION DOCUMENT DOES NOT PROVIDE THE COMMITTEE INFORMATION NECESSARY TO BALANCE THE WEIGHT OF EVIDENCE*

As detailed above, the statute, regulations, and this Committee's own published DART Criteria all require that in determining whether the "weight of the scientific evidence" supports a conclusion that a chemical has been "clearly shown to cause reproductive toxicity," this

Committee must consider the ***quality*** of each study as well as the findings reported in each study. An effect or effects reported by one or more studies of low or questionable quality should be questioned or discounted altogether if the same effects should have been observed and reported, but were not observed and reported, in a high-quality study.

The highest quality reproductive and developmental toxicity animal studies available on deltamethrin are the guideline regulatory and Good Laboratory Practice-compliant studies, which EPA, CDPR and other regulatory authorities around the world have relied upon for hazard and risk assessments and ultimately to determine whether to grant pesticide registrations. The guidelines followed in these studies were developed by national and international authorities based upon the input of researchers with appropriate expertise and were designed to be both robust and sensitive. The results of such studies are reproducible and can be readily linked to adverse outcomes.

While the OEHHA Hazard Identification Document on deltamethrin identifies the "fact" that some of the studies on deltamethrin are studies "conducted for the purpose of pesticide registration per guidelines of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)," the discussion of the results of the studies in the Hazard Identification Document fails to acknowledge, much less discuss, the profound qualitative differences between these "FIFRA studies," compared with studies reported in the "open scientific literature," and in fact, with one significant exception discussed below, describes the effects reported in all of the studies as though the studies are all of equal quality and all the reported effects of equal weight and plausibility. This is despite the fact all of the published studies suffer from at least one, and frequently more than one, deficiency with respect to the DART IC criteria for sufficient animal data summarized above. For example, in the HID "Executive Summary," which presumably presents the findings that are considered the most robust, page 5 presents results from studies in which the test article was administered *via* intraperitoneal (i.p.) injection or subcutaneously as evidence of male reproductive toxicity, despite the fact that neither route is relevant to expected human exposure and only a single dose level was administered in the i.p. study. Reported findings from one other publication in the male reproductive toxicity section also come from a single-dose study.

In actuality, in the HID "Executive Summary" from pages 5 to 7, OEHHA simply lists all of the effects reported in ***any*** of the studies, with no discussion of which studies report which effects or whether the effects reported in some studies are contradicted by the findings of other studies. Of particular importance, there is no summary provided of the overall results of the guideline studies, which have been found acceptable by EPA and CDPR, to enable comparison of published findings against the existing regulatory standard. Similarly, in OEHHA's tabular summaries of male reproductive effects and developmental effects "seen in animal studies" (HID pages 24-25, 36-38), and in OEHHA's "integrative evaluations" purporting to summarize the weight of evidence as to potential male reproductive, female reproductive and developmental toxicity (HID pages 25-26, 28, and 39-40), OEHHA likewise simply lists every "adverse" effect reported in any study as if all such reported effects are well-founded, making no attempt to discuss the quality of the studies in question and no mention of the fact that effects reported in

the "open literature studies" were frequently not reported in, and thus contradicted by, the higher quality "FIFRA studies."

The attached Critical Evaluation, prepared by the scientists at Bayer, addresses this substantial deficiency in the Hazard Identification Document and sets forth in detail, study by study, the significant deficiencies that call into question the reported findings of the "open literature studies" uncritically recited in the Hazard Identification Document. These deficiencies are discussed specifically and at length in the Critical Evaluation, and are summarized in tabular form in Tables 1-3 at pages 24-28 of the Critical Evaluation. The Critical Evaluation also explains in detail, as the HID does not, how each of the reported findings of the various open literature studies is contradicted by the data from the more robust FIFRA studies. If the open literature findings were valid, despite the design deficiencies in the published studies, one would reasonably expect to see ***some*** related effects in the FIFRA studies, which is not the case.

Furthermore, the Critical Evaluation refers to additional information that is necessary to properly interpret findings in the guideline studies, such as decreased male and female reproductive tissue weights being associated with decreased body weight and many other tissue weights; without such clarification, it appears reproductive tissues were selectively affected, which was not the case. All of this information should have been included in the HID itself, or at a minimum, acknowledged in the HID as "missing information" that this Committee must consider, rather than simply accepting each reported effect recited in the HID as if all are scientifically valid.

As noted above, there is one significant exception in the Hazard Identification Document in which OEHHA does discuss the "quality" of one of the studies on deltamethrin, and based on that discussion, decides not to consider or even report the findings of the study in question. Specifically, with regard to a three-generation reproductive toxicity study in rats (Wrenn, 1980) that reported "no adverse effects on the reproductive system...at any level tested...," OEHHA states: "The study had severe limitations such as lack of test article purity, the lack of adequate dose level justification and absence of full histopathology of parental animals. CDPR concluded that this study was not adequate for the purposes of pesticide registration." HID at page 17. OEHHA therefore ***did not include*** the Wrenn study (or its findings of no adverse effects) in its tabular summary of male reproductive effects in Table 6 on pages 24-25, or in OEHHA's "integrative evaluation" of male reproductive toxicity on pages 25-26, despite the fact that no published study has evidence of test article purity or adequate dose level justification or complete histopathology.

Similarly, OEHHA repeated the same language about the deficiencies of the Wrenn study in its discussion of female reproductive toxicity on page 27, and again omitted any references to its findings of no adverse effects in its integrative evaluation on page 28. Finally, in discussing developmental effects on page 32, OEHHA repeated that the "[Wrenn] study had severe limitations and CDPR concluded this study was not adequate for pesticide registration; ***hence, the information from this study is not presented.***" (Emphasis added.) In short, based on nothing more than a DPR determination that the Wrenn study was not "adequate for purposes of pesticide ***registration,***" OEHHA effectively concluded that it was of no scientific value ***at all***, to

the point that OEHHA entirely disregarded its findings of no adverse effects and did not include those findings in its data summaries or its integrative evaluations.

As indicated above, it is appropriate and indeed, required by law and this Committee's own guidance criteria to evaluate every study's ***quality***, and it is therefore at least potentially appropriate to discount or even disregard a particular study's findings if the study's deficiencies are severe. It is ***not*** appropriate, however, to consider the quality of studies only selectively and use inconsistent evaluation criteria, and yet that is clearly what OEHHA has done. As demonstrated in the attached Critical Evaluation, ***all of the open literature studies cited uncritically in the Hazard Identification Document suffer from deficiencies the same as, and in many cases worse than, the deficiencies cited by DPR with respect to the Wrenn study.*** *See* Critical Evaluation generally, and Tables 1 to 3 for a summary of such deficiencies. It is true that DPR did not reach any such "conclusions" with respect to the open literature studies, but of course none of those studies were ever submitted to DPR. Nor did any of those studies remotely approach the level of quality to be considered "adequate for pesticide registration."

Stated simply: the findings of the open literature studies are subject to much ***more*** doubt and uncertainty than the findings of the Wrenn study, and in fact the absence of reproductive toxicity reported in the Wrenn study is confirmed by the results of the guideline reproductive toxicity report (Hoberman, 1992). In almost every case, the effects reported in the open literature studies are contradicted by the FIFRA studies.

4. THE WEIGHT OF THE EVIDENCE INDICATES THAT DELTAMETHRIN SHOULD NOT BE LISTED

The Critical Evaluation further demonstrates, using the required "weight-of-evidence" approach, that deltamethrin does not cause adverse reproductive or developmental effects, and should not be listed as a reproductive toxicant for purposes of Proposition 65. Briefly, the high-quality data from Guideline studies show no adverse reproductive or developmental effects. By contrast, the data cited in the HID as evidence of adverse effects all suffer from serious flaws, and should be discounted if not disregarded.

The most relevant studies for evaluating deltamethrin include two-generation reproduction and developmental neurotoxicity studies in the rat and developmental toxicity studies in the rat and rabbit. The two-generation reproduction study in the rat showed no effect on reproduction or developmental endpoints at any dietary level (Hoberman, 1992), supporting the finding of no adverse effects in the three-generation reproduction study in the rat which, although not accepted by DPR to support a pesticide registration, remains valuable as a source of comparative data. The developmental toxicity study in the rat showed no evidence of developmental toxicity in the fetus at any dose level (Schardein, 1990). The developmental toxicity study in the rabbit showed no evidence of developmental toxicity (Richard, 2001). The developmental neurotoxicity study in the rat showed a slight delay in onset of preputial separation, but only at the upper-level dose of 200 parts per million, where there were signs of maternal and systemic toxicity (Gilmore *et al*, 2006). All of these studies were accepted by US EPA and DPR.

CONCLUSION

For all of the reasons above, we believe that the HID should be withdrawn and revised to present a balanced discussion of the test data in a document more amenable to conducting the weight-of-evidence assessment that Proposition 65 requires. In our opinion, the body of published data that meet the standards for scientific credibility is so limited that deltamethrin does not need to be evaluated further. If the Committee is to consider deltamethrin nonetheless, then it should conclude, taking into account the weight of the evidence, that deltamethrin has not been "clearly shown, through scientifically valid testing according to generally accepted principles, to cause reproductive toxicity," and should not be listed under Proposition 65.

A finding that deltamethrin should not be listed would be consistent with the findings of various respected regulatory bodies. Deltamethrin has been evaluated comprehensively by pesticide regulatory agencies around the world, including the US EPA, DPR, the Health Canada Pesticide Management Regulatory Agency ("PMRA"), the Swedish Chemicals Agency ("KemI")[4] (acting on behalf of the European Union for Annex 1 listing for both Plant Protection and Biocidal Products), and the World Health Organization ("WHO")[5]. None of these agencies has concluded that deltamethrin causes adverse reproductive or developmental effects.

Respectfully submitted,

Christian Volz
Stanley W. Landfair
Counsel for Bayer CropScience LP

cc: George Alexeeff, Ph.D., Director, OEHHA
Carol Monahan-Cummings, Chief Counsel, OEHHA

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4 May 2011 Assessment Report by Sweden for the Inclusion of Deltamethrin on Annex 1 to Directive 98/8 (EU biocidal products) at 12: ("No effect on mating performance or fertility was noted in the rat two-generation (feeding) study. Clinical signs (indicating neurotoxic effects), reduced body growth and histopathological changes (gastric erosions) were noted in adult rats. In offsprings [sic] reduced pup body weights, increased pup deaths (F1 generation) and reduced lactation (F1 generation) were noted at maternal toxic doses." "No developmental toxicity was noted at maternal toxic doses. Increased incidence of supernumerary ribs was noted in offspring at doses with maternal toxicity.") Document available at: http://www.shema.gov.rs/media/204202/deltamethrin.pdf.

5 WHO Specifications for Public Health Pesticides, FAO/WHO Evaluation Report 333/TC (April 2005), at 69: "Deltamethrin is not a skin/eye irritant, nor a skin sensitizer, and there is no evidence of genotoxic, carcinogenic, mutagenic, teratogenic or reproductive effects." Document available at: http://www.who.int/whopes/quality/Deltamethrin_eval_specs_WHO_Jan_2010.pdf.

ATTACHMENT

(Nov. 1993) CRITERIA FOR RECOMMENDING CHEMICALS FOR LISTING AS "KNOWN TO THE STATE TO CAUSE REPRODUCTIVE TOXICITY"

1. General Principles

   A. The criteria included herein shall be utilized by the Office of Environmental Health Hazard Assessment Science Advisory Board Developmental and Reproductive Toxicant (DART) Identification Committee to identify chemicals to be recommended as known to the State to cause reproductive toxicity, for purposes of the Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65").

   B. These criteria shall be updated periodically, as appropriate, to incorporate contemporary scientific views dealing with the evaluation of reproductive toxicity.

   C. These criteria are intended to give the DART Identification Committee maximal flexibility in evaluating all pertinent scientific information in determining whether a chemical is known to the State to cause reproductive toxicity. These criteria are not intended to limit the scope of the Committee's consideration of appropriate scientific information, nor to limit its use of best scientific judgment.

   D. In evaluating the sufficiency of data, a "weight-of-evidence" approach shall be used to evaluate the body of information available for a given chemical.

2. Definitions

   A. Chemicals known to the State to cause reproductive toxicity include those that have been clearly shown to be toxic by "scientifically valid testing according to generally accepted principles" (Health and Safety Code, Section 25249.8(b)).

   B. For purposes of these criteria, "reproductive toxicity" includes "developmental toxicity", "female reproductive toxicity", and "male reproductive toxicity".

   C. "Developmental toxicity" is defined to include adverse effects on the products of conception (i.e., the conceptus), including but not limited to:

(1) Embryo/fetal mortality (including resorption, miscarriage/spontaneous abortion, or stillbirth), malformations, structural abnormalities and variations, altered fetal growth, and change in gestational age at delivery.

(2) Postnatal parameters including growth and development, physiological deficits and delay, neurological, neurobehavioral and psychological deficits, altered sex ratio, abnormal sexual development or function, and morbidity or mortality.

(3) Transplacental carcinogenesis.

(4) Somatic or genetic (germ cell) mutations in the conceptus.

D. "Female reproductive toxicity" is defined to include effects on the adult or, where appropriate, developing female organism, including, but not limited to:

(1) Adverse effects on reproductive structure or function including:

a. Genetic damage to the ovum or its precursors.

b. Alterations in ovulation, menstrual (estrous) cycle and/or menstrual (estrous) disorders.

c. Impaired or altered endocrine function.

d. Complication of pregnancy.

(2) Impaired reproductive performance (e.g., sub fertility or infertility, including:

a. Increased pregnancy wastage (e.g., miscarriage/spontaneous abortion or stillbirth).

b. Inability or decreased ability to conceive (e.g., time to conception).

c. Adverse effects observed in sexual behavior, onset of puberty, fertility, gestation, parturition, lactation, or premature reproductive senescence.

E. "Male reproductive toxicity" is defined to include effects on the adult or, where appropriate, developing male organism, including, but not limited to:

(1) Adverse effects on reproductive structure or function including:

a. Genetic damage to the spermatozoon or its precursors.

b. Impaired sperm and/or seminal fluid production, including alterations in sperm number, morphology, motility, and ability to fertilize.

c. Impaired or altered endocrine function.

(2) Impaired reproductive performance (e.g., sub fertility, infertility, or impotence).

3. Developmental, and female and male reproductive effects shall meet at least one of the following criteria for recommendation as known to the State to cause reproductive toxicity.

A. Sufficient evidence in humans.

(1) Includes any of a variety of epidemiological studies, so long as the study or studies are scientifically valid according to generally accepted principles and provide convincing evidence to support a causal relationship between exposure to the chemical, and the developmental or reproductive effect in question. This requires accurate exposure and toxicity endpoint classification and proper control of confounding factors, bias, and effect modifiers.

(2) Clinical cases can be used if carefully delineated with respect to the presence of a specific syndrome (or developmental/reproductive toxicity endpoint) and if the reports consistently show an association between exposure to the agent and the occurrence of the particular endpoint of developmental or reproductive toxicity. Exposure to the agent should have occurred at the developmental or reproductive stage relevant to the endpoints identified.

(3) Weight of evidence considerations.

a. Data from multiple studies increase the confidence for classification of an agent as a developmental or reproductive toxicant, and unless there is an exceptionally strong study (see below), effects should occur in more than one human study for a chemical to be recommended for listing on the basis of epidemiologic evidence alone.

b. Data from a single well conducted epidemiologic developmental or reproduction toxicity study showing a clear relationship between exposure and effect may be sufficient to classify an agent as a developmental or reproductive toxicant, provided there are not equally well conducted studies which do not show an effect and which have sufficient power to call into question the repeatability of the observation in the positive study.

B. Limited evidence or suggestive evidence in humans, supported by sufficient experimental animal (mammalian) data, as described below.

C. Sufficient evidence in experimental animals (mammals), such that extrapolation to humans is appropriate. "Sufficient" animal data would, in most cases, be based on the adequacy of the following:

(1) The experimental design, including overall protocol and numbers of animals, and presence of appropriate controls.

(2) The exposure, in terms of route of administration, is relevant to expected human exposures, and in terms of timing, with regard to critical periods of development for developmental toxicity, sexual maturation, stage of pregnancy, or other critical periods for female reproductive toxicity, and sexual maturation, spermatogenesis, or other critical periods for male reproductive toxicity.

(3) Number of dose levels, so that the presence of a dose-response relationship can be evaluated. It is desirable that the high dose level should elicit maternal toxicity in developmental studies, and systemic toxicity in female and male reproductive studies, and that the low dose should elicit no observable adverse effect for adult and offspring.

(4) Consideration of maternal and systemic toxicity.

Differentiating between (a) the effects of a toxic agent on the conceptus or reproduction and (b) the effects on the conceptus or reproduction that are secondary to the maternal or systemic toxic effects is sometimes difficult and may require special attention, on a case by case basis.

(5) Number of tests or experimental animal species.

a. In general, effects should occur in multiple studies or multiple species for a substance to be recommended for listing.

b. Weight of evidence considerations.

1. Data on a single species from a well conducted developmental or reproduction study may be sufficient to classify an agent as a reproductive toxicant provided there are not equally well conducted studies which do not show an effect and which have sufficient power to call into questions the repeatability of the observation in the positive study.

2. Data on more than one species or from more than a single study increase the confidence for classification of an agent as a reproductive toxicant.

(6) Other considerations, including, but not limited to those listed below, which can increase or decrease the confidence for classification of an agent as a reproductive toxicant.

a. Severity or consistency of findings.

b. Metabolic and pharmacokinetic data.

c. Time course of events.

4. Statistical considerations and biological plausibility.

A. Statistical analyses are important in determining the effect of a particular agent; however, the biological significance of the data should not be overlooked. Given the number of endpoints that can be quantified in developmental and reproduction studies, a few statistically significant

differences may occur by chance alone. Conversely, apparent dose-related trends may be biologically relevant even though statistical analyses do not indicate a significant effect.

B. In determining whether a chemical is to be recommended to be listed as known to the State to cause reproductive toxicity, the biological plausibility of the association between the adverse reproductive effects observed and the chemical in question should be considered. Confidence is increased when, based on known principles of developmental and reproductive biology, physiology, and toxicology, a sound scientific basis exists for the observed adverse effects and the known characteristics of the particular chemical. Conversely, confidence is decreased if the observed adverse effects are contradictory to the known characteristics of the particular chemical.

BCS US0323

Bayer CropScience

CRITICAL EVALUATION *of*

HAZARD IDENTIFICATION DOCUMENT *for*

DELTAMETHRIN

prepared for

DEVELOPMENTAL & REPRODUCTIVE TOXICANT IDENTIFICATION COMMITTEE

by

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December 11, 2012

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SUMMARY

A full complement of guideline developmental toxicity, developmental neurotoxicity and reproductive toxicity studies has been performed with deltamethrin, in accordance with US EPA guidelines and in compliance with GLP standards. These studies have been reviewed and accepted by the US EPA, California DPR and other authorities to support product registrations for products that contain deltamethrin, with the determination that deltamethrin is not a developmental or reproductive toxicant. These studies are summarized herein, and are powerful evidence that deltamethrin should not be designated as a reproductive toxicant for purposes of California's Proposition 65.

In addition to the studies referred to above, the Hazard Identification Document (HID) also includes summaries of some studies from the public literature that claim to show reproductive or developmental toxicity. These reported findings are modest and inconsistent, relative to the findings from studies performed according to generally-accepted scientific principles and standards accepted in the regulatory community that show no such effects.

Based on the weight-of-evidence, deltamethrin should not be listed as a reproductive toxicant. This position is consistent with reviews conducted by the U.S. Environmental Protection Agency (US EPA), California's Department of Pesticide Regulation (DPR), Health Canada Pesticide Management Regulatory Agency (PMRA), the European Food Safety Authority (EFSA), the World Health Organization (WHO) and other health authorities around the world.

BACKGROUND AND PURPOSE

Deltamethrin (CAS No. 52918-63-5) is a pyrethroid insecticide that has been registered since 1974 for a wide variety of agricultural, residential and pest control uses throughout the world. Deltamethrin is also widely used in mosquito abatement and vector control programs in Africa, Asia, Middle East, Latin America and Southern European countries. Indoor residual spray products and deltamethrin-incorporated bed nets are approved for malaria control programs under the World Health Organization Pesticide Evaluation Scheme.

These uses of deltamethrin are regulated extensively, by agencies that require and evaluate toxicological data prior to issuing "registrations" or other licenses that allow the substance to be used as a pesticide. Because deltamethrin is used in so many countries, there is an extensive dossier of regulatory studies on deltamethrin, which has been reviewed by authorities around the world.

Proposition 65 requires the publication of a list of chemicals "known to the state" of California to cause cancer or reproductive toxicity. The regulations specify

that "a chemical is known to the state to cause reproductive toxicity...if in the opinion of the state's qualified experts the chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause reproductive toxicity...."

In 2011, the California Office of Environmental Health Hazard Assessment (OEHHA) initiated a preliminary review of data to determine whether an evaluation was warranted for deltamethrin. The preliminary review was initiated because the number of articles/studies available in the open literature concerning the development and reproductive toxicity of deltamethrin met the minimum screening criteria (15) set by OEHHA (2004), and was not triggered by any authority concluding deltamethrin to be a reproductive or developmental hazard. After reviewing abstracts of the publications, the Developmental and Reproductive Toxicant Identification Committee (DART IC or Committee) recommended that deltamethrin be evaluated further, along with 5 additional chemicals, noting a lower priority for deltamethrin than for others (transcript of July 13, 2011 DART IC meeting, page 14).

On January 20, 2012, OEHHA announced plans to prepare the HID for deltamethrin, surprisingly ahead of most of the other chemicals reviewed at the June 2011 meeting, despite deltamethrin being given a lower priority by the DART IC. Bayer CropScience (BCS) responded by providing comments, including a summary of both guideline and published developmental and reproductive toxicity studies (Sheets, 2012).

On October 12, 2012, OEHHA issued a draft HID for deltamethrin for public comment. The document contains reviews of publications and guideline studies for eventual consideration by the DART IC as to whether deltamethrin should or should not be listed under Proposition 65. Since the HID does not discuss important limitations of the publications and findings, it appears to indicate or imply that all studies are of equal weight and value.

The purpose of this document is to provide a critical assessment of the studies and findings cited in the current version of the HID, in order to assist the Committee to make scientifically-sound conclusions.

SUMMARY OF STUDIES FOLLOWING GENERALLY ACCEPTED GUIDELINES FOR ASSESSING DEVELOPMENTAL AND REPRODUCTIVE TOXICITY

The most relevant information to evaluate deltamethrin for developmental and reproductive toxicity (DART) is derived from the DART studies that were performed in accordance with U.S. EPA and international (OECD) test guideline requirements, which include ***two-generation reproduction*** and ***developmental***

neurotoxicity studies in the rat and ***developmental toxicity studies*** in the rat and rabbit.

These studies have been accepted to satisfy the requirements of the California DPR and the US EPA to identify adverse DART effects of potential relevance to humans and to establish No-Observed-Adverse Effect Levels (NOAELs) for use in risk assessments. All elements of experimental design and conduct (*e.g.*, the selection of species / strain, sample size, the number of dose groups, the rationale for dose selection, the route and duration of dose administration, test material and dose characterization, and the selection of endpoints) are based on experience that establishes the suitability and reliability of these studies to identify adverse effects and provide data suited for human health risk assessments.

These studies were also performed in compliance with Good Laboratory Practice (GLP) standards, which provide rigorous documentation to verify the resulting information accurately reflects the reported study conditions, test methods and results. Assessing the quality of data and suitability of the testing procedures includes the availability of historical control data to demonstrate appropriately-low levels of variability between studies to assist in identifying treatment-related effects. The use of internationally-validated test guidelines to investigate effects on development and reproduction in experimental animals helps to ensure the sensitivity, reliability, reproducibility and relevance of study results to predict potential effects on human health.

The following is a summary of the studies that were performed specifically to investigate developmental and reproductive toxicity with deltamethrin and which have been evaluated by the World Health Organization, US EPA, other national regulatory agencies and California DPR. Considerably more detail regarding these studies is available in evaluations that were performed by the U.S. EPA or California DPR.

1. ***Three-generation reproduction study.*** In this study, 10 male and 20 female SD rats per dose level were treated via the diet with 0, 2, 20 or 50 ppm deltamethrin technical (98% purity) (Wrenn, 1980). This study was performed before current test guidelines were established and therefore did not meet all the guideline requirements that were imposed after the study was completed (missing parental histopathology and microscopic examination in pups was limited to F3b weanlings). Also, the highest dose level produced insufficient evidence of toxicity to satisfy the guideline requirements, with evidence of toxicity limited to a modest reduction in body weight at the highest dietary level (50 ppm; approximately 2.5 mg/kg/day). In order to satisfy existing guideline requirements a two-generation reproduction study was performed (Hoberman, 1992). Despite

these shortcomings, this study has significant value and is well-suited to support the determinations from the guideline two-generation reproduction study, to verify that doses as high as 2.5 mg/kg/day deltamethrin do not affect reproduction or development.

2. *A two-generation reproduction study* was performed in accordance with USEPA (FIFRA 83-4) guideline requirements (Hoberman, 1992). In this study, 30 male and 30 female SD rats per dose group were treated via the diet with 0, 5, 20, 80 or 320 ppm deltamethrin technical (99.7% purity) for two generations. These dietary levels resulted in doses of approximately 0, 0.4, 1.4, 5.7, or 22 mg/kg/day in parental animals and 0, 0.4, 1.6, 6.2 or 26 mg/kg/day in F1 animals, respectively. Decreased body weight gain, clinical signs consistent with a type II pyrethroid and mortality in adult and pups demonstrate the highest dietary level was a maximum-tolerated dose. The NOAEL was 80 ppm, based on reduced body weight and increased pup mortality during the lactation period when exposure is especially high due to high consumption of the treated feed. ***There was no effect on reproduction or developmental endpoints at any dietary level.*** Furthermore, there was no effect on reproductive tissue weights (e.g., uterus/cervix, ovary, pituitary, testis and epididymis, seminal vesicle and coagulating gland and prostate) or microscopic lesions in male or female reproductive tissues. California DPR considered this study to be acceptable, with a reproductive toxicity NOAEL 320 ppm (corresponding to 21.2 to 24.9 (M) and 21.8 to 37.3 (F) mg/kg/day), based on no effects at the highest dietary level, and a developmental toxicity NOAEL of 80 ppm (5.8/6.7 mg/kg/day in males and females, respectively), based on decreased body weight and increased mortality at 320 ppm.

3. *A developmental toxicity study in rats* was performed in accordance with USEPA (FIFRA 83-3(a)) guideline requirements (Schardein, 1990). In this study, groups of 25 mated female Sprague-Dawley Crl:CD VAF/Plus rats were dosed by gavage with deltamethrin technical (99.2% purity) at 0, 1, 3.3, 7.0 or 11 mg/kg/day on gestation days 6 through 15, with fetuses collected by caesarean section on gestation Day (GD) 20 to examine for gross, visceral and skeletal alterations. Maternal toxicity was evident at 7 and 11 mg/kg/day as death or moribund sacrifice, decreased body weight and clinical signs typical for a type II pyrethroid. By comparison, there was ***no evidence of developmental toxicity in the fetus at any dose level.*** California DPR considered this study acceptable, with NOAELs for maternal and developmental toxicity of 3.3 and 11 mg/kg/day, respectively.

4. A ***developmental toxicity study in rabbits*** was performed in accordance with USEPA (OPPTS 870.3700) and O.E.C.D. (TG 414) guideline requirements (Richard, 2001). This study was not included in the preliminary review performed by the DART IC. In this study, groups of 24 pregnant NZW rabbits per group received deltamethrin technical (99.1% purity) by gavage at 0, 3, 10 or 32 mg/kg/day from gestation days 6 to 28, with fetuses examined following caesarean section. Maternal toxicity was limited to the high dose, with decreased food consumption and body weight gain. ***There was no evidence of developmental toxicity*** (*e.g.,* fetal mortality, developmental malformations or variations) at any dose level tested. California DPR considered this study acceptable and established a maternal toxicity NOEL of 10 mg/kg/day and a developmental toxicity NOEL of 32 mg/kg/day.

5. A ***developmental neurotoxicity study was p***erformed in accordance with USEPA (OPPTS 870.6300) and OECD (TG 426) guideline requirements (Gilmore *et al.*, 2006). This study was also not included in the preliminary review performed by the DART IC. ***California DPR has determined this study was complete and acceptable.*** In this study, groups of 20 Wistar rats per dose group were treated via the diet with deltamethrin technical (98.8% purity) at 0, 20, 80 or 200 ppm (1.64, 6.78 and 16.1 mg/kg/day) from GD 6 to lactation Day (LD) 21. Tests used to evaluate the offspring for evidence of toxicity and developmental neurotoxicity included automated tests of motor activity, auditory startle habituation, and cognition (passive avoidance and water-maze tests for learning and memory), with gross and microscopic brain measurements and extensive microscopic analysis of peripheral and central nerve tissues for evidence of pathology. Findings at 200 ppm consisted of decreased body weight and weight gain in the dams and decreased body weight and clinical signs of toxicity during the period of exposure, with an associated slight delay in onset of preputial separation. The NOAEL for the maternal and developmental toxicity was 6.78 mg/kg/day.

Treatment-related findings in these studies were non-specific and secondary to decreased body weight at high dose levels. Based on the collective results from guideline studies, the US EPA and California DPR, as well as other major regulatory bodies (PMRA, EU, WHO), have concluded deltamethrin is not a developmental or reproductive toxicant.

In contrast to the studies described above, the experiments reported in the open literature were not conducted according to any recognized guideline, and the many differences in experimental design and missing details of test procedures among these studies severely limit the opportunity to assess the biological significance or reproducibility of a given finding. Tables 1, 2 and 3 in Appendix I

compare the study designs and qualities of publications and regulatory studies for male reproductive, female reproductive and developmental toxicities. Full analysis of each published study is reported later in this document in the next section of this document, below.

PUBLISHED DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

These studies were not conducted in accordance with established test guidelines or GLP standards. While this does not necessarily mean that the data from these studies have *no* value or relevance, it is appropriate to scrutinize the study designs, methods and results for reliability and relevance to humans. In fact, the non-guideline studies included in the HID represent investigative (basic) research with deltamethrin used as a model compound and have multiple deficiencies in common that substantively limit their relevance to identify human health effects.

- *Uncertain reliability and consistency of results.* These papers generally report all differences from control as a treatment-related effect, without demonstrating the results for treated animals exceed the range of biological variability in control animals (historical control) or whether a finding is dose- related or can be repeated (robust). The sample size in such studies should be sufficiently large to accommodate for biological variability, especially if there is only one dose level for comparison to a concurrent control.
- *Test substance purity and dose levels not verified.* Without verification, the treatment administered to the animals is less certain or unknown.
- *Test substance is an unidentified mixture.* In some studies, the test material was a commercial formulation, with only 2.5% or 5% deltamethrin and the balance (95-97.5%) consisting of undefined formulating agents.
- *Route of administration.* Routes of human exposure to deltamethrin are generally limited to oral (dietary or hand-to-mouth) or percutaneous, with only a small fraction absorbed through the skin. Other routes of administration that were used in these studies (*i.e.,* subcutaneous or intraperitoneal) are of unknown relevance to man, due to differences in the kinetics of absorption, distribution, metabolism (by-pass gut and liver) and elimination.
- *Single dose level.* Testing only one dose level greatly diminishes the opportunity to evaluate the biological significance of the reported findings (e.g., to evaluate biological variation / consistency among dose groups and a trend associated with dose level (dose-response)). As such,

corroborating evidence is required to determine whether a difference from control represents a treatment-related effect or biological variability between two groups.

The following comments include reference to these and other limitations for the principal studies that were cited in the HID review.

BCS ASSESSMENT OF PRINCIPAL STUDIES CITED IN THE HID REVIEW

This section includes the information that is provided in the Executive Summary of the HID, which is presented as summaries of studies or data showing male or female reproductive toxicity or developmental toxicity (Iyer *et al.*, 2012), along with BCS comments for each of the cited studies and a concluding weight-of-evidence assessment for each of the subject areas. These comments are supplemented by tables that summarize key elements of study design and interpretation (Tables 1-3, respectively), using criteria designed to evaluate data reliability for use in hazard or risk assessment (Klimisch *et al.*, 1997).

1. MALE REPRODUCTIVE TOXICITY

HID Review. At page 5 of the HID, the Executive Summary states:

"Several studies have examined the effect of deltamethrin exposure on the male reproductive system are available. These include studies in the mouse, rat and rabbit, as well some studies conducted *in vitro*. Adverse effects noted in the studies are outlined below.

- Decreased live sperm and plasma testosterone levels:
  - In a rat study, oral administration of deltamethrin for 65 consecutive days (to cover a complete spermatogenic cycle) decreased sperm concentration and the conception rate in non-treated females that were mated with treated males. The decrease in live sperm and plasma testosterone levels continued and was noted 21 days after administration of the chemical was stopped. Degenerative changes in testicular and accessory gland structures were also noted."

BCS Comments on HID Review:

The statement above describes the findings reported in Abd el-Aziz *et al.*, 1994. For the reasons below, these data would not support listing.

It is important to note the test material was a formulation (Decis 5 Flowable) with only 5% deltamethrin; therefore, it should be considered that any findings associated with treatment may be due to one or more of the formulating agents rather than to deltamethrin. This position is also supported by evidence that

this formulation is more toxic than technical-grade deltamethrin (purity >97%). The sample sizes (5/group for organ weights and 8/group for mating) are also insufficient to support any conclusions; by comparison, the guideline two-generation reproduction study had 30 rats/sex/dose level. Furthermore, the animals in this study were fed an unusual diet of milk and barley, which would have uncertain impact on their health and response to treatment. Moreover, the determination that a cholinesterase inhibitor (diazinon; identified only as a 50% oily solution) produced similar effects also casts some doubt as to whether these differences from control are due to treatment or are incidental findings (biological variability with small sample size). Finally, the guideline two-generation reproduction study is the most definitive study to evaluate effects on reproduction. The results of this guideline study determined that deltamethrin (99.7% purity) had no effect in P or F1 males on testis or prostate weight or histopathology for these three tissues or fertility at much higher doses and a longer duration of exposure, except for decrease in multiple tissue weights secondary to decreased body weight at the high dose of 24.9 mg/kg/day (Hoberman, 1992). Therefore, the study by Abd el-Aziz *et al.*, 1994 is poorly suited to evaluate the potential for deltamethrin to affect male reproduction in man and the reported findings are not supported by the guideline two-generation reproduction study.

HID Review. At page 5 of the HID, the Executive Summary States:

"Subcutaneous exposure to deltamethrin to rats at doses as low as 0.003 mg/kg-day for a period of 45 or 60 days produced an arrest of spermatogenesis and a significant decrease ($p \leq 0.05$) in plasma follicle stimulating hormone concentration compared to controls. Effects were not observed after 30 days of exposure."

BCS Comments on HID Review:

The statement above summarizes the data reported in Issam *et al.*, 2009. For the reasons below, these data would not support listing.

In this study, deltamethrin was given by subcutaneous administration to male Wistar rats (6/dose group), with testis histopathology and measures of sex hormones and oxidative stress at termination. This study represents investigative research, with substantial deficiencies to evaluate effects on human health and findings that are not supported by results from guideline studies. Notable limitations and uncertainties include unknown test material purity, uncertain relevance of this route of administration to human circumstances of exposure and an insufficient sample size. With subcutaneous administration, the internal dose is likely much higher than via oral exposure, due to by-passing first-pass metabolism in the gut and liver. Therefore, these results would require confirmatory research to establish relevance to human circumstances of

exposure. Given the deficiencies of this study and the lack of effect on testis and epididymis weights and histopathology in the more definitive guideline two-generation reproduction study, with longer exposure to much higher doses (Hoberman, 1992), these findings do not support concerns for reproductive effects in man.

HID Review. At page 5 of the HID, the Executive Summary states:

"Testicular effects and reproductive behavior:

- Intraperitoneal injection of deltamethrin to male rats at 1 mg/kg was shown to induce testicular apoptosis."

BCS Comments on HID Review:

The statement above describes data reported in El-Gohary *et al.*, 1999. For the reasons below, this study would not support listing.

This study represents basic research with substantial deficiencies and findings that are not supported by results from guideline studies. The most notable limitations include treatment via intraperitoneal injection, a route of uncertain relevance to human exposures (by-pass metabolism in the gut and liver), testing a single dose level and lack of characterization of the test material and doses. Moreover, histopathology was not evident in the testis of P or F1 rats in the guideline two-generation reproduction study, with exposure at much higher doses through a full cycle of spermatogenesis (Hoberman, 1992).

HID Review. At page 5 of the HID, the Executive Summary states:

"*In utero* and lactational exposure of rats to 4.0 mg/kg deltamethrin via the oral route induced subtle changes in the reproductive behavior and physiology of male offspring (reduction in the number of animals with ejaculate) along with a decrease in testicular and epididymal absolute weights and the diameter of seminiferous tubules."

BCS Comments on HID Review:

The statement above describes data reported in Andrade *et al.*, 2002. For reasons below, this study would not support listing.

The findings attributed to deltamethrin in this study were limited to decreased absolute (not relative) testis and epididymis weights and diameter of seminiferous tubules in a small number (5) of animals at the single dose level, 4.0 mg/kg. The authors noted the changes were subtle and of unknown consequences. It appears these differences from control were secondary to

decreased body weight at the highest dose tested, since relative tissue weights (which take decreased body weight into account) were not different from control. Unfortunately, other tissue weights were not provided for reference to assist with the interpretation. In the context of other papers cited in the HID, it should be noted that testosterone and sperm morphology and the onset of preputial separation were not affected in this study. As discussed below, the guideline two-generation reproduction study showed these and many other absolute tissue weights were affected, but only at a much higher dose (24.9 mg/kg/day), which was secondary to decreased body weight gain during growth and development (Hoberman, 1992). Therefore, these findings do not provide evidence of reproductive toxicity and do not raise human health concerns.

HID Review. At page 6 of the HID, the Executive Summary States:

"In a two-generation reproduction study in rats, the absolute mean weights of the epididymides and testes of the F1 males exposed to 320 ppm deltamethrin in diet were significantly less than those of the controls. There was also a significant decrease in the ratio of the weights of these organs (epididymides and testes) to brain weight. Increased mortality was noted in animals at this dose-level."

BCS Comments on HID Review:

The statement above describes data reported in Hoberman, 1992. For reasons below, this study would not support listing.

In this study, differences in absolute testis and epididymis weights, relative to controls and relative to brain weights, were not specific to males or reproductive tissues. Rather they represent a non-specific effect, as many other tissues were similarly affected in both sexes and were secondary to a decrease in body weight and weight gain during growth and development, at a dietary level that exceeded a maximum-tolerated dose (*e.g.,* pup lethality). By comparison, relative tissue weights (which account for differences in body weight at the time tissues were collected) were increased, relative to controls, to show partial compensation for the body weight reduction and absolute brain weight was spared, as brain tissue is preferentially conserved in such cases, relative to other tissues. Therefore, these findings do not provide evidence of reproductive toxicity.

HID Review. At page 6 of the HID, the Executive Summary states:

"Sperm motility and abnormalities:

Oral administration at 5 mg/kg-day of deltamethrin resulted in significantly decreased sperm count, motility and viability and a significantly increased percentage of morphologically-abnormal spermatozoa compared with the controls in mice. Deltamethrin and dimethoate administered together had similar effects."

BCS Comments on HID Review:

The statement describes data reported in Abdallah *et al.*, 2010. For reasons below, this study would not support listing.

This study reports a decrease in sperm count, motility and viability and increased morphologically-abnormal spermatozoa in mice, with no effect on testis or epididymis weights (a difference from other studies). The organophosphorus insecticide dimethoate, which has a very different toxicity profile (cholinesterase inhibition), had the same profile of effects, casting some doubt whether these differences from control are due to treatment or represent incidental findings (*e.g.,* biological variability). Study deficiencies include the use of mice as the test species (rat is the standard model), of undefined age and weight, insufficient details about the test material, dose verification and test procedures, and testing only one dose level. Moreover, the animals were not treated for a full cycle of spermatogenesis (21 days versus 43-day cycle), whereas the testis and epididymis expressed no histopathology in the guideline two-generation reproduction study in rats, with treatment through a complete cycle of spermatogenesis at a 5-fold higher dose level (Hoberman, 1992). Therefore, this study represents basic research with substantial deficiencies that requires confirmatory evidence to support.

HID Review. At page 6 of the HID, the Executive Summary states:

"Rabbits exposed orally to deltamethrin exhibited decreased ejaculate volume and sperm concentration and an increase in percentage of dead spermatozoa."

BCS Comments on HID Review:

The statement describes findings reported in Salem *et al.*, 1988. For reasons below, this study would not support listing.

The findings cited from this study are unreliable or preliminary, at best, given the very small sample size (3/dose group) and the reported findings were only slight. Such findings could easily be within the range of biological variability

between small groups of untreated animals, as there was no reference to the historical control range. The organophosphorus insecticide dimethoate, which has a very different toxicity profile (inhibition of acetylcholinesterase activity), was reported to have similar effects, casting further doubt as to whether these differences from control are due to treatment or incidental findings. Furthermore, the rabbit is not the preferred model to predict effects on male reproduction, there are no details of test material composition, the dose levels were not defined and doses were not verified, and the results are not presented in sufficient detail. The dose levels were also inadequately defined as 1/10 and 1/100 the LD50, which severely limits evaluation of the findings relative to other information for deltamethrin. Finally, the guideline two-generation reproduction study in rats showed no effect on the testis or epididymis, based on tissue weights (only secondary to decreased body weight) and histopathology (Hoberman, 1992). While these are different endpoints, histopathology would be expected if there were biologically-significant effects on ejaculate volume and sperm.

WEIGHT-OF-EVIDENCE ASSESSMENT

The results from all available information support the conclusion that deltamethrin is not a male reproductive toxicant and should therefore not be listed as a reproductive toxicant under Proposition 65. The two-generation reproduction study (Hoberman, 1992) is the most definitive assay, which was conducted in accordance with guideline requirements and has been accepted by the California DPR and the US EPA. The results of this study demonstrate that deltamethrin is not a reproductive toxicant in males, even at overtly-toxic dose levels. Studies cited from the published literature have significant limitations and do not provide consistent or sufficient evidence to challenge the determination that deltamethrin is not a reproductive toxicant in males.

2. FEMALE REPRODUCTIVE TOXICITY

HID Review. At page 6 of the HID, the Executive Summary states:

"Three studies reported adverse female reproductive effects.

- Uterine and Pituitary weights:
  - In a two-generation rat reproductive study, parental females exposed to 320 ppm in diet demonstrated a decrease in the absolute mean weight for the non-gravid uterus ($p<0.01$) and the absolute mean pituitary weights ($p<0.05$) compared to those of the control group. Increased mortality was noted in animals at this dose-level."

BCS Comments on HID Review:

The statement above describes data reported in Hoberman, 1992. For reasons below, this study would not support listing.

As noted in comments above, many other absolute (not relative) tissue weights were reduced in this study in males, as well as females, at the highest dietary level. Decreased tissue weights were secondary to decreased body weight. Therefore, these differences from control represent non-specific toxicity at an overtly-toxic dose and provide no evidence of reproductive toxicity.

HID Review. At page 6 of the HID, the Executive Summary states:

"Implantation and fertility:

- Blastocyst-endometrium interactions in rats were examined subsequent to deltamethrin exposure and reduction in the number of implantation sites and alterations in histopathology of the sites were noted."

BCS Comments on HID Review:

The statement above describes findings reported in Lemos *et al.*, 2011). For reasons below, this study would not support listing.

It is important to emphasize the test material was a formulation (Decis 25CE), which contains only 2.5% deltamethrin; therefore, any findings associated with treatment are more likely due to the formulating agents than to deltamethrin. It is also very difficult to imagine a plausible mechanism by which the biological pesticide XenTari (B. thuringiensis) would produce similar effects, casting considerable doubt whether these differences from control are due to treatment or incidental findings (biological variability for groups of 5 rats each). Finally, the results from guideline developmental toxicity and reproduction studies with

deltamethrin show no effect on the number of implantation sites or viable offspring, even at much higher dose levels and with treatment continuing through (and following) delivery. Therefore, these results represent basic research with a formulation containing only 2.5% deltamethrin and an insufficient sample size that is not supported by findings with technical-grade deltamethrin in guideline studies.

HID Review. At page 6 of the Executive Summary, the HID states:

"In another study in rats, a smaller number of pups and reduced fertility was noted subsequent to deltamethrin exposure."

BCS Comments on HID Review:

The statement describes findings reported in Lemos *et al.*, 2012. For reasons below, this study would not support listing.

As noted for Lemos *et al.*, 2011, the test material in this study was a formulation (Decis 25CE), which contains only 2.5% deltamethrin; therefore, any findings associated with treatment are more likely due to the formulating agents than to deltamethrin. This conclusion is supported by other evidence of toxicity that is not associated with deltamethrin. Also as with the Lemos *et al.,* 2011 publication, uncertainty or doubt is raised by the biological pesticide XenTari (*B. thuringiensis*) being reported to produce similar effects, which is simply not plausible. Most importantly, there was no decrease in litter size in guideline studies with deltamethrin, including the developmental neurotoxicity study (Gilmore *et al.*, 2006) or the two-generation reproduction study (F1 and F2 generations) at much higher dose levels (Hoberman, 1992). Therefore, this study provides no credible evidence of effects that would raise concerns for human health.

WEIGHT-OF-EVIDENCE ASSESSMENT

The results from the two-generation reproduction study and other guideline studies, which have been accepted by the California DPR and US EPA, have shown deltamethrin is not a reproductive toxicant in females. The results from the two studies cited from the published literature do not raise concerns for human health, since the studies have considerable deficiencies for hazard identification or risk assessment and the reported findings are not supported by results from developmental and reproduction studies of known reliability.

3. DEVELOPMENTAL TOXICITY

HID Review. At pages 6-7 of the Executive Summary, the HID states that

"Several studies examining the effect of in utero deltamethrin exposure in laboratory animal species are available.

- Developmental Neurotoxicity:
  - A developmental neurotoxicity study in rats demonstrated adverse effects such as reduced fixed female brain weight and increased resistance at removal with vocalization in males exposed during the prenatal and postnatal periods to 16.1 mg/kg-day."

BCS Comments on HID Review:

The statement above describes findings reported in Gilmore *et al.*, 2006. For reasons below, this study would not support listing.

In this study, decreased absolute (not relative) brain weight was reported at the highest dose tested in term (10-week-old) female offspring, but not in term male or 21-day-old male or female offspring. This finding was associated with a dose that produce decreased body weight during growth and development. In accordance with the test guideline, other tissues were not weighed for reference to verify the lack of specificity; however, in the two-generation study multiple tissue weights were reduced at the highest dose tested and relative brain (to adjust for decreased body weight) was not reduced. The reported increased incidence of males showing resistance to removal from home cage with vocalization at the high dose may represent a transient neurotoxic effect but is otherwise of unlikely relevance and was not evident on subsequent test occasions. Therefore, these findings do not raise concerns for developmental toxicity or developmental neurotoxicity.

HID Review. At page 7 of the Executive Summary, the HID states:

"Maternal exposure to 0.08 mg/kg-day during the organogenesis period in rats resulted in decreased locomotion frequency and increased immobility in the open field in male offspring."

BCS Comments on HID Review:

The statement above describes data reported in Lazarini *et al.*, 2001. For reasons below, this study would not support listing.

As noted for other studies, the testing of only one dose level in this study precludes assessment of whether differences between one treated and one control

group represent biological variability or treatment-related effects. Furthermore, the differences from control were not consistent across activity measures or sex (*e.g.,* modestly higher rearing and decreased immobility in males and no difference in rearing with slightly higher immobility score in females). Information from the guideline developmental neurotoxicity study determined that technical-grade deltamethrin (98.8% purity) administered at a range of much higher dose levels (1.64, 6.78 or 16.1 mg/kg/day) and longer duration (GD6 to PND 21) did not affect performance in a swimming test of cognitive function, nor did it alter activity or the number of rearing events in an open field during detailed clinical observations or automated measures of motor and locomotor activity in the figure-eight maze (Gilmore *et al.*, 2006). Therefore, the findings reported in this study differ from the results from the guideline developmental neurotoxicity study, which provides a much more definitive assessment of treatment-related effects on neurobehavior, motor function and cognition.

HID Review. At page 7 of the HID, the Executive Summary states:

"Alterations in biochemical and behavioral parameters as well as effects on the ontogeny of specific enzymes noted in other studies in rats suggest that prenatal exposure to a low dose of deltamethrin may cause alterations in offspring motor and dopaminergic activity systems as well as perturbations in biochemical parameters."

BCS Comments on HID Review:

The statement above describes findings reported in Lazarini *et al.*, 2001. For reasons below, this study would not support listing.

This study reports an effect on striatal dopamine levels in rats treated during gestation to a low dose (0.08 mg/kg/day) of deltamethrin. A critical review of study design limitations (*e.g.*, a single dose level) is provided above. It is unknown whether these findings are robust, persistent or an adaptive change that is rapidly reversible, or whether they represent an effect at all. As noted above, the associated effects on swimming behavior and motor activity reported in this study are not consistent with the results from the guideline developmental neurotoxicity study with defined test material and doses administered at considerably higher levels and a larger sample size (Gilmore *et al.*, 2006). Therefore, the results reported by Lazarini *et al.*, 2001 represent basic research with no known relevance or significance to human health.

HID Review. At page 7 of the HID, the Executive Summary states:

"Offspring viability, growth and malformations:

- One study in rats and one study in rabbits reported no adverse developmental effects."

BCS Comments on HID Review:

The statement describes data reported in Schardein, 1990 and Richard, 2001. For reasons below, this description is incomplete.

These are the developmental toxicity studies that were performed with technical-grade deltamethrin, in accordance with US EPA guidelines and accepted by California DPR. It should be noted there was also no evidence of developmental toxicity in rats in the two-generation reproduction (Hoberman, 1992) or developmental neurotoxicity (Gilmore *et al.*, 2006) studies performed in accordance with US EPA test guidelines and accepted by California DPR. The source of these determinations (no adverse developmental effects in rat or rabbit) should be noted in the Executive Summary, since the guideline studies are the most relevant for evaluating deltamethrin for evidence of developmental toxicity.

HID Review. At page 7 of the HID, the Executive Summary states:

"Oral maternal exposure to 0.08 mg/kg-day during the organogenesis period resulted in a delay in the day of eyes opening for male and early vaginal channel opening in female offspring in rats."

BCS Comments on HID Review:

The statement describes findings reported in Lazarini *et al.*, 2007. For reasons below, this study would not support listing.

As noted for Lazarini *et al.*, 2001, the test material purity used in this study was not provided, doses were not analyzed, and only one dose level was tested, which severely limits assessment to determine whether differences from control are due to treatment or inherent biological variability between two groups. This uncertainty is supported by the lack of consistency, with evidence of a developmental delay for one endpoint in males and another endpoint in females. The reported delay in eye opening in male pups is also inconsistent with the lack of effect on eye opening, startle reflex and righting reflex at higher doses (1.25 to 5 mg/kg/day; GD7-21) reported by others (Kavlock *et al.*, 1979). In the guideline developmental neurotoxicity study with technical-grade deltamethrin, deltamethrin had no effect on the onset of vaginal patency, at dose levels as high

as 16.1 mg/kg/day (200-fold higher than tested in this study) and a longer duration of exposure (Gilmore *et al.*, 2006). Therefore, this study represents investigative research that is not supported by other data, including results from the more definitive guideline developmental neurotoxicity study.

HID Review. At page 7 of the HID, the Executive Summary states:

"Mean age of attainment of preputial separation of male pups was delayed at maternal exposure to 16.1 mg/kg-day in the developmental neurotoxicity study in rats where the parameter was evaluated."

BCS Comments on HID Review:

The statement above describes data reported in Gilmore *et al.*, 2006. For reasons above, this study would not support listing.

The delay in preputial separation reported in this study was modest and associated with reduced body weight gain during growth and development at the highest dose level tested. Such a delay in preputial separation is common in studies with exposure through post-natal development at doses that reduce body weight and weight gain in the offspring, with no persistent reproductive consequences. Therefore, this finding does not represent evidence of developmental toxicity and is not relevant to human health concerns.

HID Review. At page 7 of the HID, the Executive Summary states:

"A study in rats reported a decrease in uterine weight, an increase in the percentage of resorbed fetuses as well as malformed fetuses in a dose-dependent manner (at 13.38 and 26.75 mg/kg-day) along with a decrease in average body weight of the fetuses and incomplete ossification. A decrease in maternal body weight gain during gestation with signs of lethargy was also reported."

BCS Comments on HID Review:

The statement above describes data reported in Kandil, 2006. For reasons below, this study would not support listing.

The test material in this study was an emulsifiable concentrate, with only 5% deltamethrin; therefore, any findings associated with treatment are more likely due to the formulating agents than to deltamethrin. Moreover, the reported findings are expressions of overt toxicity, rather than reproductive toxicity, with excessive maternal toxicity (*e.g.,* decreased maternal body weight during pregnancy and lethargy) and fetal toxicity/lethality. Decreased uterine weight reported to occur on GD20 would adversely affect fetal growth and development,

as shown by increased percentage of resorbed and malformed fetuses at a lethal dose; an associated decrease in fetal body weight and incomplete ossification are lesser expressions of toxicity at excessively toxic doses, rather than evidence of developmental toxicity. The HID rightly notes that only summary data and brief descriptions of the methodology were available for evaluation. Given the test material (5% deltamethrin), excessive toxicity at the doses tested and lack of study details, this study provides no useful information to evaluate deltamethrin for developmental or reproductive toxicity.

WEIGHT-OF-EVIDENCE ASSESSMENT

The results from guideline studies designed to investigate developmental toxicity and developmental neurotoxicity have shown deltamethrin is not a developmental toxicant and there is no consistent evidence of developmental toxicity in studies cited from the published literature. Based on the weight-of-evidence, deltamethrin should not be listed as a developmental toxicant.

REFERENCES

Guideline Studies

1. Wrenn, J (1980). Three Generation Reproduction Study in Rats. CDPR. Mattawan, MI, International Research and Development Corporation (IRDC).
2. Hoberman, AM (1992). Deltamethrin: Reproductive Effect of Deltamethrin Administered Orally in the Diet to Crl:Cdbr Vaf/Plus Rats for Two Generations Project Id. 818-001. Horsham, PA, Argus Research Laboratories, Inc. 136.
3. Schardein, JL (1990). Developmental Toxicity Study of Deltamethrin in Rats. Mattawan, MI, International Research and Development Corporation (IRDC).
4. Richard, J (2001). Deltamethrin: Prenatal Developmental Toxicity Study by Oral Route (Gavage) in Rabbits. Evreaux, France, CIT.
5. Gilmore, RG, LP Sheets and HE Hoss (2006). A developmental neurotoxicity screening study with technical grade deltamethrin in Wistar rats. Stilwell, Kansas 66085-9104, Bayer CropScience LP Toxicology.

Other reports or studies from the open literature

1. Soderlund, DM, JM Clark, LP Sheets, L Mullin, V Piccirillo, and JP Stevens (2002). Mechanisms of Pyrethroid Neurotoxicity: Implications for Cumulative Risk Assessment. Toxicology 171, 3-59.
2. Iyer, P, L-H Li, KL Wu and AN Kim (2012). "Evidence on the Developmental and Reproductive Toxicity of Deltamethrin." California Office of Environmental Health Hazard Assessment: 1-106.
3. Sheets, LP (2012). "Deltamethrin: Consideration to List as a Developmental and Reproductive Toxicant under California Proposition 65." Bayer CropScience report US0269.
4. Klimisch, HJ, M Andreae and U Tillmann (1997). "A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data." Reg Toxicology and Pharmacology 25: 1-5.
5. Abd el-Aziz, MI, AM Sahlab and M Abd el-Khalik (1994). "Influence of Diazinon and Deltamethrin on Reproductive Organs and Fertility of Male Rats." DTW. Deutsche tierarztliche Wochenschrift 101(6): 230-232.
6. Issam, C, H Samir, H Zohra, Z Monia and BC Hassen (2009). "Toxic Responses to Deltamethrin (Dm) Low Doses on Gonads, Sex Hormones and Lipoperoxidation in Male Rats Following Subcutaneous Treatments." The Journal of Toxicological Sciences 34(6): 663-670.

7. El-Gohary, M, WM Awara, S Nassar and S Hawas (1999). "Deltamethrin-Induced Testicular Apoptosis in Rats: The Protective Effect of Nitric Oxide Synthase Inhibitor." Toxicology 132(1): 1-8.

8. Andrade, AJ, S Araujo, GM Santana, M Ohi and PR Dalsenter (2002). "Reproductive Effects of Deltamethrin on Male Offspring of Rats Exposed During Pregnancy and Lactation." Regulatory Toxicology and Pharmacology: RTP 36(3): 310-317.

9. Abdallah, BF, AB Slima, I Dammak, L Keskes-Ammar and Z Mallek (2009). "Comparative effects of dimethoate and deltamethrin on reproductive system in male mice." Andrologia 42(3): 182-186.

10. Salem, MH, Z Abo-Elezz, GA Abd-Allah, GA Hassan and N Shaker (1988). "Effect of Organophosphorus (Dimethoate) and Pyrethroid (Deltamethrin) Pesticides on Semen Characteristics in Rabbits." Journal of Environmental Science and Health. Part. B, Pesticides, Food Contaminants, and Agricultural Wastes 23(3): 279-290.

11. Lemos, AJJM, V Wanderley-Teixeira, AAC Teixeira, FdCA Silva, JV Oliveira and HAA de Siqueira (2011). "Response of Blastocyst-Endometrium Interactions in Albino Rats to Sublethal Doses of Biological and Synthetic Insecticides." Food and Chemical Toxicology 49(10): 2541-2547.

12. Lemos, AJ, HA Siqueira, V Wanderley-Teixeira, FC Maia, AA Teixeira, EJ Silva and JV Oliveira (2012). "Effect of Sub-Lethal Doses of Bacillus Thuringiensis Subsp. Aizawai and Deltamethrin with Regard to Fertility and Organ Toxicity in Pregnant Albino Rats." Experimental and Toxicologic Pathology.

13. Lazarini, CA, JC Florio, IP Lemonica and MM Bernardi (2001). "Effects of Prenatal Exposure to Deltamethrin on Forced Swimming Behavior, Motor Activity, and Striatal Dopamine Levels in Male and Female Rats." Neurotoxicology and Teratology 23(6): 665-673.

14. Lazarini, CA, IP Lemonica, SF Habr and MM Bernardi (2007). "Prenatal Deltamethrin Low Dose Effects on Physical Development of Rats." Pesticidas 17: 47-58.

15. Richardson JR, Caudle WM, Dean ED, Wang MZ and Miller GW (2004); Perinatal exposure to deltamethrin alters dopaminergic neurochemistry in the developing mouse brain. Neurotoxicology 25(4):714-5 (Abstract only)

16. Kandil, AM (2006). "Toxic Effects of Deltamethrin on the Pregnant Rats and Their Fetuses." J. Drug Res. 27: 82-89.

17. Kavlock, R, N Chernoff, R Baron, R Linder, E Rogers, B Carver, J Dilley and V Simmon (1979). "Toxicity Studies with Decamethrin, a Synthetic Pyrethroid Insecticide." Journal of Environmental Pathology and Toxicology 2(3): 751-765.

APPENDIX I

SUMMARY CRITERIA USED TO EVALUATE STUDIES HID CITED AS EVIDENCE OF REPRODUCTIVE OR DEVELOPMENTAL TOXICITY

TABLE 1: *Male Reproductive Toxicity*

	Hoberman, 1992	Abd el Aziz *et al.*, 1994	Issam *et al.*, 2009	El-Gohary *et al.*, 1999	Andrade *et al.*, 2002	Abdallah *et al.*, 2010	Salem *et al.*, 1988
Test Guideline / GLP compliance	2-generation repro / GLP	Not a guideline study or GLP	Not a guideline study or GLP	Not a guideline study or GLP	Not a guideline study or GLP	Not a guideline study or GLP	Not a guideline study or GLP
Test Material Purity / Composition	Verified high purity and dietary levels	Decis 5 Flowable; 5% deltamethrin	Purity & doses not tested	Purity & doses not tested	98.8%; doses not tested	Purity & doses not tested	Purity & doses not tested
Doses / Duration	4 dietary levels / Pre-mating P-gen thru PND 21 of F2 generation	1 or 2 mg/kg x 65 days (mated to un-treated females)	2 ppm x 30 d; 20 ppm x 45 d; 200 ppm x 60 d	1 mg/kg x 21 days	1, 2 or 4 mg/kg x GD1 to LD21	5 mg/kg x 21 days	1/10 and 1/100 LD50 dose / 6 weeks 6 weeks recovery
Dose Verification	Yes	None	None	None	None	None	None
Route / Relevance to man	Dietary / relevant	Oral / relevant	Subcutaneous in ethanol/ uncertain	i.p. in corn oil / uncertain	Oral / relevant	Oral / relevant	Oral (capsule) / relevant
Species / Strain	Rat / SD	Rat / "albino"	Rat / Wistar	Rat / "albino"	Rat / Wistar	Mouse / Swiss	Rabbit / Bauscat
Sample size	Sufficient (30/dose)	Insufficient (5-8)	Insufficient (6/group)	Insufficient (8/group)	Sufficient (15/dose)	Marginal (10/dose)	Insufficient (3/group)
Details of test methods	Sufficient	Insufficient	Insufficient	Insufficient	Sufficient	Insufficient	Insufficient
Details of results	Sufficient	Insufficient	Insufficient	Insufficient	Sufficient	Insufficient	Insufficient

TABLE 1: *Male Reproductive Toxicity*

	Hoberman, 1992	Abd el Aziz *et al.*, 1994	Issam *et al.*, 2009	El-Gohary *et al.*, 1999	Andrade *et al.*, 2002	Abdallah *et al.*, 2010	Salem *et al.*, 1988
Findings	↓ testis & epididymal wts (secondary to ↓bwt at 320 ppm)	↓ live sperm; testosterone & wt M repro organs (F not tested); ↓conception	Arrest in spermatogenesis; ↓ FSH	Apoptosis in testis; Vacuoles in sertoli cells	↓ number with ejaculate; ↓testis & epididymal abs. wt & diameter seminiferous tubules	↓ sperm count, motility & viability; ↑ percent abnormal sperm	↓ bwt, libido, ejaculate volume & sperm conc.; ↑ percent dead spermatozoa
Dose-Response Relationship (support reliability of findings)	Yes (high-dose)	Yes	No	No	Yes	No	Yes
Other Comments	Multiple tissue wts reduced due to bwt; No histopathology	Diet milk & barley; associated with severe toxicity, small sample, similar effect with an OP (diazinon)	No assessments for overt toxicity; histopathology inconsistent with 2-gen repro study	No assessments for overt toxicity; histopathology inconsistent with 2-gen repro study	Difference in tissue wt due to bwt (as in the 2-gen study); No effect on PPS	Similar effect with an OP (dimethoate) or combination; no effect on epididymis or testis weights	Similar effect with an OP (dimethoate) or combination

Based on Klimisch *et al.*, 1997.

TABLE 2: *Female Reproductive Toxicity*

	Hoberman, 1992	Lemos *et al.*, 2011	Lemos *et al.*, 2012
Test Guideline / GLP compliance	2-generation repro / GLP	Not a guideline study or GLP	Not a guideline study or GLP
Test Material Purity / Composition	Verified high purity and dietary levels	Decis 25CE (2.5% deltamethrin); doses not tested	Decis 25 CE (2.5% deltamethrin); doses not tested
Doses / Duration	3 dietary levels / Pre-mating P-gen thru PND 21 of F2 generation	1, 2 or 4 mg/kg / GD0-6	3 doses x GD0-6 or GD0-LD1
Dose Verification	Yes	None	None
Route / Relevance to man	Dietary / relevant	Oral / relevant	Oral / relevant
Species / Strain	Rat / SD	Rat	Rat / "albino"
Sample size	Sufficient (30/dose)	Insufficient (5/dose)	Insufficient (5/group)
Details of test methods	Sufficient	Insufficient	Insufficient
Details of results	Sufficient	Insufficient	Insufficient
Findings	↓ abs uterine and pituitary wts with increased mortality	↓ number of implantation sites histopathology of the sites	↓ number of pups & ↓ fertility
Dose-Response Relationship (support reliability of findings)	Yes (high-dose)	No	Yes
Other Comments	↓ Multiple tissue wts due to ↓ BWG during development; No histopath.	Effects not seen in guideline rat dev tox study; Similar effects seen with the biological pesticide B. thuringiensis	Insufficient sample size, Similar effect with B. thuringiensis, No similar effect in guideline studies

Based on Klimisch *et al.*, 1997.

TABLE 3: *Developmental Toxicity*

	Gilmore *et al.*, 2006	Lazarini *et al.*, 2001	Lazarini *et al.*, 2007	Richardson 2004	Kavlock *et al.*, 1979	Schardein, 1990	Richard, 2001	Kandil, 2006
Test Guideline / GLP compliance	Developmental neurotoxicity / GLP	Not a guideline study or GLP	Not a guideline study or GLP	Not a guideline study or GLP	Not a guideline study or GLP	Developmental Toxicity / GLP	Developmental Toxicity / GLP	Not a guideline study or GLP
Test Material Purity / Composition	Verified high purity & dietary levels	Purity & doses not tested	Purity & doses not tested	Purity & doses not tested	Technical from Roussel Uclaf / doses not tested	Verified high purity and dose levels	Verified high purity and dose levels	Purity & doses not tested
Doses / Duration	3 dietary levels (GD6 - LD21)	0.08 mg/kg x GD6-15	0.08 mg/kg x GD6-15	single (3 mg/kg)	3 dose levels / GD7-16 (mice) or GD7-20 (rat)	3 dose levels (GD 6-15)	3 dose levels	3 dose levels / GD 8-16 or GD 1-20
Dose Verification	Yes	None	None	None	None	Yes	Yes	No
Route / Relevance to man	Dietary / relevant	Oral / relevant	Oral / relevant	Not specified	Oral / relevant	Oral / relevant	Oral / relevant	Oral / relevant
Species / Strain	Rat / SD	Rat	Rat	Mouse	SD rat & CD-1 mouse	Rat / Wister	Rabbit / NZW	Rat
Sample size	Sufficient (20/dose)	Insufficient	Insufficient		Sufficient (30/dose)	Sufficient (20/dose)	Sufficient (20/dose)	
Details of test methods	Sufficient	Insufficient	Insufficient	Insufficient	Insufficient	Sufficient	Sufficient	No
Details of results	Sufficient	Insufficient	Sufficient	Insufficient	Insufficient	Sufficient	Sufficient	No

TABLE 3: *Developmental Toxicity*

	Gilmore *et al.*, 2006	Lazarini *et al.*, 2001	Lazarini *et al.*, 2007	Richardson 2004	Kavlock *et al.*, 1979	Schardein, 1990	Richard, 2001	Kandil, 2006
Findings	↓ fixed F brain wt at term with ↓ bwt; ↑ resistance to handling (M)	Emotionality as ↓ locomotion frequency, ↑ immobility in open field, and ↓ latency to float in swimming test	Delayed eye opening in males and vaginal patency in females	Alteration in motor and dopaminergic activity	No adverse effects at any dose	No adverse effects in dam or fetus at any dose	↓ bwt & food consumption in does; no adverse effects in fetus	↓ dam BWG, lethargy, ↓uterine wt, ↑resorptions & malformed fetuses, ↓fetal bwt, incomplete ossification
Dose-Response Relationship (support reliability of findings)	Yes (high-dose)	No (one dose)	No (one dose)	No	Not applicable	Not applicable	Yes	Yes
Other Comments	Associated w/ ↓ bwt at MTD; no effect in term M or PND 21 M or F	No similar effect in DNT study with doses to 16.1 m/k/d	No similar effect in other studies at much higher doses, including guideline DNT study	Abstract only – never published	No effect on # implantation sites; no effect on F offspring activity			Only summary data & a brief description of methods

Based on Klimisch *et al.*, 1997.

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