FINAL STATEMENT OF REASONS
TITLE 27, CALIFORNIA CODE OF REGULATIONS

SECTION 25705(c). SPECIFIC REGULATORY LEVELS POSING NO SIGNIFICANT RISK

IMAZALIL

This is the Final Statement of Reasons for a No Significant Risk Level (NSRL) for imazalil**,** a chemical listed as known to the State to cause cancer under Proposition 65.[1] On September 23, 2011, the Office of Environmental Health Hazard Assessment (OEHHA) issued a proposed amendment to adopt an NSRL for imazalil in Title 27, California Code of Regulations, section 25705(c).[2] The Initial Statement of Reasons set forth the grounds for the proposed amendment. A public comment period was provided from September 23 until November 7, 2011. A request for a public hearing was received by OEHHA and the hearing was scheduled for October 27, 2011. To allow time for review of any oral or written comments presented at the hearing, the public comment period was extended to November 21, 2011. No public comments were made at the October 27, 2011 public hearing. OEHHA received written comment from Janssen Pharmaceutica NV, on November 4, 2011.

On September 23, 2011, OEHHA provided the notice of proposed rulemaking and the initial statement of reasons for the proposed NSRL for imazalil to the members of the Carcinogen Identification Committee for their review and comment as required by Section 25302(e). No comments were received from any committee members.

SUMMARY AND RESPONSE TO COMMENTS RECEIVED

Written comments were submitted by William R. Goodwine, representing Janssen PMP (a division of Janssen Pharmaceutica NV) and Makhteshim Agan of North America Inc. The comments are comprised of William Goodwine's submittal letter, and an attached consultant's report authored by Douglas G. Baugher, Ph.D. of EXP Corporation, Aspers, Pennsylvania. The comments are summarized or quoted below and are followed by OEHHA's responses.

Comment 1:
The consultant's report states that "The California Office of Environmental Health Hazard Assessment (OEHHA) has published a notification to list imazalil as a carcinogen under Proposition 65 with a proposed No Significant Risk Level (NSRL) of 11 µg/day based on the USEPA Q_1^* and an oral route of exposure representing an absorbed dose." [see EXP Report, page 3]

[1]The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code, section 25249.5 *et seq*., hereafter referred to as "Proposition 65" or "The Act".
[2] All further references are to sections of Title 27 of the California Code of Regulations, unless otherwise noted.

Response 1:
To clarify, imazalil was listed as a carcinogen under Proposition 65 on May 20, 2011; thus OEHHA's proposed rulemaking notice was not "a notification to list imazalil as a carcinogen under Proposition 65." The proposed rulemaking is to adopt a NSRL for imazalil. The comments are discussed here only as they relate to the proposed NSRL.

The comment is correct that the NSRL is based on the U.S. EPA's estimate of cancer potency, Q_1^*, for the chemical. As discussed in the Initial Statement of Reasons, the document relied upon for the NSRL is the 2003 U.S. Environmental Protection Agency (U.S. EPA) Reregistration Eligibility Decision (RED) for Imazalil.[3] The comment is incorrect that the NSRL applies only to the oral route and is for absorbed dose. The NSRL calculated by OEHHA is a daily intake level, not an absorbed dose, and applies to all routes of exposure.

Comment 2:
William Goodwine commented in his transmittal letter that "OEHHA's current quantitative risk assessment methodology should be followed, which gives a calculated NSRL for imazalil of 32 µg per day instead of 11 µg per day." He further commented that OEHHA should use a "consistent approach to NSRL calculation methods across all programs, including Proposition 65." He emphasized that OEHHA should follow the updated methods for calculating cancer potency values that it adopted for its drinking water public health goal and air toxics programs, and has proposed a regulation to bring the Proposition 65 program interspecies conversion calculation into conformity with these other programs.

Response 2:
As discussed in responses to comments 3 and 4 below, the NSRL of 11 µg per day is consistent with OEHHA's and U.S. EPA's current risk assessment methodology. OEHHA derived the NSRL based on the U.S. EPA's cancer potency estimate for imazalil of 6.1×10^{-2} $(mg/kg/day)^{-1}$ in its 2003 RED for imazalil.[4] However, OEHHA confirmed that estimate by reproducing it using current methodology. The discrepancy between the estimate of 32 µg per day in William Goodwine's letter and the NSRL of 11 µg per day is due to errors in the consultant's report in applying the interspecies scaling factor to convert the imazalil animal cancer potency to human cancer potency, and in omitting to adjust for study length. This resulted in the consultant incorrectly calculating the NSRL, as described in more detail in subsequent responses.

In a separate OEHHA regulatory action, OEHHA amended Section 25703(a)(6) on November 11, 2011, to bring the Proposition 65 NSRL calculation methods in line with the current interspecies conversion factor used by the U.S. EPA and the OEHHA air

[3] U.S. EPA, 2003. Reregistration Eligibility Decision for Imazalil. Chemical List B. Case No. 2325. Office of Prevention, Pesticides and Toxic Substances, U.S. EPA, Washington DC [Available at URL: http://www.epa.gov/oppsrrd1/REDs/2325red_imazalil.pdf].
[4] U.S. EPA, 2003. Reregistration Eligibility Decision for Imazalil. Chemical List B. Case No. 2325. Office of Prevention, Pesticides and Toxic Substances, U.S. EPA, Washington DC [Available at URL: http://www.epa.gov/oppsrrd1/REDs/2325red_imazalil.pdf].

and drinking water programs. The amended regulation specifies that "interspecies conversion of animal cancer potency to human cancer potency shall be determined by multiplying by a scaling factor equivalent to the ratio of human to animal bodyweight, taken to the one-fourth power." This conversion factor was used to establish the NSRL for imazalil.

Comment 3:
The consultant's report states, "As a response to the OEHHA proposal, we attempted to verify the Q1* and the NSRL… USEPA likely used the software application ToxRisk or another DOS-based application that is now no longer commercially available, supported, or compatible with modern PC operating systems… We cannot confirm the older calculations… Using current EPA cancer risk assessment guidelines and current EPA software, we have calculated a new slope factor for use in risk assessments for imazalil" of 0.0219 $(mg/kg/day)^{-1}$. [see EXP Report, pages 3 – 4]

Response 3:
As discussed in the response to comment 4, the calculations converting animal doses to human equivalent doses presented in the comments were performed incorrectly. In addition, the calculation of human cancer potency presented in the comments neglected to account for the less-than-lifetime duration of the male mouse study that serves as the basis for the cancer potency estimate. Since the male mouse study was only 100 weeks in duration, a correction factor of $(104/100)^3$ should be applied as a multiplier to the cancer slope estimate. This factor was applied by U.S. EPA and is applied by OEHHA to adjust for less than lifetime exposure in estimating cancer potency. This factor is based on the assumption that the lifetime incidence of cancer increases with the third power of age. These two errors in the potency calculations – in interspecies scaling and in correcting for less than lifetime exposure - explain the inability of the commenter to confirm the U.S. EPA's potency calculations for imazalil. Thus calculation errors, and not software applications, explain the discrepancy between the correct U.S. EPA potency value of 0.061 $(mg/kg/day)^{-1}$ and the comment's incorrect "new slope factor" of 0.0219 $(mg/kg/day)^{-1}$.

Using the correct human equivalent doses presented in the response to comment 4 below, and accounting for the less-than-lifetime duration of the male mouse study, OEHHA has reproduced and confirmed the U.S. EPA's cancer potency estimate for imazalil of 0.061$(mg/kg/day)^{-1}$.

OEHHA notes that in addition to ToxRisk and other specialized software applications that have been used by the U.S. EPA and others to perform these types of calculations, software programs such as Excel and Mathematica are also readily available and can be used to estimate cancer potency. OEHHA utilizes a number of different software applications to estimate cancer potency using the linearized multistage model, including software programs developed in Excel and Mathematica, and specialized applications such as ToxRisk and MSTAGE.

OEHHA further notes that since both ToxRisk and the dichotomous Multistage Cancer Model in the U.S. EPA's Benchmark Dose Software (BMDS) package employ the linearized multistage model to evaluate cancer risk from dose-response data, both software programs are expected to arrive at very similar if not identical estimates of cancer potency. OEHHA has confirmed the U.S. EPA's cancer potency estimate for imazalil using the BMDS software and the dichotomous multistage cancer model with a benchmark response (BMR) of 0.05.[5]

Comment 4:
The consultant's report states, "We also do not know if EPA used the cross-species dose scaling factor for animal-to-human doses of (mg/kg BW/day) $^{2/3}$ or the current recommended scaling factor of (mg/kg BW/day) $^{3/4}$… With male mouse doses scaled to the ¾ power and the default BMR (Benchmark Response) of 0.10, the first degree polynomial model gave the best results (see Appendix A)…" [see EXP Report, page 4].

Appendix A [see EXP Report, page 7] includes the table reproduced below, presenting the dose-response data used in the comments to calculate the cancer potency:

Male Mouse Liver Tumors

mg/kg	mg/kg^(3/4)	N	Incidence
0	0	50	10
6.76	4.19	47	8
28	12.17	50	17
88	28.73	48	22

Response 4:
The method of interspecies scaling described in the comments and thus the scaled doses used in the calculations presented in the comments (and included in the table in Appendix A) incorrectly applied the mathematical conversion to go from animal doses to human equivalent doses. The animal dose itself (in mg per kg bodyweight) is not raised to the ¾ power; rather, the administered dose is scaled from animals to humans on the basis of mg of imazalil normalized by the ¾ power of body weight per day. The correct equation to convert animal doses to human equivalent doses is as follows:

$$\text{Equivalent human dose} = \text{animal dose} \times \left(\frac{\text{animal bodyweight}}{\text{human bodyweight}}\right)^{1/4}$$

The U.S. EPA calculated the Q_1* for imazalil using body weights of 0.03 kg for male mice and 70 kg for humans, and a ¾'s scaling factor for interspecies extrapolation[6] .

[5] Using the correct human equivalent doses, and after adjusting for the less than lifetime duration of the study.
[6] U.S. EPA 1995. *Memorandum: Imazalil, Quantitative Risk Assessment, Two-Year Charles River SPF Swiss Albino Mouse Dietary Study.* Office of Prevention, Pesticides and Toxic Substances. March 7, 1995.

Using these values in the equation above, the following human equivalent doses are derived:

Animal Dose in mg/kg-day	Human Equivalent Dose in mg/kg-day
0	0
6.8[7]	0.978
28	4.03
88	12.7

ALTERNATIVES DETERMINATION

In accordance with Government Code section 11346.5(a)(7), OEHHA has, throughout the adoption process of this regulation, considered available alternatives to determine whether any alternative would be more effective in carrying out the purpose for which the regulations were proposed, or would be as effective and less burdensome to affected private persons than the proposed action. OEHHA has determined that no alternative considered would be more effective, or as effective and less burdensome to affected persons, than the proposed regulation. The proposed calculations for the NSRL offered in the public comments are inaccurate and do not comply with the guidance in the regulation. Therefore, OEHHA declined to use that approach.

For chemicals listed under the Act as known to cause cancer, the Act exempts discharges to sources of drinking water and exposures of people without provision of a warning if the exposure poses "no significant risk" of cancer (Health and Safety Code, section 25249.10(c)). The Act does not specify numerical levels of exposure that represent no significant risk of cancer.

The purpose of this regulation is to provide a "safe harbor" level for a particular chemical exposure. This regulation establishes the numerical No Significant Risk Level for one carcinogen, imazalil. At or below this level, the Act does not require a warning regarding cancer or prohibit discharges to sources of drinking water based on carcinogenicity concerns associated with imazalil. Thus, this level will allow persons subject to the Act to determine whether a given discharge to sources of drinking water or exposure to people involving these chemicals is subject to the warning requirement and discharge prohibition provisions of the Act related to the risk of cancer (Health and Safety Code sections 25249.6).

Although section 25703 describes principles and assumptions for conducting risk assessments to derive safe harbor levels, many businesses subject to the Act do not

[7] The U.S. EPA identified the lowest dose administered in the male mouse study to be 6.8 mg/kg-day (U.S. EPA, 1999. Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Imazalil (Third Review). Cancer Assessment Review Committee. Health Effects Division. Office of Pesticide Programs. December 7, 1999).

have the resources to perform these assessments. Yet each business with ten or more employees needs the ability to determine whether its activities or products are subject to the discharge prohibition or warning requirements of the Act. Given the use and occurrence of the chemical covered by this regulation, the absence of this regulation would leave numerous businesses without an efficient way of determining if they are in compliance with the Act without the expenditure of significant resources on their part.

LOCAL MANDATE DETERMINATION

OEHHA has determined this regulatory action will not pose a mandate on local agencies or school districts nor does it require reimbursement by the State pursuant to Part 7 (commencing with section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. It should be noted that Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, these regulations do not impose any mandate on local agencies or school districts.