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January 17, 2012

Isagro USA Inc.:
Tetraconazole: Proposition 65:
Response to Notice of Intent to List
CAS No. 112281-77-3

Submitted by e-mail

Dr. George Alexeeff, Acting Director
Office of Environmental Health Hazard Assessment
Department of Pesticide Regulation
1001 I Street
Sacramento, CA 95814

Dear Dr. Alexeeff,

On behalf of the Isagro USA Inc., we are responding to the Office of Environmental Health Hazard Assessment's (OEHHA's) December 2, 2011 Notice of Intent to List tetraconazole (CAS No. 112281-77-3) under the authoritative bodies listing mechanism (OEHHA, 2011a) of California's Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). The public comment period for this Intent to List ends January 17, 2012. The US Environmental Protection Agency (US EPA) is cited as the "authoritative body" for tetraconazole and a report by the US EPA's Cancer Assessment Review Committee (CARC) (US EPA, 2000) is cited as evidence the US EPA "formally identified" tetraconazole as a carcinogen (OEHHA, 2011a).

Request: We request that OEHHA postpone further action on this Notice of Intent to List until later in this calendar year when new scientific data, not considered by the Authoritative Body, are finalized and submitted to the US EPA and OEHHA. Isagro's discussions with the US EPA on the intent and design of these data, and the impacts of similar data on the classification of structurally-related ingredients, indicates that these new data are likely to impact the US EPA's current cancer classification of tetraconazole which is the basis of the current Notice of Intent to List by OEHHA. We also request a meeting with OEHHA so that we may discuss

tetraconazole and our present request.

Isagro Submissions to OEHHA on the Listing of Tetraconazole under Proposition 65. On December 21, 2010, Isagro responded to OEHHA's October 22, 2010 Request for Relevant Information on the potential listing of tetraconazole under the Authoritative Bodies listing mechanism of Proposition 65. OEHHA proceeded to the next phase of the Authoritative Bodies process, and issued the Notice of Intent to List, dated December 2, 2011. This response describes our proposed submission of new mode-of-action data on the carcinogenicity of tetraconazole that is similar to the mode of action data that caused the US EPA to issue a different cancer classification for other structurally-related triazole antifungal agents that also cause mouse liver tumors. We also further describe structure activity relationships of tetraconazole based on conclusions of the US EPA.

Subsequent Activities, New Data, and Request to OEHHA. Subsequent to our original response to OEHHA, Isagro met with the US EPA on the Agency's classification of tetraconazole in October, 2011. At that meeting, the US EPA agreed with Isagro that providing the Agency with new, specific mode of action data on tetraconazole would help resolve the human relevance of the current cancer data on tetraconazole (Graben, 2011). The Agency concurred that similar data on other triazole antifungal agents has altered the Agency's conclusions on the human relevancy of their cancer data. Therefore, the Agency's expectation is that there is an underlying likeliness that a similar altered conclusion could be generated from tetraconazole-specific mode of action data. The protocol for the requested data has been agreed upon and is scheduled to commence within a month. The 28-day study is being conducted at Integrated Laboratory Systems (ILS), a laboratory that contracts to the National Toxicology Program, and the final report is likely to be available within six months. We will be submitting the new scientific data to the US EPA and, as a supplement to this current response to the Notice of Intent to List, to OEHHA as soon as the final study is available later within this calendar year. We, therefore, request that OEHHA postpone further consideration of tetraconazole under Proposition 65 until these new and directly relevant scientific data, which were not considered by the Authoritative Body, are submitted and considered by OEHHA and the Authoritative Body, the US EPA.

Proposition 65 requires OEHHA to determine if new scientifically valid data are available that the Authoritative Body did not consider in its listing process that clearly establish that the chemical does not fit the listing criteria. Key new data on tetraconazole will be available soon. Analogous scientific data, submitted to evaluate the mode of action for other compounds have altered the US EPA conclusions for these other triazole antifungal agents and, in similar fashion, the new scientific data on tetraconazole are likely to cause the US EPA to change their conclusion on the human relevance of the existing tetraconazole mouse liver carcinogenicity data (e.g., as occurred for cyproconazole and metconazole). We respectfully request

postponement of tetraconazole Authoritative Bodies listing process under Proposition 65 until the new data has been received and reviewed. We also request a meeting with OEHHA so that we may further discuss these issues.

OEHHA's Basis for Potential Authoritative Body Listing. The basis of OEHHA's Notice of Intent to List is described as follows:

> *"In 2000, the US EPA published a report on tetraconazole, entitled Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Tetraconazole that concludes that the chemical causes cancer (US EPA, 2000). This report satisfies the formal identification and sufficiency of evidence criteria in the Proposition 65 regulations.*
>
> *OEHHA is relying on the US EPA's discussion of data and conclusions in the report that tetraconazole causes cancer. The US EPA report concludes tetraconazole is "likely to be carcinogenic to humans' by the oral route." Evidence described in the report includes studies showing that tetraconazole causes increases in the incidences of hepatocellular carcinomas and combined hepatocellular carcinomas and adenomas in male and female mice." (OEHHA, 2011a)*

As described by Graben (2011), these US EPA conclusions are likely to be reevaluated by the Agency in the near future.

Basis for this Submission Responding to OEHHA's "Intent to List". The US EPA's conclusions on the human relevance of mouse liver tumors produced by triazole antifungal agents have changed since the assessment of tetraconazole (US EPA, 2000) and OEHHAs response on structural analogs of tetraconazole (OEHHA, 2011b) may differ from the current thoughts of the Authoritative Body, the US EPA. We have discussed with the US EPA development of new mechanistic data on tetraconazole. These data will result in a new US EPA evaluation of their conclusion on the human relevancy of tetraconazole carcinogenicity and associated classification. The carcinogenicity re-evaluation of tetraconazole by US EPA will include the following considerations:

1. **US EPA (2000) Conclusion Regarding Malignancy is Incorrect.** OEHHA cites the US EPA as concluding that tetraconazole causes increases in carcinomas in male and female mice. In fact, no increase in carcinomas was found in females at dose levels that were not considered by the US EPA to be excessive. In males, only a small difference in the occurrence of carcinomas was found between the control and the highest dose level[1]

[1] The incidence of hepatocellular carcinomas in control males was one. The incidence in males at the highest dose that did not exceed the MTD (800 ppm) was four. A pairwise comparison of these incidences was not statistically significant. The historical control incidence for males cited by EPA ranged from 0% to 14%. Only one carcinoma was found in females at the 800 ppm dose level (2 %).

that did not exceed the MTD and this difference was not statistically significant and was within the historical control range. This issue will be addressed with the US EPA during their upcoming reevaluation of tetraconazole.

2. **Structural Analog Conclusions of US EPA (2000) on the Relevance of Mouse Liver Tumors may be Outdated due to New Mode of Action Data.** Although the US EPA (2000) cited the hepatocarcinogenicity of structural analogs in mice as a reason to conclude that tetraconazole should be classified as "likely to be carcinogenic to humans," more recently, the US EPA changed their conclusion on the structural analog cyproconazole that, like tetraconazole, only shows carcinogenicity in mouse liver, to "not likely to be carcinogenic to humans". The change in classification was, in part, due to new mechanistic data from new mode of action studies. The US EPA also recently gave the same "not likely to be carcinogenic to humans" classification to metconazole due to mode-of-action data that explained the mouse liver tumors. It is our understanding that none of the other triazole antifungal agents that only cause mouse liver tumors are currently classified by the US EPA as "likely to be carcinogenic to humans."[2] , including the structurally-related compounds that were used by the US EPA as a basis for the tetraconazole classification. As a result of the Agency's new conclusions on the human relevancy of mouse liver tumors caused by triazole antifungal agents, the US EPA agreed to further evaluate mechanistic data for tetraconazole to determine if it should also be reclassified (Graben, 2011). It is also worth noting that the OEHHA Cancer Identification Committee (OEHHA CIC, 2011) discussion of triazole antifungal agents suggests the thinking that several mechanisms of carcinogenicity may exist within triazole antifungal agents. Analogs that only show carcinogenicity in mouse liver were indicated as having low priority for evaluation by the CIC for listing under Proposition 65, presumably because of low concern for relevancy of the mechanism to humans (a point which is expanded upon in our discussion below). OEHHA (2011b) responded to our previous comments on tetraconazole regarding the absence of a structure activity relationship among structural analogs, by pointing out that the triazole antifungal agent epoxiconazole and the imidazone antifungal agent imazalil are listed under Proposition 65. However, there may be various mechanisms of carcinogenicity among chemicals broadly classified as structural analogs and the two compounds described by OEHHA are likely to be different because they apparently cause cancer in both mice and rats (OEHHA, 2011c; US EPA, 1999) so concerns with those chemicals extend beyond observations in the mouse liver. Accordingly, epoxiconazole and imazalil would not be good analogs for conclusions on tetraconazole. Cyproconazole and metconazole are likely to be better analogs for comparison, as detailed below.

3. **Carcinogenicity Conclusions of US EPA (2000) may be Outdated due to New**

[2] Several are listed as Group C, possible human carcinogen.

Mechanistic Data. New mode-of-action studies that have been conducted on a number of triazole antifungal agents have altered the understanding of the human relevance of mouse hepatocarcinogenicity of these agents. The mode of action for the induction of this tumor was discussed in detail at the May 24-26, 2011 FIFRA Scientific Advisory Panel (SAP) meeting concerning the use of new computational and molecular tools. A structurally-related triazole was used as a case study by the US EPA during this SAP meeting. Based upon available and relevant mechanistic data, the US EPA's CARC has, in recent years, downgraded the cancer classification for other triazoles such as cyproconazole.

4. **New Data are being Developed that are Likely to Change US EPA Conclusions on the Human Relevance of Tetraconazole Carcinogenicity.** Isagro and the US EPA have agreed on a protocol for a short-term study that is likely to lead to a change in the US EPA classification of the carcinogenicity of tetraconazole (Graben, 2011). On October 13, 2011 representatives of Isagro USA and Isagro SPA met with Vicki Dellarco, Office of Pesticide Programs Senior Scientist, and other senior EPA toxicologists to discuss the initiation of a mode of action study that is intended to allow the EPA reclassification of tetraconazole. The state-of-the-art study will identify key events at the level of the cell and genome to better understand the etiology of the tumor induction. The study design fully addresses all recommendations of the US EPA at the October 13th meeting. The US EPA agreed that successful completion of the research could change the Authority's conclusion on the relevancy of the mouse liver observations to humans and result in the use of a nonlinear model for risk assessment and the application of a descriptor such as "not likely to be carcinogenic at dose levels that are not associated with cell proliferation" (Graben, 2011)

5. **New Tetraconazole Data will be Available Soon.** This study will begin in late January and the in-life phase is scheduled to be completed in 28-days. A full study report should be available this spring and will be provided to EPA to facilitate reclassification. The protocol for this mode of action study is attached to this letter.

US EPA Reclassification of Tetraconazole Carcinogenicity is Anticipated to Agree with Other Triazole Antifungal Agents that only cause Mouse Liver Tumors. Other triazole antifungal agents that, like tetraconazole, only cause tumors in mouse liver have been assigned the US EPA cancer descriptor of "not likely to be carcinogenic to humans" along with some qualifications to that statement. Tetraconazole is currently scheduled in the US EPA's Registration Review process somewhat behind some other triazole antifungal agents that have mouse liver observations similar to those of tetraconazole. As a result, the US EPA's reevaluations of these active ingredients, including the relevance of mouse tumors to humans, are being finalized ahead of tetraconazole. The new scientific data being generated on the

mode of action of tetraconazole are likely to also trigger the US EPA's restatement of the carcinogenicity classification of tetraconazole. Two triazole antifungal agents that cause treatment-related tumors only in mouse liver and have had appropriate mechanistic data have the US EPA documentation as follows:

- **Cyproconazole:** In 1992, the US EPA third peer review committee categorized cyproconazole as a probable human carcinogen but the fourth peer review committee (CARC) changed the classification to "not likely to be carcinogenic to humans" at doses that do not cause mitogenic response in the liver (US EPA, 2007).

- **Metconazole:** The US EPA CARC found mouse liver tumors that were explained by mechanistic data and resulted in the classification of "not likely to be carcinogenic to humans" based on convincing evidence that carcinogenic effects are not likely below a defined dose range (US EPA, 2006).

Depending on the results of the new mechanistic data from the planned mode of action study on tetraconazole that was agreed with the US EPA (Graben, 2011), it is likely that the US EPA will reevaluate the cancer conclusion for tetraconazole. Based upon the precedents of other mouse-liver-only compounds, cyproconazole and metconzole, it is expected that the US EPA will conclude that tetraconazole is "not likely to be carcinogenic to humans" and they are likely to add qualifications to that classification. If so, it would be appropriate to include tetraconazole in the CIC evaluation of "triazole antifungal agents" rather than the Authoritative Bodies listing process.

Other Triazole Antifungal Agents that only cause Mouse Liver Tumors are Proceeding under the State's Qualified Experts Mechanism. Tetraconazole is a "triazole antifungal agent". Some members of this group have been classified as causing cancer and OEHHA recently asked the state's expert committee under Proposition 65, the Carcinogen Identification Committee (CIC), to prioritize this group of chemicals for listing under Proposition 65 with the option of evaluating each chemical separately. The CIC is likely to consider each chemical separately and considers the triazoles that only cause mouse liver tumors as low priority for consideration by the CIC. For example Dr. Peffer stated

> *"I was going to speak to the idea that it's not appropriate to consider them all as a class from the standpoint of they don't necessarily have a common mechanism of action. And I think I see nodding heads, and you all agree with that…. And there's – the others I think I heard what you mentioned was likely medium to high for 3 of the listed chemicals and then low for the others." (OEHHA CIC, 2011)*

Committee member Eastmond responded as follows:

> *"The three I listed would be medium and all the rest would be low. And even the propiconazole could actually go to low. It depends how you interpret the mechanistic data. There's been a ton of mechanistic data generated on that. And it depends how you interpret that data. I don't think it's – it certainly is not a high, priority from my point of view" (OEHHA CIC, 2011)*

The two triazole antifungal agents that were identified for medium priority by committee member Eastmond were triadimefon and fenbuconazole. Based on OEHHA's summary of triazole antifungal agents for the CIC Meeting (OEHHA, 2011c), both of these chemicals, in addition to having observations of mouse liver tumors, also caused thyroid follicular cell tumors in male rats. Examples of other triazole antifungal agents that, like tetraconazole, only cause treatment related tumors in mouse liver, are cyproconazole (which was indicated as likely to be placed in the CIC low priority group, OEHHA CIC, 2011) and metconazole (which was not part of CIC discussion).

Enclosed Relevant Information. The following documents are enclosed with this response:

Graben (2011). Notes on EPA October 13, 2011 Meeting with Isagro USA Regarding Tetraconazole Q* Risk Assessment Reclassification. October 18, 2011.

OEHHA (2011a). Notice of Intent to List Kresoxim-Methyl and Tetraconazole [12/02/11].

OEHHA (2011b). Response to Comments from Technology Sciences Group Inc Pertaining to the Request for Relevant Information Concerning Consideration of Tetraconazole for Listing Under Proposition 65. November 2011.

OEHHA (2011c). Chemical for CIC Consultation: Triazole Antifungal Agents. July 2011.

OEHHA CIC (2011). Meeting State of California Office of Environmental Health Hazard Assessment Proposition 65 Carcinogen Identification Committee. October 12, 2011. (see p 229)

US EPA (1999). Cancer Assessment Document, Evaluation of the Carcinogenic Potential of Imazalil (third review). December 7, 1999.

US EPA (2000). Memorandum: Tetraconazole: Report of the Cancer Assessment Review Committee. Health Effects Division. Office of Pesticide Programs. January 11, 2000.

US EPA (2006). Metconazole: Human Health Risk Assessment for Proposed Tolerance on Imported Bananas. July 6, 2006. (see p 31)

US EPA (2007). Cyproconazole: Fourth Report of the Cancer Assessment Review Committee. November 29, 2007.

Conclusion. It is not appropriate to list tetraconazole under Proposition 65 at this time due to (1) the generation of new and directly relevant data for the Authoritative Body that is the basis for the proposed listing, (2) the likelihood that these scientific data will result in a new conclusion on the human relevancy of tetraconazole carcinogenicity by the Authoritative Body that is in agreement with their existing recent conclusions on other triazole antifungal agents that also only cause tumors in mouse liver, and (3) the relatively short time period during which these changes are anticipated. If so desired, tetraconazole could be added to the existing state's expert committee listing process for triazole antifungal agents for the Committee's consideration. We believe that it would be beneficial to discuss our request with OEHHA.

We greatly appreciate this opportunity for Isagro USA, Inc. to provide comments under OEHHA's "Intent to List" process. Please contact us if you have any questions or need further information.

Sincerely,

Enclosures

Cc: Cynthia Oshita, Proposition 65 Implementation, OEHHA
Mel Graben, Isagro USA, Inc.
Barry Bedwell, California Grape and Treefruit League
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