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October 18, 2011

Mary Waller
U.S. Environmental Protection Agency
Office of Pesticide Programs
Registration Division (7504P)
Office of Pesticide Programs, EPA
One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

RE: Notes on EPA October 13, 2011 Meeting with Isagro USA Regarding Tetraconazole Q* Risk Assessment Reclassification

Dear Ms. Waller:

The purpose of this letter is to capture the highlights of our discussions on October 13, 2011 regarding the science necessary (study protocol review) for the possible removal of the Tetraconazole Q* classification to a nonlinear risk assessment method. In attendance at the meeting were:

EPA:

Greg Akerman	Nancy McCarroll	Vicki Dellarco
Anwar Durbar	Ray Kent	Mary Manibusan
Jess Roland	Mary Waller	

Isagro / TSG:

Gary Burin	Mel Graben	Sara Lamperti

Isagro representatives met with scientists from HED, Dr. Vicki Dellarco (OPP Senior Science Advisor) and Mary Waller (RD) to discuss a research program to determine the dose-response and time course of key events associated with the carcinogenicity of tetraconazole in mice. After discussion of background information and the weight of the evidence for carcinogenicity, Dr. Dellarco asked whether the research was also intended to show that mouse carcinogenicity finding were not relevant to humans. She noted that this would likely require more extensive investigation than the research program that is being proposed. Isagro explained that their goal was to provide sufficient understanding of the MOA to

support revision of the cancer classification descriptor and the use of a nonlinear approach to risk assessment.

Following discussion of the proposed study design EPA suggested that the concentrations used be limited to 0, 90, 400 and 800 ppm. Dr. Gary Burin, a consultant to Isagro, asked whether a phenobarbital positive control group should be included in the study and EPA said that it was helpful to include a positive control to be able to compare the cell proliferation response of tetraconazole to an agent that was known to induce cell proliferation. EPA noted that sacrifice of groups of animals on days 1, 4, 14 and 28 is appropriate based upon knowledge of the time course of key events with other triazoles *e.g.,* propiconazole, but Dr. Nancy McCarroll of HED agreed to examine the pharmacokinetics of tetraconazole and other triazoles to ensure that the pharmacokinetics of tetraconazole are comparable to other members of the triazole class of fungicide (to confirm the 4 day sacrifice timeframe). The number of 6 animals at each interval was considered to be acceptable by EPA scientists and the parameters that were proposed for investigation were considered to be appropriate for the goal of research program. EPA agreed that successful completion of this research program could result in the use of a nonlinear model and the application of a descriptor such as “not likely to be carcinogenic at dose levels that are not associated with cell proliferation.” It was specifically mentioned that the use of CAR knockout mice is not deemed necessary for this study.

EPA advised that it would be helpful to the Agency if Isagro additionally prepared an evaluation of all available data following the format and logic of the ILSI/IPCS Human Relevance Framework after the completion of the proposed research.

We believe the above represents the results of our discussions. If you have any questions, comments or disagree with the notes above, please do not hesitate to contact me.

Sincerely,

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cc: Sara Lampert, Isagro S.p.A.
Gary Burin, TSG