February 5, 2010
Mary-Ann Warmerdam
Director
Department of Pesticide Regulation

Dear Director Warmerdam:

The findings of the special review of the Scientific Review Committee follow:

Report of the Scientific Review Committee on Methyl Iodide to the Department of Pesticide Regulation

February 5, 2010

John R. Froines (Chair)
Paul Blanc
Katharine Hammond
Dale Hattis
Ed Loechler
Ron Melnick
Tom McKone
Theodore Slotkin

This letter transmits the assessment of the special Scientific Review Committee (SRC) on the health risk assessment of methyl iodide prepared by the Department of Pesticide Regulation (DPR). The SRC was composed of eight members who met as a group with representatives of the DPR on September 24-25, 2009 (including public testimony) and again in follow-up on January 25, 2010.

In addition to this transmittal letter with its findings, we also provide as Appendices: 1. A text that summarizes the SRC's views in follow-up to the initial face-to-face meeting with the DPR (in the context of the initial draft documents that we reviewed); 2. Written comments from the SRC addressing a revised risk assessment document that the DPR had prepared in response to the initial SRC oral and written comments; 3. The SRC's comments made at the January 25 meeting in a final session with key DPR staff. At that final session, the DPR staff committed to a series of modifications to the final risk assessment document as delineated in the Appendix.

Given the unavoidable time and logistical constraints inherent in this process, the SRC will not be able to meet again to review the precise wording and format of the anticipated DPR modifications. We have every reason to believe that all of the agreed-upon modifications will indeed be carried out and our transmittal letter is predicated on this presumption. Appendix 3 is meant to provide a record of what our expectations are in this regard so that the SRC position on matters of substance remains unequivocal. Thus, you should view this transmittal letter and its three Appendix documents as our final conclusions. Nonetheless, we retain the option of follow-up that would highlight those areas in which, contrary to our understanding and expectations, the DPR document as modified falls short.

From the outset, I and my fellow colleagues on the SRC would like to compliment DPR staff on their diligence, their hard work, and the quality of their risk assessment. I also want to acknowledge the collegial nature of the interactions they had with all of us; the personal and scientific interactions we had were superb and it was a pleasure to work with DPR. While there have been some disagreements, these were based on content and we all worked assiduously to bridge such gaps. Moreover, we recognize that there are inherent differences between the routine conventions of regulatory risk assessment as opposed to the precepts and approach of scientific enquiry epitomized by hypothesis-driven research. In the end, we believe that meeting the demands of both approaches leads to a better ultimate document.

In addition to thoroughly reviewing the text of the DPR risk assessment (with related oral presentations), the SRC also heard presentations from the manufacturer of methyl iodide (Arysta), the U.S. EPA, various advocacy groups (including the Pesticide Action Network), and statements from individuals, including farm workers who appeared to represent both worker and grower positions. While all of this was valuable, the comments provided by the farm workers made a particular impression on the SRC by providing a real world perspective specifically based on their experience with the analogous toxin, methyl bromide. From this testimony (predominantly from a group organized by growers), it was abundantly clear that respiratory protection, despite strict regulations on paper, is commonly inappropriate, inadequate, or inaccessible.

An equally important element in our review was the data that we would have wished to assess but that was insufficient or non-existent altogether. This palpable lack of sufficient data raises serious doubts about the adequacy of any risk assessment to fully estimate the risks that would be associated with the introduction of methyl iodide into the general environment. The lacunae in our knowledge about methyl iodide are particularly wide and deep in relation to key aspects of its potential toxicity such as neuro- and other developmental effects, neuro-toxicity beyond the development stage (in particular, following chronic exposure), and mechanisms of carcinogenicity. Further, data derived from simulated field exposures was limited (e.g., carried out under cooler winter conditions rather than in the heat of summer on a windless day) and data on the actual environmental fate of methyl iodide were fragmentary at best.

Surprisingly, in testimony to the SRC the manufacturer could not state with precision what the mechanism of action is for methyl iodide in its target pesticidal application; its original scientific developer opined that its lethality may be through its potency to methylate (add a methyl group to) biological materials. It is abundantly clear from basic chemistry that methyl iodide reacts readily with macromolecules, including with DNA, creating long lasting changes. In DNA, the effects of these methylated additions are mutagenic events that ultimately give rise to cancer. There is some data to also support a promoting action by methyl iodide, in addition to its unequivocal status as a mutagenic agent. This raises its threat level further.

The SRC also took note that the required precautions that may be warranted in order to partially attenuate worker and wider population exposures (if only to the unacceptably high levels projected through theoretical modeling) are very difficult, if not impossible, to achieve in practice. For example, large variability in achieved protection is observed even through rigorous

respirator application (e.g., under controlled experimental conditions). Projected models also cannot easily take into account factors such as skin contact through untoward but periodically occurring events, as will be discussed in greater detail below.

Based on the data available, we know that methyl iodide is a highly toxic chemical and we expect that any anticipated scenario for the agricultural or structural fumigation use of this agent would result in exposures to a large number of the public and thus would have a significant adverse impact on the public health. Due to the potent toxicity of methyl iodide, its transport in and ultimate fate in the environment, adequate control of human exposure would be difficult, if not impossible. This is clearly shown in the DPR risk calculations and the evidence of the toxicity of methyl iodide upon which these conclusions are based is compelling. In addition to the evidence for significant toxicity there is a lack of information that adds further uncertainty to the evaluation of the toxicity. We have concluded there is little doubt that the compound possesses significant toxicity.

Furthermore, this is coupled with a major lack of critical health effects data that could make the upside to all of the risk calculations even higher, as noted above. Specifically, several areas in the exposure assessment could lead to estimated margins of exposure even smaller than those presented in the report; examples include: inhalation rates, environmental temperature, emission rates, skin exposure, the assumption of the adequacy of the respirator protection factors, the hours in a workday, and potential water contamination. The SRC was unequivocal in the view that the DPR should avoid "single value" assumptions for many of its exposure parameters because the uncertainties and variabilities in these parameters could result in substantial underestimations of individual exposure risk. In practice, alternative assumptions must be considered and used to provide alternative values to those which may be put forward as the estimate favored by the DPR in their summary findings. Examples include: a protection factor of 50% for respirators, higher effort-related breathing rates for workers consistent with OSHA exposure assumptions, a 10-hour workday as is most common in the field, and opportunities for inadvertent skin exposure. DPR indicated that alternative exposure values consistent with these assumptions would be included in the final document so that they could be compared to scenarios that yield lower exposure levels that may not have taken these real-world issues into account.

Unresolved issues of mechanism and toxicokinetics, in addition to the exposure scenarios issues raised above, can also lead to underestimation of methyl iodide-associated risk. Regarding oncogenicity, the SRC agrees with DPR that the genotoxicity of methyl iodide should be given prominence given its potency as a methylating agent. Methyl iodide is a strong electrophile that covalently (i.e., irreversibly) methylates macromolecules, notably DNA—a fact that readily explains its potency in causing mutations and genotoxicity. A wealth of published studies which have accumulated in the scientific literature over many decades have unequivocally established the genotoxicity of methyl iodide. These data, summarized in the DPR report, reinforce the conclusion that methyl iodide-caused carcinogenesis via a genotoxic mechanism is highly likely. The SRC is unanimous in its belief that the genotoxic mechanism is most likely, and, furthermore, the SRC supports the DPR's use of a linear projection to assign risk based on a genotoxic mechanism of action (MOA) for methyl iodide. The SRC was dissatisfied with the design of some of the bioassays, for example the mouse study was conducted for only 18 months

instead of 24 months and this undoubtedly leads to an underestimate of the cancer risk. Limitations of this and other relevant studies have been addressed in the attached SRC's documents (see Appendices). We also note that DPR proposed a second MOA for methyl iodide-associated oncogenicity. The SRC agrees with the DPR that, although this second mechanism cannot be ruled out, this pathway does not detract from the more convincing genotoxic MOA. Furthermore, the SRC agrees with the DPR that the final oncogenic risk assessment should be based on the more likely mechanism with the more significant risk, which is the genotoxic MOA with a linear exposure response.

The SRC remains concerned about calculations based on supposed measures of "neurotoxicity" when there were in fact, no robust studies of neurotoxicity actually conducted. The studies labeled as "neurotoxicity" were nothing of the sort, but rather acute general toxicity observations that including manifestations such as motor activity. Thus the extrapolations of neutotoxicty as an endpoint are based on studies that did not assess neurotoxicity appropriately in a broadly acceptable scientific sense. Of note, the contract laboratory conducting key studies in this area was demonstrably incapable of detecting neurotoxicity from positive control test compounds. Based on numerous case studies and laboratory findings, there is a strong expectation that methyl iodide is neurotoxic. The case studies were particularly insightful and demonstrated long term neurotoxic effects of methyl iodide. The mechanism for this is unclear, and therefore uncertainty factors will need to be applied in considering this endpoint.

The SRC is convinced that methyl iodide, were it to be studied appropriately, would prove to be a potent developmental neurotoxicant at exposures well below those required for overt signs of acute exposure (e.g., abnormal physical movements). Methyl iodide concentrates in the fetal brain to levels well above those in the mother (see DPR draft, Table 49). Direct neurotoxicant actions are thus likely to occur. Methyl iodide concentrates in the fetal brain to levels well above those in the mother (see DPR draft, Table 49). Direct neurotoxicant actions are thus likely to occur.

There is a high likelihood that methyl iodide is a developmental neurotoxicant and that there are multiple mechanisms contributing to that endpoint, rather than a single mechanism. Thus, a model based on a single metric such as serum iodide, cannot provide any assurance of human safety. The U.S. EPA typically applies an additional uncertainty factor for compounds for which developmental neurotoxicity is likely, and that needs to be done here. Although the DPR document does acknowledge this data gap and does include an additional uncertain factor in its modeling of the chronic neuro-toxicity endpoint, this data gap is so critical that it stands out for additional emphasis.

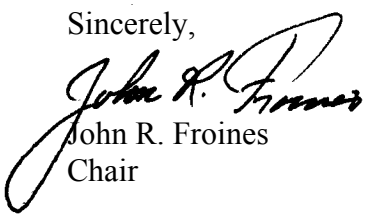
Fetal death is another major endpoint for which the DPR developed risk estimates consistent with standard regulatory approaches. The SRC agrees that this clearly represents an important endpoint, demonstrating the highly toxic nature of methyl iodide. The margin of exposure (MOE) for fetal death is the most striking of all the endpoints modeled: the acute MOE for fetal death was equal to 1 for workers and 0.1 for bystanders and residents exposed to methyl iodide, indicating that there is no margin between this critical endpoint and potential human exposures. This striking estimate makes it impossible to envision how (by what amelioration) an adequate MOE could be achieved, i.e., at least a 3000-fold reduction in human exposures. Beyond that, it

should also be pointed out that the fetal death endpoint is likely to be only one of a number of different toxic endpoints for this compound.

We have already commented on the environmental fate of methyl iodide, but this topic also warrants additional emphasis. The SRC found it alarming that there were no reliable data on the potential of methyl iodide to contaminate groundwater. The modeled calculations we reviewed indicated the potential for unacceptably high levels of iodide to accumulate in water supplies.

After thoroughly considering the DPR assessment, as well as taking into account related input such as the written comment of OEHHA and the testimony given by interested parties, we conclude that the DPR has effectively summarized the available scientific data on the exposure parameters, environmental fate, and potential health effects of methyl iodide. In particular, the DPR has attempted to systematically take into account scientific uncertainties and data gaps that touch on these matters and affect the underlying assumptions of risk modeling. By doing so, the DPR has taken a highly appropriate public health protective approach throughout this assessment. Indeed, the SRC found that in each and every instance where the DPR findings differed from the U.S. EPA risk assessment for methyl iodide, this was attributable to a more insightful and scientifically rigorous approach having been undertaken by the DPR. In that context, we were very reassured by U.S. EPA testimony to the SRC (September 25, 2009). The EPA statements implicitly acknowledged the robust nature of the DPR's approach, stating that, "Depending on the outcome of California's external peer review and final risk assessment, EPA may choose to initiate reevaluation of the methyl iodide registration. If the scientific review panel provides new information that would alter or change EPA's scientific analysis, we will include that information." [Please refer to the official meeting transcript]

Sincerely,



John R. Froines
Chair

cc: Paul Blanc
Katharine Hammond
Dale Hattis
Ed Loechler
Ron Melnick
Tom McKone
Theodore Slotkin
Marylou Verder-Carlos