UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Hon. Michael Leavitt, Administrator
And
Stephen L. Johnson, Deputy Administrator
U.S. Environmental Protection Agency
Washington, DC 20460

November 22, 2004

Dear Messrs. Leavitt and Johnson,

I am writing to inform you of my serious concern that the Agency's risk assessment for the important insecticide, malathion, will be fatally flawed unless that chemical's cancer potential is more accurately portrayed. Further, and more importantly, the public health will be endangered unless malathion's carcinogenicity is properly dealt with by this Agency, as it is not now being done.

This letter gives details of my reasoning in this matter, which focuses on a flawed review paid for by malathion's manufacturer - of the results of a cancer study. That review's citation is:

Malathion Pathology Working Group (PWG) Assessment of Hepatocellular Neoplastic Response in the Female F344 Rat, performed March 14-15, 2000. (MRID 45069401)

The subject PWG caused the Agency to change is previously agreed upon classification of the carcinogenic potential of malathion from "Likely to be Carcinogenic to Humans", to "Suggestive Evidence of Carcinogenicity." This change, caused by the Agency's (heretofore) acceptance of the flawed review, has a profound effect on how the cancer risk from malathion is managed. Specifically, under a "Likely" classification, a quantitative risk assessment is required under Agency guidelines, while the "Suggestive" finding precludes a quantitative assessment of risk. Without a quantitative risk assessment, the Agency may permit levels of exposure to malathion by the public that will cause harm that could otherwise be prevented.

You should know that others outside the Agency are well aware of the flawed nature of

the review and the impropriety of the Agency's acceptance of it, and that even if EPA chooses to continue to accept its findings at least two adverse consequences are likely: the public health will be endangered, and EPA's integrity will take an unnecessary beating.

None of these adverse consequences need occur, one simple remedy is available, namely the flawed PWG's work should be re-done by pathologists not in the employ of the registrant, using the more critical diagnostic revisions that I discuss in the detailed critique of the flawed PWG below.

Detailed Critique

The Health Effects Division's (HED) [Office of Pesticide Programs (OPP)] Carcinogen Assessment Review Committee (CARC) evaluated the carcinogenicity of malathion on February 12, 2000, classifying it as "Likely to be Carcinogenic to Humans," using the Agency's draft 1999 Carcinogen Risk Assessment Guidelines. During the registrant's "error-only" comment period, having thus learned of OPP's intended carcinogenicity classification, the registrant employed Experimental Pathology Labs, Inc. to conduct a Pathology Working Group (PWG) re-read of the crucial slides that showed tumors.

The PWG downgraded all of the original hepatocellular carcinoma diagnoses to adenoma, and several original adenoma diagnoses to hepatocellular alteration. Based upon this revised histopathology, on April 12, 2000 the CARC changed the "Likely" classification to "Suggestive Evidence of Carcinogenicity," also said to be in accord with the draft 1999 Carcinogen Risk Assessment Guidelines. Under the "Likely" classification, a quantitative risk assessment would be used to regulate malathion. Under the "Suggestive Evidence" classification, a quantitative assessment of risk is specifically precluded. So the change of classification from "Likely" to "Suggestive Evidence" has a profound effect in terms of risk mitigation.

The malathion risk assessment, which includes an assessment of cancer risk, has not yet been finalized, so there is time for the Agency to re-think this issue. It should do so because in my opinion as lead malathion toxicologist the PWG is a flawed assessment.

I have already expressed my concerns about the inadequacy of the PWG assessment. The subject of interest here is the above named 2000 PWG assessment in my April 27, 2000 memorandum to William Burnam, CARC Chairman (Exhibit 1), plus an edited version of that

same report as prepared by Mr. John Carley of former OPP Director Marcia Mulkey's staff [Carley (2000)] (Exhibit 2). Additional documents of interest include [Copley (2000)] (Exhibit 3) and [Pletcher (2000)] (Exhibit 4).

In my view the PWG was improperly conducted, is unreliable and in its present form is virtually useless, or misleading, in assessing the neoplastic potential, or dose response for malathion. Nevertheless, with certain reasonable assumptions, the PWG supports the conclusion that malathion is carcinogenic across all doses.

Specific Points at Issue

1) The PWG Chairman, EPL's Dr. Jerry Hardisty, claims that the purpose of the PWG, as commissioned by the registrant (Cheminova), was to determine the incidence of hepatic neoplasms. He advised that in addition to slides with hepatocellular neoplasm diagnoses (carcinoma and adenoma) in the original study, slides with diagnoses of hepatocellular alteration of at least moderate degree of severity were also examined by the PWG to determine if any of these original diagnoses may prove to be neoplastic lesions.

All hepatocellular alterations, no matter the degree of severity, should have been submitted to the PWG, but this was not done. In a March 20, 2000 memorandum, the registant's representative, Ms Diane Allemang of Jellinek et al. [Allemang (2000)] (Exhibit 5) claims that all such lesions were examined by the PWG. But it turns out that only those incidences of hepatocellular alteration of moderate or greater severity were reviewed by the PWG.

The chairman's passing judgment on which slides to send to the PWG introduced a potential for bias, as slides from the entire study are to be judged blind by the diagnosing pathologists. A possible reason for the chairman's not forwarding all hepatocellular alterations to the PWG was to save time in this hastily convened and performed PWG on March 15, 2000.

There is a well recognized so-called "natural history of neoplasia" for rat liver carcinogenicity. These tumors do not simply appear *de novo*, but arise from preceding alterations of normal liver that progress toward a frank tumor. The sequence is: *hepatocellular alteration > adenoma > carcinoma.* Incidences of each of these three entities are employed in assessing the neoplastic response.

In the malathion study, all three of these lesions were identified by Drs. Henry Bolte

(study pathologist) (1994) and Dr. William Busey (reviewing pathologist) (March 14, 2000). Subsequently, during the March 15 PWG all lesions reviewed retained one or other of these designations (possibly excepting rat # 5512). Carcinomas were downgraded to adenomas, adenomas that were downgraded were to hepatocellular alterations, suggesting that the "natural history of neoplasia" as defined, was operative in this neoplastic response, before and after the PWG.

Dr. Hardisty indicated that among those hepatocellular alterations originally diagnosed by the study pathologist (Dr. Bolte) and/or the reviewing pathologist (Dr. Busey), only the ones of moderate or greater severity would pose diagnostic dilemmas as possibly being reclassified as adenoma by the full PWG. Dr. Hardisty says the PWG was not asked to address the significance, if any, of the non-neoplastic findings in the liver. [Copley (2000)] (Exhibit 3). In my view, this constitutes a major flaw in the conduct of this PWG.

In answering HED's questions about the PWG, Dr. Hardisty maintained that only the incidences of tumors (adenoma; carcinoma) are of interest as offering evidence for carcinogenicity, stating repeatedly that the incidences of hepatocellular alterations of moderate or greater severity should not play a role in assessing the neoplastic response [Copley (2000)] (Exhibit 3). I disagree strongly with this view because, among other reasons, it ignores the well recognized natural history of neoplasia.

In addition, Dr. Hardisty selected to send to the PWG only those hepatocellular alterations identified as of at least moderate severity instead of all such alterations. And of great significance, there were none of these more advanced hepatocellular alterations identified in the Control Group, while several were noted in all dose Groups. This finding is clearly indicative of chemically induced progression of this neoplastic response. Furthermore, the finding of adenoma in dose groups only, and none in controls, gives more evidence that malathion induced progression to tumors.

Hepatocellular tumors in control F344 female rats are extremely rare, with historic incidences in the huge National Toxicology Program's 1998 data base of $< 0.5\%$ adenoma and essentially 0% carcinoma. Rare tumors do not require a large (or statistically significant) incidence in studies to constitute adequate evidence of carcinogenicity. To require proof of progression for such rare neoplastic responses as a condition for even considering incidences of

more advanced hepatocellular alterations in the assessment is to undermine the real evidence for carcinogenicity inherent in such incidences of advanced (or more progressed) findings.

I discussed this matter with a leading pathology expert, Dr. Robert Maronpot, of the National Toxicology Program (NTP) where PWGs are commonly performed, and where Dr. Maronpot is a participant in such reviews. A transcription of that June 8, 2000 conversation is appended, [Maronpot 2000] (Exhibit 6) I should note that Dr. Maronpot is a co-author on the Goodman et al (1994) publication, referred to below, as the source of authoritative diagnostic criteria for hepatocellular lesions employed by this PWG. Dr. Maronpot affirmed the "natural history of neoplasia" concept of progression for this neoplasia in the rat. He indicated that once hepatocellular tumors have been observed in a study, hepatocellular alterations become part of the analysis of the data. He says such lesions are to be considered as "putative neoplastic lesions.".

Dr. Maronpot concurred with my statement that hepatocellular alterations are lesions from among which tumors are more likely to arise than from normal liver. He agreed that under EPA's "key events" concept (cited below), hepatocellular alterations would satisfy as key events to be considered along with tumors. In the absence of tumors they would be ignored. But since tumors were observed (even if downgraded from carcinomas to adenomas by this PWG), these alterations cannot be ignored.

He also indicated that EPA is a conservative Agency, and if people don't like that interpretation they need to perform the proper study to rule out the use of the alterations data as key events. Dr. Maronpot also concurred that if someone selected out the more conspicuous hepatocellular alterations to refer to the PWG as the more likely to be confused with adenomas, then it is even more imperative these be considered "key events", and taken into account.

So Dr. Maronpot's interpretation agrees with my own logic, and stands in remarkable contrast to that espoused by Dr. Hardisty. In effect, Dr. Hardisty's decreed irrelevance of hepatocellular alterations in the PWG inappropriately detracts from the assessment of carcinogenicity for malathion.

EPA's 1999 Cancer Assessment Guidelines say with respect to cancer dose-response assessment: "In this discussion, 'response' data include measures of *key events* (emphasis added) considered integral to the carcinogenic process, in addition to tumor incidence. 'Key events' are precursors to cancer pathology; they may include proliferative events diagnosed as precancerous, but not pathology that is judged to be cancer. Analysis of such responses may be done along with

those of tumor incidence to enhance the tumor dose-response analysis. *If dose-response analysis of non tumor key events is more informative about the carcinogenic process for an agent, it is used in lieu of, or in conjunction with, tumor incidence analysis for the overall dose-response assessment."* (emphasis added). (p. 3-1) I emphasize that this appears in our own draft EPA Guidelines purportedly used in this malathion assessment.

As I indicated, under the "natural history of neoplasia" hepatocellular alterations would be key events in the process. So again, in the face of the very Guidelines HED's CARC claims to have followed, use of the critical "key events" element in the assessment of hepatocellular carcinogenicity has been compromised by this PWG and improperly accepted by the CARC. It is shameful that the PWG, HED's CARC and the FIFRA SAP, for whatever reasons, failed to recognize this fact.

I believe that when the PWG chairman chose to review only those hepatocellular alterations of more advanced severity (at least "moderate"), and tumors, he perhaps unwittingly, and fortuitously, selected out the proper lesions that clearly demonstrate a positive neoplastic response across all doses (and not seen in the control group). Importantly, the effect extends across all doses, exhibiting no NOAEL, even at a dose as low as 100/50 (ppm) where marginal but real cholinesterase inhibition occurred. This is not unlike the hepatocellular neoplastic response that was evident across all doses (the lowest being 100 ppm) among males in the 1994 malathion mouse carcinogenicity bioassay (MRID 43409201, including the August 8, 1998 PWG).

2) The PWG interpretation of findings in study Group IV exemplifies how positive evidence of carcinogenicity in this study was muted or excluded by this PWG.

In the PWG report, Group IV is shown as no different from Group 1 (control) in exhibiting no evidence of carcinogenicity, i.e. zero tumor incidence is entered for both Groups I and IV, and thus both groups alike are presumably entirely devoid of any evidence of carcinogenicity. (See Table 1 [Allemang (2000)] (Exhibit 5). It should be noted that Table 1 in Ms Allemang's memorandum does not incorporate the diagnoses of the peer review pathologist (Dr. Busey) as it should, for if it did that would illustrate the remarkable concordance between Drs. Bolte and Busey prior to the PWG, thus both enhancing the credibility of Dr. Bolte's diagnoses, and adding further credence to skepticism about the legitimacy of the PWG report.

Inspection of the diagnostic data presented in the PWG report, Appendix A (Exhibit 7),

shows this remarkable concordance between Drs. Bolte and Busey. In Group IV, the two pathologists concurred on two adenoma diagnoses (rat #s 4514 and 4531); Dr. Bolte diagnosed adenoma for rat # 4504 which Dr. Busey diagnosed the lesion as "hepatocellular alteration (*'marked'*)" (emphasis added), which comparative diagnoses between the two pathologists suggest the lesion must be borderline between the two characterizations. All three of these lesions were diagnosed by the full PWG as hepatocellular alteration, though not classified as to severity. One might conclude, however, absent any classification as to severity, that all three were marked (if not adenoma), given the prior diagnoses by the study and reviewing pathologists as either adenoma or hepatocellular alteration (marked).

Both Study and Reviewing pathologists diagnosed "hepatocellular alteration ('moderate')" in rat # 4534, later confirmed as hepatocellular alteration by the PWG, but again without any comment as to the lesion's severity, though it is reasonable to assume the lesion as being at least "moderate" in severity, since both Drs. Bolte and Busey said so, and was the basis upon which the PWG chairman selected them for PWG evaluation.

Rat #s 4512 and 4544 were diagnosed as hepatocellular alteration (absent classification as to severity) by PWG, diagnoses evidently missed by both Drs. Bolte and Busey. Should these be presumed as of moderate severity or not? This unknown constitutes (and serves to emphasize again) a failing of the PWG to properly address the subject. So, in summary, Group IV, even after the PWG, has three rats with hepatocellular alterations probably of marked severity, a fourth of moderate severity and perhaps two others which should be presumed (conservatively in the public interest) to be of at least moderate severity until established otherwise.

So in contrast with the control group, Group IV contains six (certainly 4) rats with hepatocellular alterations diagnoses that should have been included in the dose response assessment along with tumors (and hepatocellular alterations) that were diagnosed in Groups II, III and V, in contrast to Group I (the control). Clearly Group IV is remarkably positive versus the control under the "natural history of neoplasia" for the hepatocellular tumor response, and cannot be treated in tables of tumor data as if no different from the control, nor as contributing no evidence of carcinogenicity.

The PWG, HED's CARC and FIFRA's SAP should all know this. The fact that this positive evidence exists in Group IV adds support as positive the findings in Groups II, III and V. The neoplastic response is observed across all doses, a conclusion supported by the fact that this response qualifies as rare (by recognized definition, < 1% incidence) in the F344 female rat.

Given the rarity of this neoplastic response in the female F344 rat, only a few tumors are necessary to identify a positive response, and incidences of these taken in concert with "key events" define a dose response across all doses as EPA's 1999 Guidelines require. The fact that one dose group, in this case Group IV, may lack a tumor diagnosis as it does *after* the elimination of such findings by the PWG, does not render the several advanced "key events" ignorable in the dose-response assessment. These constitute evidence of carcinogenicity like unto that observed in Groups II, III and V, which is absent in Group I (control).

In conclusion, the PWG erred in 1) failing to classify hepatocellular alterations as to severity, and 2) in discounting the obviously more advanced form of these lesions as co-evidence ("key events"), along with adenomas, of carcinogenicity. There is positive evidence for carcinogenicity across all doses, including Group IV. The findings of adenomas in Groups II and III, cannot be disregarded as positive grounded on the bogus argument there was no effect in Group IV [see for example views to the contrary, Allemang (Exhibit 5) (item 2, p. 3)], nor can it be argued that the carcinogenic effect is confined to Group V, simply because Group IV was negative, despite the positive effects in Groups I and II. Rather, the inherent positive evidence of carcinogenicity in Group IV is reinforced by similar effects in Groups II, III and V.

The PWG was not conducted in the proper manner to characterize the hepatocellular alterations response, but nonetheless, even after all carcinomas (first diagnosed by Drs. Bolte and Busey) were downgraded to adenomas and several adenomas to hepatocellular alterations, there remains a clear positive neoplastic response across all doses when the data are evaluated according to principles set forth in the 1999 Cancer Assessment guidelines, which CARC claims to be following in its assessment. This should have been recognized by the registrant, the PWG, the HED's CARC and the FIFRA's SAP, all four participants in the risk assessment of malathion.

3) In commenting on the PWG's downgrading of all carcinomas to adenomas, HED's CARC consulting pathologist, Dr. John Pletcher, [Pletcher (2000)] (Exhibit 4), offered the following explanation in support of the veracity of the PWG: "I contacted one of the PWG members and asked him why the carcinoma diagnoses made by the Study Pathologist (Dr. Bolte) were overturned by the PWG. He told me that the working group members were nearly unanimous in their opinions, particularly so concerning changing the carcinoma diagnoses. It was his opinion that the Study Pathologist, being without the aid of another pathologist to consult with while doing the initial evaluation, used incorrect criteria."

In this explanation, Dr. Pletcher does not seem to be aware, or fails to acknowledge, that the "peer reviewing pathologist," Dr. Busey, concurred with Dr. Bolte on four of Dr. Bolte's five carcinoma diagnoses [rat #s 2522 (Group II), 3503 (Group III), 5521 (Group V), 5505 (Group V), while revising that of rat # 5514 (Group V) to adenoma. Now Dr. Busey was said to have employed on March 14 the same *"correct"* diagnostic criteria [Goodman et al (1994)] as was employed by the subsequent full PWG on the next day, March 15 [Copley (2000), p. 4] (Exhibit 3) So it is not reasonable to place the blame, if you will, on a lone pathologist employing incorrect or outmoded criteria. In fact, the remarkable concordance between Drs. Bolte and Busey on the study as a whole, where the latter is said specifically to have employed the correct criteria (Goodman et al 1994), confirms Dr. Bolte, and attests to the gentleman's credibility.

This PWG does not adequately explain the downgrading all of the carcinomas, and a number of adenomas. It is essential that this PWG present some histopathologic criteria explaining the differences between the conclusions of Drs. Bolte and Busey versus the full PWG on the carcinoma diagnoses. If the original carcinoma diagnoses were overreaching, then in certain respects these tumors might be more robust in certain ways, more advanced if you will, than the more ordinary adenoma. However, answers to this kind of question must come from the pathologists, who thus far have made no qualifying remarks, in spite of HED's requests to have them do so in our follow-up deliberations with the PWG chairman [Carley (2000), see response to question 8, p. 6] (Exhibit 2). .

In this same connection, it is to be expected that the Agency's toxicologist on a particular chemical, in this case myself (or perhaps some other HED toxicologist), should have been present at the PWG. In 1997 when the malathion mouse liver tumor findings were to undergo a PWG assessment, I discussed the matter with Dr. Robert Maronpot, NTP pathologist mentioned previously. As a follow-up to our phone conversation, he sent me a letter, a copy of which is appended, [Maronpot 1997] (Exhibit 8), in which he says in effect that an EPA toxicologist should attend the PWG. As a result of this recommendation, OPP sent me to the mouse liver PWG, also conducted by EPL with Dr. Jerry Hardisty as chairman.

As it turned out, I had many important questions, some of which were properly responded to, others to this day remain unaddressed in spite of my written correspondence with Dr. Hardisty. It was certainly plain to OPP the importance I ascribed to the need for my presence (or that of another Agency toxicologist) at such PWGs, the one on the malathion rat liver data included. Yet, though OPP knew the registrant was pursuing a hastily convened PWG in March, after the CARC's decision in February, the PWG was conducted without an Agency toxicologist present.

While EPA sent no one to this PWG, the registrant sent three people, according to the March 20, 2000 memorandum of Ms Dianne Allemang (JSC, Inc.). According to Ms Allemang: "The U.S. EPA declined to accept Cheminova's invitation to send an observer." That I would have had many legitimate questions is evident in Copley (2000) and in my memorandum of March 23, 2000 [Copley (2000), attachment] (Exhibit 3) following the PWG.

A key question of mine would have been: "What was seen microscopically by the PWG that led to changes of diagnoses first rendered by Drs. Bolte and Busey?"

There has never been a satisfactory answer to this question. The change of diagnoses of four carcinomas concurred in by Drs. Bolte and Busey, and a fifth by Dr. Bolte, prior to the PWG, which were downgraded to adenoma by the PWG without any explanation remains a principal concern. This concern is reinforced by statements of Dr. Pletcher [Pletcher (2000)] (Exhibit 4) and a quotation from Goodman et al (1994): first, Pletcher: "Nothing in the biological sciences is absolute; however, well-defined criteria have recently been published by the Society of Toxicologic Pathologists (STP Guides) *making the differentiation of carcinomas from adenomas relatively easy for a pathologist with rodent experience* (emphasis added)." ; second, Goodman et al (1994): "Hepatocellular carcinomas generally have characteristic histologic features *readily distinguishing them from other primary and secondary liver tumors* (emphasis added)." (p. 4)

Given this well recognized ease of distinguishing carcinomas, what explains the incorrect diagnoses of carcinoma concurred in by Drs. Bolte and Busey prior to the PWG? Had I been present at the PWG, with all pathologists present, I would have posed this question, and sought some explanation from Drs. Bolte and Busey, which they could have shown me under the microscope, explaining their errors of judgment. I would have wanted particularly to understand whether these lesions were very much advanced toward a carcinoma diagnosis, if not quite there. In my view, if the adenomas previously diagnosed as carcinomas are of a more advanced character for adenoma, that observation in and of itself would attest to an enhanced order of progression of this neoplastic response. To categorize these lesions as black or white is not adequate to address the question of neoplastic progression. Exemplifying this concern, is a statement made by Dr. Pletcher further along in his memorandum: ".....one person's adenoma may be another's focus of cellular alteration". When I was present at the mouse PWG, I was shown under the microscope certain anatomic features of carcinoma. "What among these features," I could have asked, "led Drs. Bolte and Busey to call carcinoma, to which the other pathologists said no?"

This problem of learning more about the character of the these lesions should be remediated by an audited inspection of the slides by National Toxicology Program (NTP) pathologists. Alternatively, a call-in of photomicrographs of the slides in question for inspection of independent pathologists such as those of the NTP might quickly achieve the same objective. In any case, photos of pertinent slides should be available for inspection by the public. Given that this is a huge public health issue, there should be no sanctuary from public inspection of such images.

In conclusion, it was improper of the Agency to deny the presence of a staff toxicologist at this PWG, especially in view of the basis for my attendance at the previous PWG. It is obvious that if the tumors originally diagnosed as carcinoma should actually be carcinoma, but not treated as such in risk assessment, the public is put at risk by the very agency entrusted to protect it.

4) Hepatocellular tumors are extremely rare in female F344 rats. Allemang [Allemang (2000)] (Exhibit 5), provides an incorrect citation to the National Toxicology Program's incidence for these tumors. Specifically, Ms Allemang cites the adenoma and carcinoma incidences as 2.3% and 0.2%, respectively. Upon my independent inspection of NTP's 1998 tumor incidence data base ("Tumor Incidence in Control Animals by Route and Vehicle of Administration F344/N Rats", Toxicology Data Management System, NIEHS, February 1998), I find the numbers she presents are more precisely the incidence data for males, which gender naturally carries a higher incidence, while for females the respective incidences are < 0.5% (adenoma) and 0% (carcinoma). Apparently, Ms Allemang employed data from an older NTP publication [Haseman et al (1990)] that was referenced by Dr. Hardisty in the PWG report. Yet, it is most obvious that the more recent (1998) NTP historical control data base should have been employed as the more relevant to the 2000 PWG re-reads. It is also possible the HLS control data (study dates 1992 and before) Dr. Hardisty and Ms Allemang cite had not been reviewed (updated) so as to accord with the pathology diagnostic criteria invoked for this PWG, namely, Goodman et al (1994).

In other words, adenomas are very rare and carcinomas essentially never found among historical control females. Hence, this neoplastic response to a test material need not rise to a level of statistical significance to constitute a carcinogenic finding. In this study, even absent carcinomas (if they are indeed absent), the large number of adenoma and hepatocellular alterations findings reveal a neoplastic response extending across all doses.

5) The PWG report implies that the full PWG assessment was done blind, i.e. slides were presented in a coded manner (by Dr. Hardisty), and decoded only after the PWG had rendered its

diagnoses. Yet, Dr. Busey evidently knew the identity of the dose groups, and had the benefit of Dr. Bolte's diagnoses when he rendered his own diagnoses. In my view, the pathology peer review should be entirely independent and truly blind. Furthermore, two of the PWG pathologists (Drs. Bolte and Busey) knew in which groups tumors, and most particularly the carcinomas resided. Dr. Hardisty also knew, since he decided which slides should go to the PWG. So it was known prior to the PWG that this study demonstrated increased incidences of tumors and the more advanced hepatocellular alterations in dosed groups only, and that any downgrading of tumors would benefit the registrant.

Hepatocellular alterations were not graded by the PWG, so the more advanced ones as noted by Drs. Bolte and Busey, along with those likely more advanced ones to result from PWG downgrades of adenoma, which taken together illustrate a positive neoplastic response under EPA's Guidelines, were obscured among the more commonly observed "minimal" graded hepatocellular alterations.

Final Conclusion

This PWG is flawed, and should not be accepted. At a minimum the more critical diagnostic revisions rendered by the PWG should be re-assessed by pathologists not in the employ of the registrant.

Sincerely,

Brian Dementi

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cc
Dwight Welch
Susan Hazen
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