29 January 2007

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RE: Docket number EPA-HQ-OPP-2004–0348

Federal Register Vol. 71, No. 229/Wednesday, November 29, 2006, pp 69114-69116.

Submitted electronically to opp-docket@epa.gov
copied to anderson.neil@epa.gov

These comments are supported by:

Farmworker Pesticide Project, Seattle, WA; Farmworker Justice, Washington, D.C.; Farmworker Association of Florida; California Rural Legal Assistance Foundation; Center for Environmental Health, Oakland, CA; Beyond Pesticides, Washington, D.C.; Institute for Agriculture and Trade Policy, Minneapolis, MN

Dear Mr. Anderson,

On behalf of Pesticide Action Network North America (PANNA), and the seven organizational co-signers of this letter, we express our appreciation of the opportunity to provide comments on EPA's Malathion Reregistration Eligibility Decision issued July 2006 (referred to here as RED 7/06).

Malathion use includes application on agricultural crops including large-area fruit fly abatement treatments (an unregistered use) and treatments within the USDA Boll Weevil Eradication Program, treatment of stored wheat grain; outdoor residential uses on ornamental plants, vegetable gardens, and fruiting trees; outdoor structural perimeter treatments; and public health uses (e.g. large-area mosquito control and head lice treatment).

In this RED, the Agency claims to have met current scientific and regulatory standards under section 4 of FIFRA and that the database to support reregistration is substantially complete and that products containing malathion are eligible for reregistration, provided the risks are mitigated either in the manner described in the RED or by another means that achieves equivalent risk reduction. The Agency also claims that:

> The Agency's human health assessment is protective of all U.S. populations, including infants and young children. The Agency's use of human studies in the malathion risk assessment is in accordance with the Agency's Final Rule promulgated on January 26, 2006, related to Protections for Subjects in Human Research, which is codified in 40 CFR Part 26 (RED 7/06 p7).

In these comments we present arguments supporting the opinion that since important data gaps remain and that important data and other information representing dissenting opinions to decisions presented in the Agency's malathion RED has been deliberately ignored, that many aspects of the Agency's assessment is NOT protective of human health.

In presenting our opinion, we would like to begin by acknowledging the substantial work that Agency scientific staff have conducted to date on malathion and have submitted for consideration of the public during public comment periods such as this one.

In particular, we reference three documents prepared by Dr. Brian Dementi, PhD, D.A.B.T., Biochemist/Toxicologist employed as the Agency's principal toxicologist on malathion for many years. In our comments, we echo the concerns expressed primarily by Dr. Dementi and supported in the public record by the many resources he cites.

These three documents (attached) are:

1) June 20, 2005 letter to EPA Administrator Stephen L. Johnson;

2) September 28, 2006 letter to EPA Administrator Stephen L. Johnson;

3) Memo submitted to "Interested persons" dated November 29, 2006 in which Dr. Dementi summarizes the arguments presented in his comments on what he understood to be the final malathion risk assessment submitted June 13, 2005, along with 27 accompanying attachments, to HED with covering memo to Sherrie Kinard. (referred to as Dementi 11/29/06)

   The June 13, 2005 comments were submitted to EPA's Health Effects Division but we could NOT find them in the public online OPP/HED malathion docket**.**

We are encouraged by the Agency's promise to evaluate "comments or data that it receives" and to "modify this assessment, as appropriate." With that expectation, we submit the following comments that focus on the following summarized points discussed in greater detail in the same numerical order:

1. **Key documents previously submitted to and included within the public record are no longer available**
2. **The cancer classification demotion from "likely" to "suggestive" is not adequately health-protective nor supported by prevailing evidence**
3. **Crucial data regarding intraspecies effects are overlooked**

4. **EPA fails to adequately evaluate non-cholinergic mechanisms of developmental neurotoxicity, especially in children**
5. **Malathion risk analyses underestimate presence and toxicity of important degradation products**
6. **Poisoning data indicate that workers and the public are inadequately protected**
7. **Evidence of inadequacy of rats as surrogates for estimates of human health effects**

DETAILED COMMENTS:

1. **Key documents previously submitted to and included within the public record are no longer available**

It is of great concern that Dr. Brian Dementi's comments on the malathion risk assessment (and 27 accompanying attachments for a total of about 700 pages) dated June 13, 2005 could not be found in the public online OPP/HED malathion docket at http://www.regulations.gov**,** search: EPA-HQ-OPP-2004-0348, or at http://www.epa.gov/oppsrrd1/op/malathion.htm; or within the Office of Prevention, Pesticides and Toxic Substances (OPPTS) web page. The comments were submitted to EPA's Health Effects Division (HED) with covering memo to Sherrie Kinard. Given that Dr. Deminti served as the Agency's principal toxicologist on malathion for many years, it appears to be a serious violation of Agency's policies of public access to information.

In addition, in his 11/29/06 memo (attachment XXIV) Dr. Dementi illustrates that despite efforts within OPP to catalogue into the public record key dissenting documents regarding malathion risk assessment, at least one (a 1/28/03 report to OPP's Hazard Identification Assessment Review Committee—HIARC) had been deleted from the draft risk assessment. Dementi gave other examples as well.

2. **The cancer classification demotion from "likely" to "suggestive" is not adequately health- protective nor supported by prevailing evidence**

In his 11/29/06 comment summary Dr. Dementi presents many arguments refuting the Agency's demotion of malathion's cancer rating from "likely" to "suggestive" and raises serious concerns regarding one crucial outcome of this decision—elimination of any regulations imposed on malathion use driven by evidence of carcinogenicity or carcinogenic potential. Furthermore, Dementi noted that the key Pathology Working Group (PWG) assessment (sponsored by the registrant—Cheminova) upon which this decision was based was seriously flawed. In addition, only upon repeated questioning at the SAP August 2000 meeting did the PWG chair answer for the registrant representative to whom the questions had been posed and gone unanswered. He admitted that National Toxicology Program (NTP)'s historical control incidence data being presented for assessment of liver histopathology findings, were in fact from a 24-month study as opposed to the relevant 18-month carcinogenicity study. The malathion carcinogenicity study under discussion, and for which interpretation of NTP's data would be relevant, was an 18-month study. Hence, the data being put forward upon which they were basing their arguments to categorize malathion as non-carcinogenic, was in fact, inappropriate (personal interview with

Dementi).

Dementi's arguments regarding this cancer rating decision were supported by many references to the literature, multiple written comments, and oral presentation to the FIFRA Scientific Advisory Panel (SAP) in August 2000. Among many arguments submitted to the SAP prior to its August 2000 meeting, Dr. Dementi demonstrated support in the literature (including Agency Guideline testing) for neoplasia in the lowest dose range tested and tumorigenic responses in several tissues and animal models. The SAP, Dementi argues, failed to respond adequately to the many arguments presented. In fact, Dementi later discovered that his comments submitted to the SAP were never reviewed by that body. Similarly, comments submitted by Dr. G.V. Alexeeff of California Office of Environmental Health Hazard Assessment were never reviewed. Both sets of comments were ignored despite the fact that they were submitted prior to the August 2000 meeting and that the final SAP report was not released until December 2000. One important argument in Alexeeff's memo was a strong disagreement with EPA's Carcinogen Risk Assessment Guidelines of that time that stated that a rating of "suggestive" does not require a quantitative risk assessment for carcinogenicity.

A third set of comments referred to by Dementi (11/29/06) were submitted to the SAP by SAP member Dr. H. Needleman in which he strongly criticizes the analytical techniques used the Agency's Carcinogen Assessment Review Committee (CARC) as "severely deficient as a standard to protect human health." These comments, submitted in response to the SAP December final report, were apparently never passed on to other members of the SAP.

In 2003 comments, Dementi reiterated his conviction that developmental neurotoxicity studies already demonstrated that offspring were much more susceptible than adults and that data were sufficient to support the "likely" classification. He also suggested that the "suggestive" rating based on testing in adult animals should *at least* (our emphasis) trigger a requirement for testing carcinogenicity in animal offspring as surrogates for human carcinogenicity testing from the infant/child stage onward. Dr. Dementi never received a response to his comments.

Hence our concern is two-fold: 1) the decision itself demoting the malathion cancer rating from "likely" to "suggestive" is not supported by prevailing evidence and has appeared to be inappropriately influenced by the registrant, and 2) the decision-making and review process blatantly failed, on a number of occasions, to both consider key evidence submitted (whether it be submitted by members of the Agency's professional staff, representatives of state agencies, or the public), or to provide responses to those who submitted comments.

3. Crucial data regarding intraspecies effects are overlooked

In a May 2002 memo Dr. Dementi presented arguments strongly criticizing the Agency's use of the Benchmark Dose (BMD) analysis of malathion offspring cholinesterase data instead of using actual offspring data generated from low dose experiments. The arguments are based on data suggesting that offspring may be at least 90 times more sensitive than adults, that effects other than cholinesterase inhibition have been documented at low levels, and that these possibly non-cholinergic effects are inappropriately and deliberately ignored using the BMD analysis. Such

effects include offspring behavioral effects and morphometric effects on the corpus callosum (nervous tissue involved in communication between the right and left sides of the brain).

A developmental neurotoxicity (DNT) study and a comparative cholinesterase study were submitted by the registrant to the Agency in 2002. In review of this study Dr. Dementi raises a number of serious concerns. Specifically, his submission of a 2004 manuscript, concurs with the malathion RED (p10) that "juvenile animals are more sensitive than adults" to the effects of cholinesterase inhibitors, but goes on to argue that resulting regulatory endpoints are not valid because they are based on flawed cholinesterase data. Dementi's arguments were subsequently supported, in the public record, by a statistician at the Office of Science and Technology. In addition, Dr. Dementi has pointed out that the DNT study results of exposures among offspring to doses below those eliciting cholinergic clinical signs resulted in notable behavioral effects. Furthermore, his extensive review of the literature supports a conclusion that the cholinesterase inhibition studies considered are not adequate to detect, reliably, low level central nervous system cholinesterase inhibition across brain regions, nor are they designed to test for changes in acetylcholine receptors.

In addition to the developmental neurotoxicity effects discussed, the recent work by Furlong et al. (2006) demonstrated that activity of the PON1 enzyme responsible for detoxifying organophosphate (OP) pesticides varied by a factor of 164 between the most robust adult and the most sensitive child in their study population. [1] The researchers analyzed the form and levels of the enzyme to predict women and children's sensitivities to two OP pesticides—chlorpyrifos and diazinon. The most sensitive newborns were 65 times more sensitive to diazinon and 131 to 164 times more sensitive to chlorpyrifos.

This result indicates that an intraspecies uncertainty factor of 10 (RED 7/06 p11) is likely to not be sufficiently protective of infants; and should at least be considered inadequate until shown otherwise through similar studies specifically focused on malathion. Furthermore, the Agency must reconsider the decision to eliminate the FQPA safety factor since that decision is based on, in part, "observed susceptibility differences between young and old are a result of postnatal exposures and ChEI data from gestational only exposures which indicate that fetuses are less sensitive than the mother at birth." (RED 7/06 p14). We argue that until similar PON1 comparisons are conducted, this decision is not justified.

4. EPA fails to adequately evaluate non-cholinergic mechanisms of developmental neurotoxicity, especially in children

In its risk assessment of malathion and all OPs as a group, EPA considers only one mechanism for neurotoxic effects—cholinesterase inhibition. It fails to require pesticide registrants to test for other mechanisms of nervous system toxicity. Neurotoxicity via non-cholinergic mechanisms is a particular concern, as indicated by an ample and continuously expanding literature illustrating the scope of such effects. While many of the studies evaluated OPs other than malathion, the results are undeniably relevant.

A brief review of the relevant literature provides sufficient evidence to raise serious doubts about the Agency's use of cholinesterase inhibition as the sole toxicological endpoint for OP pesticide exposure. We highlight a few of the relevant papers below.

- Many recent studies indicate that low-level exposure to chlorpyrifos interferes with the development of the nervous system in the mammalian fetus. Developmental effects of chlorpyrifos involve mechanisms unrelated to cholinesterase inhibition, notably events in cell signaling that are shared by non-neural targets (Meyer et al., 2004).[2]
- In 1997 and 1998, Song et al. identified several mechanisms of non-cholinergic developmental effects of chlorpyrifos in rats at subtoxic doses.[3,4]
- Several authors provide a decade of evidence implicating a host of non-cholinergic mechanisms of OP toxicity that depend upon the direct targeting of events specific to the developing brain. Neural cell replication and differentiation are both affected, with a reduction in the number of neural connections observed in exposed rats.[5]
- The relative potency of OP pesticides for producing developmental neurotoxicity via mechanisms unrelated to cholinesterase inhibition has not yet been determined.[6]
- Whyatt et al. (2004, 2001) conducted epidemiological studies involving pregnant mothers exposed to chlorpyrifos through involuntary home pesticide use and demonstrated a link between in utero exposure to chlorpyrifos and low birth weights and/or reduced head circumference of newborns in the study, most significantly for mothers whose genetic makeup is such that they produce low levels of PON1, the enzyme that is responsible for detoxifying chlorpyrifos and its oxon in the body.[7] In another New York City study Berkowitz et al. (2004) confirmed the relationship between low PON1 levels in mothers and reduced head circumference in newborns.[8]
- Colborn (2005) reviews relevant literature showing that chlorpyrifos attacks neurons that appear during the earliest stage of brain and central nervous system development.[9]
- Rawlings et al. (1998) documented the endocrine disrupting effects of chlorpyrifos; moderate doses have been shown to alter hormone levels in animal studies.[10] And Keith (1997) lists malathion and other organophosphates as endocrine disruptors.[11]

Each of these studies was conducted by independent scientists who published their work in the peer-reviewed literature. Much of this work has been done since IREDs were published for specific OPs, but these papers should certainly have been given equal (if not preferential) consideration to industry studies in the development of both the OP cumulative risk assessment and individual OP risk assessments.

In light of the substantial evidence of developmental neurotoxicity as a result of noncholinergic effects at doses lower than those causing cholinesterase inhibition, the policy of basing assessment of neurotoxic risks on the cholinesterase inhibition endpoint alone is called into question, in terms of protecting children's health. Without data on the relative potency of malathion to cause developmental neurotoxicity via mechanisms unrelated to cholinesterase inhibition, EPA cannot ensure that the current use of malathion does not adversely affect infants and children.

In addition to the non-cholinergic effects described above, Dr. Dementi points out in his 11/29/06 comments that people in malathion spray zones have claimed a number of adverse health effects, at least some of which (e.g. serious nosebleeds) are not listed or considered in the RED.

5. Malathion risk analyses underestimate presence and toxicity of important degradation products

In a September 2002 memo Dr. Dementi recognized the submission of information to the Agency establishing that on storage malathion rearranges to **isomalathion** in a time/temperature-dependent manner and that isomalathion is much more acutely toxic, cholinergically, than malathion. The concern was that the malathion risk assessment failed to adequately consider isomalathion formation and subsequent risk of human exposure under conditions of use, for example, for medfly, mosquito and boll weevil control.

The Agency did subsequently conduct product sampling, albeit at two Cheminova distribution centers, rather than under field conditions, specifically just prior to application to human populations. Furthermore, sampling results should clear the product where isomalathion content is concerned prior to application. This should be pursued for such period as necessary to confirm quality control.

The 7/06 malathion RED was issued as the Agency is awaiting results of additional studies on isomalathion in storage as well as toxicity studies of malathion product with 0.4% isomalathion (the certified limit is 0.2% by weight). While the current RED (p 94) does state that the "registrant has also agreed to add to malathion product labels an amended storage stability statement," it is of concern that this information is not yet available.

Similarly, the Agency points out throughout the RED that data gaps exist regarding the metabolite **malaoxon**, admittedly a more potent cholinestrase inhibitor than malathion. These data gaps, including acute toxicity data, repeated dose comparative data, data on conversion rates on hard, dry surfaces, and limited data on fate properties, affect many of the protective measures set in the RED. The greatest potential for malaoxon formation occurs when malthion residues deposit on hard, dry surfaces which can be inadvertently contaminated during wide area applications. The Agency has estimated toddler post-application exposures from potential contact with malaoxon residues on wood decks and playground equipment following aerial ULV sprays for public health mosquito treatment, boll weevil eradication, and fruit fly treatment.

However, the most notable data gap is the agency's lack of acute toxicity data and subsequent determination of an acute Toxicity Adjustment Factor (TAF) of 61x that is frequently used as a basis for determining other protective levels in the RED. EPA states that in absence of the data needed for the TAF, the TAF is "assumed to be health protective in assessing single (acute) exposures to malaoxon in adults as well as both acute and repeated exposures to the young." (p 56). The agency goes on to assume the 2004 Call-In for the missing data will provide confirmatory data. These are very dangerous assumptions and it is not appropriate for a regulatory agency to make assumptions when it comes to protecting human health.

6. Poisoning data indicate that workers and the public are inadequately protected

Ongoing use of malathion also results in ongoing risks of acute poisoning episodes with potential long-term health effects for workers and others in agricultural areas. A malathion poisoning case in June of 2002 in Washington State is illustrative. Six workers labored in a vineyard tying up grape vines and installing posts. A helicopter flew over them and started spraying the adjacent orchard. The workers immediately felt symptoms of pesticide poisoning, including burning eyes, tingling skin and severe nausea. They ran but could not escape the spray. Emergency medical services arrived and they were treated at the scene and then taken to hospitals. Fortunately, the baby daughter of one of the workers was inside their nearby house when the episode occurred.

Workers continue to experience health problems from this malathion exposure episode to this day. One of the workers who has testified at state administrative and legislative hearings seeking better protections for workers, has ongoing debilitating dry eyes and dizziness which make it dangerous for her to drive.

The course of attempted enforcement in this case highlights the realities that can face workers injured by malathion and other pesticides. It highlights the need for greater EPA oversight of state agencies delegated to enforce pesticide laws. While the Pesticide Division within the Washington State Department of Agriculture (WSDA) issued a notice of intent to suspend the license and assess a civil penalty in this very clear-cut case, the pilot objected and requested an adjudicative hearing. Unfortunately, the Director of WSDA did not stand by her inspectors when the Administrative Law Judge ruled against them. She denied the workers' request for reconsideration. The workers petitioned for judicial review, and won in the Superior Court. The Court reversed the Director's order, finding it was not supported by substantial evidence. The Court of Appeals upheld the Superior Court. But an appeal to the state's Supreme Court further delayed enforcement in the case. At this writing, the workers have had to wait over four years for even basic enforcement.

A review of California data on reported pesticide-related illnesses between 1998 and 2004 listed 121 cases that had adequate information to classify cases as definitely, probably, or possibly related to malathion exposure. Most cases were due to drift and residue exposure and occurred in single family homes and on school grounds (including one large exposure of 20 students and a teacher).

Table 1. Reported cases of malathion poisoning in California 1998-2004.

A	**Cause of exposure**	**Number of cases reported**
	Drift	25
	Residue	18
	Direct spray or spill	9
	Ingestion	8
B	**Location of exposure**	**Number of cases reported**
	Single family home	30
	School	27

On farm	12
Landscape	12
Multi unit housing	8

Source: California Department of Pesticide Regulation, Pesticide Illness Surveillance Program.

While the state of California has arguably the best pesticide illness reporting program in the U.S. we know that for many reasons documented elsewhere, many, perhaps most cases never get reported.[12] Therefore, the numbers shown here illustrate a much more serious problem and suggest that current regulations are sorely inadequate to protect the public from occupational and non-occupational exposures to malathion. While the RED (p 61) does include a discussion of some of the California data with an emphasis on an apparent decline in systemic poisonings from 1990-96 to 1999-2003, it does not discuss the problems of under-reporting.

Accidents happen, and malathion can cause severe immediate effects and debilitating long-term effects as illustrated in the Washington case. Again, improper storage of malathion can result in buildup of more acutely toxic materials than malathion itself, such as isomalathion, which increases the potential of the product to elicit adverse health effects among persons exposed within treatment zones. Through the years of widespread public spraying, it is now recognized that proper storage and other controls were not instituted so as to protect the public and workers from tainted malathion.

7. Evidence of inadequacy of rats as surrogates for estimates of human health effects

Dr. Dementi identifies the absence in humans of a key enzyme (ali-esterase) responsible for malathion degradation in the primary animal model—rats. Without this enzyme, humans are missing key barrier to malathion poisoning. This raises serious concern that rat models are inappropriate for estimating human susceptibility to malathion. The Agency uses a Toxicity Adjustment Factor (TAF) of 61x to account for differences in susceptibility between adults and offspring to the malathion breakdown product malaoxon, but fails to address in the RED the absence of ali-esterase activity in human serum.

Conclusions & Recommendations

1. Restore all relevant malathion documents to the public record available electronically on the EPA website at http://www.regulations.gov, or at http://www.epa.gov/oppsrrd1/op/malathion.htm.
2. Immediately reinstate the previous cancer classification of "likely" and re-evaluate the data already presented e.g. liver tumor response in mice, liver tumor response in rats, leukemia in malaoxon rat study, testicular tumor incidence in rats, and nasal and oral cavity tumor response in rat; as well as any new data regarding carcinogenicity.
3. EPA should modify its risk assessment policy to include non-cholinergic endpoints in addition to cholinergic endpoints already considered. In the interim, the important non-cholinergic data gaps should require a precautionary approach with the application of a child specific FQPA factor of 10, a 10-fold intraspecies factor and 10-fold interspecies factor.

4. The risk assessment process must be modified to include sampling of malathion product for presence and quantity of isomalathion under field conditions and just prior to applications where human exposure is likely to occur. Furthermore, such results of sampling should clear the product's composition where isomalathion content is concerned prior to application of the material. This applies to intentional applications to populated areas for mosquito control as well as agricultural applications where exposure to workers or bystanders may occur.
5. EPA must fill the multiple data gaps on malaoxon.
6. EPA should reevaluate the adequacy of the rat as a model for human toxicity considering, for example, the absence of the enzyme ali-esterase. The Agency should evaluate alternative and possibly more appropriate models, and reassess the interspecies uncertainty factor for use of rat data.
7. Until many of these substantial changes are implemented, the Agency should rescind its reregistration eligibility decision on malathion.

Sincerely,

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ATTACHMENT 1

Hon. Stephen L. Johnson June 20, 2005
Administrator
U.S. Environmental Protection Agency
Washington, D.C. 20460

Dear Mr. Johnson:

At this stage in my role as toxicologist on the pesticide malathion, having now reviewed and submitted comments (June 13, 2005) on the latest draft of the risk assessment on this organophosphate (entitled: "*Malathion: Updated Revised Human Health Risk Assessment for the Reregistration Eligibility Decision Document (RED). PC Code: 057701. Case No.0248. DP Barcode: D315906"*), given the complexity of the analysis of several toxicology parameters and regulatory endpoints, I consider it needful to bring together in one place a listing of my principal dissenting views, each briefly stated. This is a very verbose risk assessment that in my view does not provide reliable in-depth analysis of scientific and public health issues. In numerous places, for inexplicable reasons, this risk assessment sidesteps or down plays actual evidence of toxicity of malathion, particularly in reference to carcinogenicity and neurotoxicity in the young.

It is not my intent to justify these dissenting views with rationale and documentation put forward in this brief memorandum, but refer you to my comments on the risk assessment and its associated documents [e.g. Hazard Identification Assessment Review Committee (HIARC), Carcinogenicity Assessment Review Committee (CARC), FQPA Safety Committee, Scientific Advisory Panel (SAP), etc. reports] and their many attachments for such documentation. My objective is to consolidate in one place a briefly worded expression of my overall dissenting or alternative views with respect to those of the Health Effects Division now going out in this risk assessment.

My justification in setting forth these dissenting opinions resides with my sense of duty, and in the hope the risk assessment will be suitable to protect public health, including infant/child. This pursuit derives from both a sense of duty and a commitment to perform this duty, irrespective of the stress it brings to me.

1) Having reviewed the many carcinogenicity bioassays on malathion/malaoxon, and having discussed this subject with many experts, in my view the carcinogenicity of malathion under the Agency=s carcinogenicity risk assessment

guidelines should be classified as "*Likely to Be Carcinogenic to Humans"*.

2) The malathion cancer assessment did not take up the question of possible enhanced child susceptibility under more recent Agency Guidelines [(Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens (EPA/630/R-03/003)]. Since carcinogenicity bioassays usually involve life time testing in *adult* animals, cancer assessment must take into consideration child sensitivity, i.e. the likelihood that expressions of carcinogenicity, whatever they might be in adults, would have been enhanced, or more evident, had lifetime testing begun with young animals (offspring) rather that from the adult stage only.

3) Positive findings of carcinogenicity (leukemia; thyroid C-cell) for malaoxon in chronic bioassays of record must be acknowledged in this risk assessment as opposed to the unequivocal erroneous claims that Amalaoxon is non-carcinogenic@.

4) The evidence for *low dose* carcinogenic effects need further characterization.

5) Conservatively and for public health protection, in the case of malathion the quantitative risk assessment should be employed for regulatory purposes, even if the classification of carcinogenicity remains under HED=s governance as *" Suggestive Evidence of Carcinogenic Potential" . In my view, failure of HED (and others) to invoke the cancer quantitative risk assessment for malathion is perhaps the foremost public health protection flaw or failing in the risk assessment for malathion.*

6) An External Peer Review of the entire malathion mutagenicity data base is essential to addressing the mutagenicity component of malathion carcinogenicity.

7) A principal deficiency in this malathion risk assessment is its failure to properly acknowledge and appraise the magnitude of enhanced offspring (surrogates for infants/children) brain cholinesterase inhibition, and its implications for offspring behavioral effects, as required under FQPA.

8) The risk assessment does not own up to the need for additional assessment of behavioral effects vulnerability in infants/children (and actually in adults) given that a behavioral effect was seen in rat offspring at low doses without a NOEL. Behavioral effects *at low doses* have been identified in offspring in the developmental neurotoxicity study (DNT), but further assessment of behavior is not being pursued as needed to fully characterize what could be more diverse behavioral effects, most needed to protect the nation=s young population

9) The malathion DNT/cholinesterase study lately disclosed the reality, as probably expected, of behavioral effects in offspring across all doses, absent a NOEL. Since doses were already low, this study underscores the potential for low level cholinesterase inhibition to alter behavior, especially given the ubiquitous presence and neurologic function of cholinesterase within the central nervous system. However, the extent to which this effect may occur at yet lower doses, and the breadth to which behavior of varied nature may be involved, requires further definition as well in the quest to protect the nation=s infants/children.
10) This risk assessment failed (for inexplicable reasons) to put forward (acknowledge) the full breadth of offspring versus adult susceptibility in spite of the wishes of Congress as manifested in the FQPA.

11) The Bench Mark Dose (BMD) method of analysis as applied to offspring cholinesterase data study (yielding ANOAELs of 13.6 mg/kg (acute) and 7.1 mg/kg/d (short-term)@ (Table 4.1e in risk assessment), for the malathion developmental neurotoxicity/cholinesterase study, should not be employed for risk assessment in lieu of use of actual cholinesterase inhibition data in offspring showing a lower LOEL (5 mg/kg) and no NOEL (testing not performed at doses less than 5 mg/kg) that would drive a more conservative regulation of malathion. Actual cholinesterase inhibition in offspring at 5 mg/kg/d with no NOEL may drive behavioral effects also seen as a LOEL of 5 mg/kg/d, absent a NOEL. Neither cholinesterase inhibition nor proper behavioral assessment in offspring should be short circuited by this manipulation of data. I must express my continuing disagreement with this use of the BMD to in essence undermine the essential importance of the actual low dose findings, long suspected, but now confirmed in this new DNT study. The Agency must either accept the 5 mg/kg/(d) dose level as constituting LOELs for cholinesterase inhibition and behavioral effects in offspring, or respect these findings enough to require additional low dose assays rather than resort to the BMD method as a way around the implication of these actual findings

12) Since results on offspring behavior in the DNT/cholinesterase study did not identify a NOEL, more study is needed to characterize offspring behavioral effects in the lowest dose range for the protection of infants/children under mandates of FQPA. Also, more study is needed to characterize brain cholinesterase inhibition in offspring versus adults at low doses.

13) As obtained from the DNT/cholinesterase study of malathion, the Food Quality Protection Act (FQPA) safety factor for the protection of infants/children actually exceeds 10X, and while more cholinesterase and behavioral effects data in offspring is needed to more accurately quantify the safety factor, data in hand at this time suggests the safety factor as more on the order of 90X or higher. To use

10X is inappropriate for protection of the younger population.

14) Deficiencies with regard to the recently reviewed cholinesterase inhibition study of malathion *in humans* (MRID 45125602) preclude its being used for regulatory purposes, as for example in the setting of the acute RfD for malathion.

15) OPP should avoid using a recently received cholinesterase study of malathion in humans for risk assessment until Congress has settled its current debate over the used of human testing in regulating pesticides.

16) The Moeller and Rider (1962) human cholinesterase study, employed by the Agency for many years, until recently, for establishing the malathion chronic RfD, should not be abandoned for that purpose. This human study is also worthwhile in illustrating the enhanced sensitivity of the human versus rat (surrogate test species for man) as gleaned by metabolic differences between the two.

17) Audit should be performed of Huntington Labs records of the malathion DNT/cholinesterase study, focused especially to explain the highly variable cholinergic toxicity of malathion and assessment of reported changes in the size of corpus callosum (brain region) in offspring.

18) Information has been received that upon storage, particularly at elevated temperatures, malathion product will undergo degradation, resulting in elevated levels of more toxic elements such as isomalathion. As I understand, this degradation has not been adequately investigated to know whether labeled malathion as used in large quantities for medfly eradication and boll weevil eradication, for example, remains within labeling specification at the time of application. This needs to be determined by analytical sampling and analysis before populations are exposed. There should be EPA on-site inspections during spraying until the storage issue is resolved. Such activity might be viewed by some as impractical, but that is no excuse when faced with the responsibility to insure public confidence in the safety of the product to which they are directly exposed in various pest eradication measures.

19) a) The low order of malathion acute toxicity reflected in Toxicity Categories of III and IV claimed in the risk assessment are not reflective of the much more severe order of toxicity seen for offspring in the DNT/cholinesterase study, and absent any qualification of Toxicity Categories as presented is misleading to the public as reflective of vulnerability of infants/children. b) A statement (p.1 of risk assessment) reads: AMalathion exhibits low acute toxicity via the oral, dermal and inhalation routes (Toxicity Categories III, IV).@ This statement is categorically untrue with respect to offspring (infant/child) as taken by the oral route and presumably so by the dermal and inhalation routes, though offspring have not yet

been tested by the latter two routes of exposure.

20) Public expressions of health related experiences of citizens during medfly eradication, and other uses, should be responded to and clearly portrayed in the risk assessment (for example, the March 25, 1995 correspondence of Deborah Bechtel to EPA=s Dr. Lynn Goldman).

21) The established HIARC (1998) requirement for a repeat subchronic inhalation study on malathion must be expedited, and certainly not withdrawn as a data requirement, particularly in view of the evidence of: nasal histopathology across all doses in the existing rat inhalation study and even after only two weeks dosing in the rat range-finding inhalation study; existing evidence of nasal tissue histopathologic effects in chronic studies; complaints by citizens of nosebleeds commensurate with medfly spraying.

22) Given my expressed concerns over the PWG (2000) for female liver tumor response in the 1996 malathion chronic toxicity/carcinogenicity bioassay (MRID 43942901), the liver histopathology slides used by the PWG should be examined by independent pathologists not in the employ of the malathion registrant. Photomicrograps of liver tumors slides from the malathion study employed by the PWG should be submitted for review of EPA=s pathologists and archived within the Agency to make them available for public inspection. My principal concern in this request is that such information not be maintained only off limits in an organization=s private files.

23) A subchronic dog study should be required to resolve certain tox issues in the dog, for example vulnerability to cholinesterase inhibition.

24) HED or an external entity (e.g. contractor) should re-review the malathion Guideline Reproduction Study for evidence and degree of offspring enhanced susceptibility, which I feel certain is real and substantial despite attempts within HED to water down this positive effect. The re-review is needed because when originally reviewed there was no focus driven by FQPA to identify or quantify evidence for offspring versus adult susceptibility.

25) In citing background materials, this malathion risk assessment must include the January 28, 2003 HIARC report along with the other earlier HIARC reports listed. The most recent HIARC report appearing to be listed is that of June 13, 2002. The January 2003 report contains additional citations of my alternative opinions versus those of the HIARC, which must be in the record. Furthermore, it is in the January 28, 2003 report that HIARC affirmed as inappropriate the use of the BMD method of analysis to get around using positive evidence of low dose cholinesterase inhibition in offspring, as observed in the DNT/cholinesterase

study, for regulatory purposes. Deleting reference to this HIARC report which claims as inappropriate the use of BMD methodology is of particular concern to me where transparency of the risk assessment is concerned.

26) The External Peer Review (Drs. Hartung, Decker and Douerson) (1998) on HIARC (1997) malathion toxicology issues (both Agency questions posed to the external toxicology experts and the answers they provided) must be clearly cited and represented in the malathion risk assessment so that its presence and role (if any) in the assessment is made transparent to the public, as are SAP reports of external experts which support HED=s apparent downplaying the risk.

27) There should be an investigation of the *adequacy* of HED=s FQPA Safety Factor Committee=s consideration of the FQPA imposed 10X safety factor, and the *legitimacy* of its recommendation to remove that 10X factor for malathion (August 6, 1998 FQPA committee report on malathion). Did this FQPA Safety Factor Committee take into consideration HED=s External Peer Review by three outside expert toxicologists who addressed HIARC toxicologic issues? See February 28, 2000 memorandum of B. Dementi to OPP=s John Carley.

28) It should be noted in the risk assessment that the claimed use of malathion in fruit fly (medfly) control programs is not a registered use, but the use has been granted by the Agency under Emergency Exemption (Section 18) for perhaps 25 years or more, amounting to a de facto registration. This use has never satisfied the rigors of the registration process. Furthermore, I am not aware that any malathion registrant has sought registration of malathion for this purpose. It appears to be a use granted to the Department of Agriculture and states, as requested.

29) There should be a review of the Agency=s laboratory audit program to determine if malathion studies have been properly audited.

30) There should be an evaluation by the FIFRA Scientific Advisory Panel on all issues reviewed by HED=s Hazard Identification Assessment Review Committee (HIARC), and other toxicology issues that have arisen since the demise of the HIARC. The one External Peer Review (Drs. Decker, Douerson and Hartung) does not satisfy in fulfilling this objective, and should not be deemed so.

31) The evidence for *low dose* [< 100 ppm (mouse); < 100/50 ppm (rat)] carcinogenic effects and *low dose* [< 5 mg/kg/d (rat)] offspring behavioral effects and cholinesterase inhibition need characterization. These low dose findings are uppermost issues among my concerns, particularly given that food tolerances for malathion is 8 ppm, not that far removed from the doses possibly eliciting carcinogenic effects, and given the varied reasons why people may be more vulnerable than rats to behavioral effects given varied life styles, medications

taken, stresses, behavioral problems, age, etc. when then exposed to cholinesterase inhibiting compounds.

I address this letter to you having done all I am able within the sphere wherein I practice toxicology. All of the background documentation in support of my conclusions summarized in this letter has already been generated and submitted to various committees and panels to whom I have responded in my work. Former OPP Director, Ms Marcia Mulkey, was generous to me in allowing my dissenting scientific assessments to be appended to various committee reports, where they now reside. I will be requesting that this very letter to you summarizing my views, to also be included as an addendum to the risk assessment document.

I trust that you and your staff will seriously consider what amounts to my petition for a more reliable, public health protective, risk assessment than that which is currently on the HED launch site.

Sincerely,

Brian Dementi, Ph.D., D.A.B.T.
Senior Toxicologist
Health Effects Division/OPP

ATTACHMENT 2

Hon. Stephen L. Johnson September 28, 2006
Administrator
U. S. Environmental Protection Agency
Washington, D.C. 20460

Dear Mr. Johnson:

I am sending this additional detailed information and analysis to make it very clear to you that: (1) there are reliable data indicating that infants/children can be expected to be more sensitive than adults to the effects of malathion, even at very low doses, and likely to other organophosphate pesticides as well; and (2) the potential behavioral effects on children are of sufficient concern that such pesticides must be restricted so that infants/children will have zero exposure.

Inasmuch as we (NTEU, myself and others) maintain concern under the Food Quality Protection Act (FQPA) (1996) that proper regulatory controls be instituted to protect infants/children from organophosphate exposures, the following text is being submitted to you as an addendum to my memorandum to you of June 20, 2005. In that letter I consolidated in a timely manner my principal dissenting views expressed the week before (June 13) in my comments on the draft malathion risk assessment. These views are presented in detail, with supporting documentation (27 attachments), in those comments on the risk assessment as addressed to Health Effects Division's (HED) Ms Sherrie Kinard in that submission of June 13, 2005.

Elements from three diverse, yet reliable sources of information, converge in presenting a picture of concern for children's health in the case of the organophosphate, malathion, which may well extend to other organophosphates. These sources of information are identified, accompanied by a few comments, as follows:

1) **The National Academy of Sciences (NAS)(1993) report: "Pesticides in the Diets of Infants and Children",** a publication developed in response to a 1988 request from Congress. Among the manuscript's many conclusions, it indicated that by the panel's estimate some children are being exposed to levels of organophosphate that exceed the *acute* Refrence Dose (RfD) for cholinesterase inhibition, whereby some children may be experiencing clinical signs of cholinergic toxicity. (see p. 7) I should note that the acute RfD in question in this NAS assessment is probably that derived from adult animal testing, and to the extent the corresponding offspring acute RfD is lower than in adults, as is true in the case of malathion, the number of infants/children in exceedance of the adult acute RfD would be dwarfed in comparison by the number in exceedance of the offspring acute RfD, were that RfD established as such. This NAS (1993) report may have spawned the Food Quality Protection Act (1996);

2) **Research on the organophosphate sarin, performed at Lovelace Biomedical and Environmental Research Institute, Albuquerque, NM, under U. S. Army Medical Research and Material Command contract [Henderson, et al (2001), pre-publication report; later published: Toxicol. Appl. Pharm. 184, 67-76 (2002)]**, where biochemical studies in the rat revealed *brain cholinesterase inhibition* and *alterations in brain muscarinic cholinergic*

receptors at doses of sarin which, by study design, were not sufficient to elicit clinical cholinergic signs. Furthermore, the neural biochemical effects were observed at doses that *did not yield evidence of brain cholinesterase inhibition by wet chemical analysis*, as conducted by procedures (Ellman assay) of the type employed in Office of Pesticide Programs (OPP) Guideline studies submitted by registrants to OPP. However, in Henderson, et al, though brain cholinesterase inhibition was not observed by wet chemical methods, such inhibition was observed using a sensitive histochemical technique not employed in OPP. These findings led the authors of the study to conclude that doses of this organophosphate not sufficient to elicit clinical signs, or to yield brain cholinesterase inhibition detectable by the Ellman assay, could elicit (spawn) behavioral effects. Quote: "These findings demonstrate that the rat model of sarin exposure is an important first step for identifying brain systems that are involved in the development of cognitive dysfunctions with subclinical sarin exposure.

"The goal of this study was to determine if exposure to levels of sarin that did not produce noticeable clinical effects would cause more subtle adverse health effects that might persist long after the exposure. Our results indicate that rats exposed to low levels of sarin, particularly under heat-stress conditions, sustain alterations in muscarinic receptor sites in critical areas of the brain, and that most of these alterations appeared long after the exposure occurred. Thus, repeated exposures to levels of sarin that would not be noticed clinically resulted in delayed development of brain alterations that could be associated with memory loss and cognitve dysfunction." (p. 22);

3) **Combined Developmental Neurotoxicity Study(DNT)/Cholinesterase Inhibition Study [MRID: 45646401/45566201] on malathion**, submitted by the registrant, where conducted as required to maintain registration. This new data requirement came as a result of FQPA (1996) in an effort to address infant/child susceptibility. In these malathion studies, DNT/Cholinesterase, doses of malathion to *rat offspring* that were also, as in Henderson, et al, *not sufficient to elicit cholinergic clinical signs in offspring,* resulted in a behavioral effect, erythrocyte cholinesterase inhibition and possible morphometric effects on the corpus callosum, across all doses, absent a NAOEL for these three endpoints. Brain cholinesterase inhibition in offspring in the attendant acute four dose study, was manifest at the top three doses (markedly so at the top two doses, 81-84% and 44-48% inhibition, respectively), and, in my view, though not found at the lowest dose, the lack of detection of brain cholinesterase inhibition in that instance may have been an artifact of use of perhaps too few animals to achieve reliable assay sensitivity to capture inhibition; or whole brain assays may have been inadequate to detect cholinesterase inhibition at specific brain regional locations, as was done by the methodology mentioned above in Henderson, et al. In contrast with this effect in offspring, comparative brain cholinesterase inhibition in adult rats was not observed at any of the same four doses as those employed in the acute offspring study, thus clearly demonstrating profoundly enhanced susceptibility of offspring versus adult rats. I should note that this study in offspring was deficient in that while the study embraced testing in offspring begining at postnatal day (PND) 11, neonates at PND 1-11 were not tested, where susceptibility may be most remarkable in offspring and most relevant to address human *infant* susceptibility (see January 28, 2003 HIARC report on malathion; TXR NO. 0051549, p. 19)

So clearly in the case of malathion, offspring were more susceptible than adults, and taking into consideration the findings in NAS (1993) explained above, we are confronted with the specter that to the extent some infants/children are exposed to levels of organophosphate exceeding the adult acute RfD, exceedance of the corresponding offspring acute RfD would be expected to be

resident in a markedly greater fraction of infants/children. Indeed, this malathion DNT/Cholinesterase study, newly required under FQPA, disclosed what can happen in more fundamental biochemical ways, at doses not only commensurate with cholinergic clinical signs, but also below such levels of exposure that portend cognitive/behavioral effects adversity. Taking into consideration findings with sarin as uncovered in Henderson, et al, such effects as alterations of brain muscarinic cholinergic receptors and brain cholinesterase inhibition may be present in subclinical studies but go undetected by methodologies commonly used by the EPA . Brain cholinesterase inhibition is detectable by special methodology, e.g. histochemical techniques, well below levels at which wet chemical cholinergic assays fail to detect inhibition. Such methodologies are not required or employed in OPP Guideline testing requirements, and accordingly, such Guideline procedures may miss neural cholinesterase inhibition and other neurochemical effects of concern. Henderson, et al note that these neural biochemical effects could explain cognitive/behavioral effects.

My discussion/overview here is not detailed for any of the cited three references. I must note my perspectives are presented in much depth in my September 19, 2004 memorandum to former Administrator Michael Leavitt, a copy of which is to be found, as Attachment XIII, in my June 13, 2005 comments on the draft malathion risk assessment addressed to HED's Ms Sherrie Kinard. Upon submitting these comments, I was assured by HED/OPP the manuscript would be retained in the malathion docket, and made available to the public for review. Also, there is a full review by me as co-reviewer of the malathion DNT/cholinesterase study in HED files.

I would advocate that you examine NAS (1993); Henderson et al (2001)(Dr. Rogene Henderson, phone 505-348-9464); and the HED review on the malathion DNT/cholinesterase study in order to witness for yourself the common thread in this body of work pointing to probably subtle cognitive/behavioral effects in infants/children resulting from very low level, subclinical, exposure to organophosphate and possibly other cholinesterase inhibiting compounds. I say subtle cognitive effects, but would suspect these could be more dramatic as expressed in a diverse human population with some persons harboring preexisting behavioral conditions, taking medications, living in stressful environments, exposed to potentially numerous other xenobiotics, etc.

Thus I would reiterate what was spoken here at the outset, a conclusion that the potential behavioral effects on infants/children is of sufficient concern that organophosphate pesticides must be restricted so that our "little ones" will experience zero exposure.

Respectfully,

Brian Dementi, PhD, D.A.B.T.
Biochemist/Toxicologist
7519 Oakmont Drive
Richmond, VA 23228

ATTACHMENT 3

Interested persons:

Back on June 13, 2005, I submitted to HED under a covering memorandum to Sherrie Kinard, comments on what I understood to be the *final* draft Malathion Risk Assessment. This submission of my comments included various documentation, in the form of some 27 attachments, intended to support those comments to the risk assessment.

The purpose of this present memorandum is to identify those 27 attachments, accompanied by a few comments directed to each attachment, as a means of conveying to the reader something of the substance of the entire body of information directed to the risk assessment, in the hope of enhancing interest among others to obtain and read not only the comments to the draft risk assessment, but the attachments as well. This submission should be available, as I was promised it would be, from the OPP/HED malathion docket. I should note that certain of these 27 attachments incorporates its own body of attachments in support of the content/views in the text of the attachment, thus enhancing beyond 27 the total number of attachments arguably submitted in support of the draft Malathion Risk Assessments comments offered by me on 6/13/05.

My comments on the draft Malathion Risk Assessment itself are introduced into the text of the draft risk assessment in bold/italics for ready identification. Since many of my comments are in essence my conclusions regarding various scientific findings, and the veracity of the risk assessment, this entire submission is considered by me as a legitimate dissenting opinion of the risk assessment, and justifiably so, given my having worked for many years as the Agency's principal toxicologist on malathion. This draft risk assessment including my comments inserted therein spans some 149 pages, exclusive of attachments. The 27 attachments consists of some 550 pages. Hence, the entire comments package on the draft Malathion Risk Assessment which I submitted to Ms Kinard was of about 700 pages in length. Given my confidence in the analyses and evidence I have presented, nothing could be quite so rewarding as to have the outside world's examination/appraisal of the evidence, and candid views regarding reliability of my findings.

It is noteworthy that when the comments to the draft risk assessment were being developed, I was advised to submit the package in hard paper copy, as opposed to electronically. Therefore, the entire 6/13/05 package was submitted to Ms Kinard in paper copy. Subsequent to that submission, OPP's Mr. Thomas Moriarty rendered the comments, with all attachments, into electronic rendition. Toward this objective, at his request I submitted to him all that I possessed of the package in electronic form, which included the basic comments to the draft risk assessment, and all attachments of the 27 that I had in electronic form. I identified for Mr. Moriarty all of the remaining attachments that were not in electronic form [see memorandum (Email) of Brian Dementi to Thomas Moriarty (August 24, 2005): "Location of documents I am advocating for the recent record of my dissenting opinions concerning the malathion risk assessment"]. Accordingly, he scanned all that were not electronic, and rendered these into electronic form, and then assembled the entire 6/13/05 submission, comments including the 27 attachments, into one electronic file. It is my belief that with the entire comments and attachments thence in electronic form, it would be of no particular difficulty to send/forward the entire submission to any party requesting the interest in obtaining the full submission. This is an open file that I was assured would be publicly available from the malathion docket. Furthermore, I should add my perspective, that for someone seeking access to the comments/attachments,

there should be no roadblocks, or obscurities of location, affording difficulty of gaining access.

Identification of Attachments

Attachment I) Journal publication: Main and Braid (1962), Biochem. J., 84, 255-263: "Hydrolysis of Malathion by Ali-Esterases *in vitro* and *in vivo* ". This is a lengthy research publication on certain enzymes that detoxify malathion/malaoxon. A notable finding, among many in this study, is that human blood serum, in contrast to that of the rat, a species widely employed as an experimental model of toxicity, and surrogate species for human testing, lacks this enzyme activity. Leading the authors to conclude: "The complete absence of ali-esterase activity in human serum means that at least one important barrier to malathion poisoning present in rats is absent in humans" (p. 262)

Attachment II) Memorandum of Brian Dementi, Senior Toxicologist (Ph.D., D.A.B.T.) to Michael Leavitt, Administrator and Stephen Johnson, Deputy Administrator, U.S. Environmental Protection Agency (November 22, 2004), with accompanying memorandum of endorsement by NTEU of the same date, also addressed to the Administrator and Deputy Administrator, signed by Dwight Welch, President (B.S. Entomology), Dr. Arthur Chiu, Vice-President (M.D., Ph.D., Pathology) and Dr. William Hirzy, Vice-President (Ph.D., Chemistry). This memorandum of Dr. Dementi, some 12 pages, focuses on a flawed 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 its previously agreed upon classification of the carcinogenic potential of malathion from "Likely to be Carcinogenic in Humans", to "Suggestive Evidence of Carcinogenicity", a revised classification rendered by CARC 2 (April 28, 2000; TXR 013991), which freed malathion from any regulation imposed upon its use driven by evidence of carcinogenicity, or carcinogenic potential. This PWG was sponsored by the registrant, and hastily performed by a contractor, during an "error only" comment period provided the registrant after being notified by the Agency that the HED Carcinogen Assessment Review Committee (CARC) at its February 2, 2000 meeting had classified (or was prepared to classify) malathion as "Likely to be Carcinogenic in Humans". Under the "Likely" classification, a quantitative risk assessment would be used to regulate public exposure to malathion, while by contrast, under the "Suggestive Evidence" classification, a quantitative assessment of risk is specifically precluded. Thus, the change of classification by CARC following this flawed PWG, from "Likely" (CARC 1) (2/2/00) to "Suggestive Evidence" (CARC 2) (4/28/00) has (had) a profound effect in terms of risk mitigation. My memorandum of 11/22/04 presents considerable detail (which I will not attempt to summarize here) regarding the fallacious PWG that was performed. I can only emphasize the importance of interested persons being accorded the opportunity of reviewing these entire comments pertaining to the evidence for carcinogenicity of malathion arising from NCI's and EPA's Guideline studies in animal (rat/mouse) models.

The comments in **Attachment II** are supported by some eight appended exhibits, identified as follows: ***Exhibit 1)*** Memorandum of Brian Dementi, Senior Toxicologist, to William Burnam, Chairman, CARC (April 27, 2000) (11 pages) setting forth many concerns pertaining to the veracity of the March 20, 2000 PWG procedures and report; ***Exhibit 2)*** Memorandum of John Carley to Brian Dementi (April 27, 200), his revision (improvement, if you will) on my April 27, 2000 memorandum to William Burnam; ***Exhibit 3)*** Memorandum of Marion Copley/Sanjivani Diwan to Paula Deschamp/Patricia Moe (April 25, 2000): "Evaluation of the Cheminova Report

Titled: A Pathology Working Group Review of Liver Slides from the 24-month Toxicity/Oncogenicity Study in the Rat" (some 35 pages, including five (5) attachments. Much information/discussion is incorporated in this Exhibit 3; ***Exhibit 4)*** Memorandum of John Pletcher, DVM, MPH, DACVP, Consulting Pathologist (CARC) to Sanjivani Diwan, Executive Secretary (CARC) (March 28, 2000): "Review of Pathology Working Group (PWG) conduct and findings for Proliferative Lesions of the Liver in Female Rats in a 24-Month Oral Toxicity/Oncogenicity Study of Malathion; ***Exhibit 5)*** FAX Memorandum of Paul Whatling (Jellinek, Schwartz & Connolly, Inc.) to Patricia Moe (U.S. EPA) (March 20, 2000): Re: "Malathion: Pathology Working Group Review of Liver Slides From the 24-Month Toxicity/Oncogenicity Study in the Rat (MRID 43942901)", signed by Diane Allemang, Jellinek, Schwartz & Connelly, Inc., Authorized Representative for Cheminova A/S; ***Exhibit 6)*** Memorandum of Brian Dementi (undated), providing "Typed Transcript of Handwritten Record of a *June 8, 2000 Phone Conversation* with NTP's Dr. Robert Maronpot Concerning the Interpretation of Hepatocellular Alterations in the F344 rat."; ***Exhibit 7)*** Selected pages (24-29: Appendix A: "PWG Consensus Diagnoses for Individual Animals Reviewed in Each Group") from the Environmental Pathology Laboratories, Inc., Research Triangle Park, NC 27709; Report Entitled: "Pathology Working Group (PWG) Peer Review of Proliferative Lesions of the Liver In Female Rats In A 24-Month Oral Toxicity/Oncogenicity Study of Malathion (MRID 43942901); Author: Jerry F. Hardisty, D.V.M.; ***Exhibit 8)*** Memorandum of R. R. Maronpot, DVM, Chief, Laboratory of Experimental Pathology, National Institutes of Health; National Institute of Environmental Health Sciences, Research Triangle Park, NC to Dr. Brian Dementi, U.S. Environmental Protection Agency, Washington, DC (July 24, 1997), in which Dr. Maronpot justifies the need for peer review of liver histopathology in the case of a malathion mouse oncogenicity study, and sets forth certain conditions for the proper conduct of a PWG. He indicates: "It would be beneficial to have yourself or another EPA toxicologist *participate in the peer review process as an observer to insure that all important questions you might have are resolved* (emphasis added)."

Attachment III) Memorandum of Brian Dementi, Ph.D., DABT, Toxicologist, Health Effects Division, OPP, directed to the FIFRA SAP : "PRESENTATION OF DISSENTING OPINION AND QUESTIONS FOR THE AUGUST 17-18 SAP MEETING ON MALATHION" (July 26, 2000). This document places in writing Dr. Dementi's views and questions for the upcoming SAP, at which meeting he presented dissenting opinions with respect to those of HED/OPP. An important document of some 22 pages in which I present my views concerning analyses of cancer studies (many aspects), and discuss evidence for neoplasia in the lowest dose range tested in animal models. Dr. Dementi also presents evidence for liver tumorigenic response in the B6C3F1 mouse; liver tumorigenic response in male and female F344 rats; plus the following tumorigenic responses in the F344 rat: thyroid C-cell (males) and much that is of concern in the manner in which CARC addressed this response, thyroid follicular cell (males), nasal tissue (both sexes) and much that was of concern in CARC's interpretation, oral tissue squamous cell, testicular interstitial cell, leukemia response among males under White House Office of Science and Technology Policy (OSTP) (1985) definition of carcinogen, leukemia (males) in the malaoxon F344 rat study. Questions changes made through the years on evidence on malathion mutagenicity. There is much information in this report requiring input from an outside unbiased panel, such as SAP. In my view, the SAP failed to respond to the many issues Dr. Dementi presented in this written report, and in his oral presentation on August 17-18 **(Attachment IV).**

Attachment IV) Written text of the oral presentation of Dr. Brian Dementi to the SAP convened August 17-18, 2000.

Attachment V) Memorandum of Brian Dementi, Ph.D., DABT, Toxicologist, Health Effects Division, OPP: "COMMMENTS DIRECTED TO THE DECEMBER 14, 2000 REPORT FOR THE FIFRA SAP MEETING HELD AUGUST 17-18, 2000 ON MALATHION (SAP REPORT NO. 2000-04)" (January 18, 2001). These comments were submitted to the SAP docket file for the August 17-18, 2000 SAP meeting, and is where the memorandum should still reside. According to my understanding, this SAP file is open to the public and all documents in the file can be reviewed in person and copied as desired. On submitting this important manuscript, which in part questions the SAP report's technical accuracy, as composed under Dr. Dementi's own initiative after independently retrieving and reading the December 14 SAP report, he naively expected the memorandum would be responded to by SAP, and corrections, if agreed to, would be made to the December 14 SAP report. However, as I now understand, comments submitted to the SAP file after meetings are never seen by SAP members, and thus never receive a response. In my view, should it be true that SAP does not see or comment on such submissions to the file is, in itself, egregious, whereby possible mistakes/errors identified in SAP reports never get corrected, nor do commenters ever receive responses from SAP regarding their observations and questions which could be quite important. There is much of a worthy nature raised in these January 18, 2001 comments.

Attachment VI) Memorandum of Brian Dementi, Ph.D., Senior Toxicologist/HED to Paul Lewis, Designated Federal Official, FIFRA Scientific Advisory Panel (September 21, 2000) *forwarding* a July 18, 2000 memorandum of George V. Alexeeff, Ph.D., D.A.B.T., Deputy Director for Scientific Affairs, California Office of Environmental Health Hazard Assessment, addressed to Information Resources and Services Division, OPP, Environmental Protection Agency, Washington, DC, in which Dr. Dementi recommended that the 7/18/00 memorandum of Dr. Alexeeff be included in the docket of the August 17-18 SAP meeting on malathion, and circulated to SAP members. According to my understanding, though Mr. Lewis responded to his memorandum by placing Dr. Alexeeff's memorandum in the docket, it was never seen by the SAP, since the memorandum was placed in the docket after the August 2000 meeting, and was consequently never seen nor responded to by SAP.

Although Dr. Alexeeff's July 18,2000 memorandum was directed to the malathion carcinogenicity assessment issue, and should have been forwarded to the SAP docket prior to the August 17-18 meeting, for unknown reason(s) it was not placed there, and was not seen by the SAP preceding the August 17-18 meeting on malathion. These comments from California are extremely important and should have been witnessed by SAP. A notable quote from Dr Alexeeff's memorandum reads: "Following the committee's *(meaning HED's April 28, 2000 CARC)* (clarification added) re-assessment as "suggestive", the report states that quantitative risk assessment for carcinogenicity is not required for this classification. While this approach is consistent with the recommendations of the draft Carcinogen Risk Assessment Guidelines, we disagree with the Guidelines, and suggest that it would be useful to present an estimate of the potency. Clearly, prior to the re-assessment of the histopathological findings, the committee was convinced of the potential carcinogenicity of malathion. Given the nature of the carcinogenicity findings, namely, large incidences of tumors in treated animals, it seems that it would be of value to the public to present a quantitative assessment of risk." I believe there should have been a response from SAP to these and other views expressed in this CalEPA memorandum, which was

in fact submitted to the Agency in timely manner before the SAP meeting of August 17-18, 2000.

Attachment VII) Memorandum of Paul Lewis, Designated Federal Official, FIFRA Scientific Panel to OPP Docket (September 21, 2000) forwarding the attached comments dated September 20, 2000 from FIFRA SAP member Dr. Herbert Needleman in reference to the August 17-18, 2000 Malathion FIFRA SAP meeting. These comments of Dr. Needleman do now reside in the SAP docket for the August 17-18 meeting, and can be reviewed there by the public. Dr. Needleman's comments also appear here under **Attachment VII**, i.e. appended to Mr. Lewis' 9/21/00 memorandum. However, as with the submission from CalEPA **(Attachment VI)**, these comments reached the malathion SAP docket after the August meeting, and were thus presumably never seen nor addressed by the remainder of the membership of the SAP, even though the SAP's report of the meeting did not appear until December 14, 2000, which afforded adequate time to examine and address such comments as those from CalEPA and Dr. Needleman, even though these dates post-date the August 17-18 meeting. It would appear as though SAP affords no opportunity for itself to address comments appearing after a meeting, yet preceding the final report of the SAP meeting in question.

Dr. Needleman's 9/20/00 comments are extremely important in their entirety. His comments in part challenge the "data analytic techniques" employed by CARC 2 in downgrading the estimation of the carcinogenic properties of malathion from "likely" to "suggestive".

Further he says: "The conclusions drawn by CARC 2 violate the canons of epidemology. If written up and submitted to a journal of high quality, they would be rejected out of hand and would never see the light of day. As a basis for estimating the risks of malathion, they are severely deficient as a standard to protect human health."

Attachment VIII) Journal Publication: Huff, et al (1985), Environ. Res., 37, 154-173: "Malathion and Malaoxon: Histopathology Reexamination of the National Cancer Institute's Carcinogenesis Studies". It is noteworthy that one of the five authors on this publication, E. E. McConnell, was an SAP member who played a critical role at the August 17-18, 2000 SAP consideration of malathion. This 1985 publication reported the results of a PWG reevaluation of the histopathology of National Cancer Institute (NCI) studies of malathion in Osborne-Mendel and F344 rats and malaoxon in F344 rats. The important carcinogenic finding in this PWG assessment, not uncovered in the original NCI evaluation of the same study, was that of positive combined adenoma/carcinoma thyroid C-cell response in animals of both sexes as evidenced by positive Fisher exact test at the high dose (males: $p = 0.035$; females: $p = 0.045$), and by positive dose response trend in both sexes (see p. 168 of the publication). In my view this is none other than a clear positive carcinogenic finding identifiable by the EPA's own prescribed guidelines of pathology assessment in concert with statistical analysis. There is other information in this published PWG that merits public consideration. I do not believe the SAP in August 17-18, 2000, when considering malathion, sought to address this published neoplastic response in the earlier NCI study.

Attachment IX) Memorandum of Penelope Fenner-Crisp, Ph.D, Director, Health Effects Division to Anne Lindsay, Director, Registration Division (April 24, 1991): "Review of the Health Risk Assessment of Aerial Application of Malathion-Bait submitted by California Department of Health Services". Included within a general perspective rendered as gained from California's 1991 "Health Risk Assessment of Aerial Application of Malathion-Bait", there is

recognition ".....that aerial application of malathion in urban areas be reconsidered in light of the results of the health risk assessment." This HED memorandum evidences OPP's recognition that during medfly treatment, such as carried out in California, some citizens residing in aerial treatment areas may be exposed to levels of malathion that exceed the RfD for cholinesterase inhibition. The memorandum also affirms that : "For non-nursing infants and children up through age twelve, the dietary exposure ranges between 175% and 250% of the RfD." (p. 3) I should note that the RfD referred to in these instances would have been derived from adult animal testing, not taking into consideration the possible enhanced sensitivities/susceptibilities of infants/children. Exhibits appended to this 4/24/91 memorandum are 1) an April 18, 1991 "Exposure Estimation...", by HED's Mark Dow, Ph.D., Occupational and Residential Exposure, and 2) an April 19, 1991 "California Health Risk Assessment...." reviewed by Brian Dementi, Ph.D., D.A.B.T., Toxicologist, HED.

Attachment X) Memorandum of Brian Dementi, Ph.D., D.A.B.T., Toxicologist, to Air Docket, Environmental Protection Agency, EPA Docket Center (EPA/DC), Office of Air and Radiation (April 28, 2003). These comments were submitted in reference to Public Docket Number OAR-2003-0008, which concern a) EPA/630/R-03/003, a February 2003 external review draft: "Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens"; and b) EPA/630/P-03/001A; NCEA-F-0644A, a February 2003 "Draft Final Guidelines for Carcinogen Risk Assessment". These comments contain the following exhibit: Memorandum of Brian Dementi, Ph.D., D.A.B.T, Toxicology Branch/HED to Dr. James Cogliano, Office of Research and Development, USEPA (December 18, 2001) proving comments on the draft July 1999 Agency Guidelines for Carcinogen Risk Assessment, and in turn these 12/18/01 comments have appended: a) the July 18, 2000 memorandum of CalEPA's Dr. George Alexeeff identified in **Attachment VI**, above; b) Memorandum of Linda J. Fisher, Deputy Administrator and Chair, Science Policy Council (1102A) to Assistant Administrators, Associate Administrators, Regional Administrators and Science Policy Council (November 27, 2001)

Comments rendered to both of the draft documents contain many substantive views that merit outside scrutiny. Without going into all of these, it is noted here that in reference to the first draft: EPA/630/R-03/003: "Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens", Dr. Dementi raises the question that to the extent this draft affirms that early life exposure to carcinogens may enhance the incidence of cancer or decrease the latency of cancer versus that obtained from adult testing only, should a chemical classified by the Agency as a "Suggestive Evidence of Carcinogenicity" be enhance in classification in the absence of data derived from exposure testing during "Early-Life"? He expresses this question in the form of suggestions as follows in his 4/18/03 comments to the Air Docket: "Conservatively, and in the interest of public health protection, I would suggest that the "Suggestive Evidence of Carcinogenic Potential" classification based upon testing in adult animals trigger either: 1) a requirement for testing for carcinogenicity employing offspring, or 2) a) a reclassification of the agent as "Likely to be Carcinogenic to Humans", and/or b) a requirement to quantify risk, pending receipt of additional evidence that offspring (infants/children) are not sufficiently more sensitive as to alter the "Suggestive" classification, or the need for quantitative risk assessment currently based only upon the adult animal testing." Of course, as expressed elsewhere, he was already of the conviction that in the case of malathion, for example, offspring were shown in the recent DNT/cholinesterase study to be much more susceptible than adults for parameters tested,

and the carcinogenicity testing data base in adult animals is already sufficient to support the "Likely" classification, in accordance with procedures set forth in the Agency's Carcinogen Guidelines. Dr. Dementi never received a response to his comments on these two draft documents, but I remain convinced of the efficacy of his comments.

Attachment XI) Memorandum of Brian Dementi, Ph.D., D.A.B.T., Senior Toxicologist, HED/OPP, to Yvette Hopkins/DC/USEPA**;** cc: Christine Whitman, J.P. Suarez, Marcia Mulkey, John Carley, Elizabeth Doyle, John Hirzy (September 26, 2002): "Comments on May 2 letter of G.N. Jones to C.T. Whitman"

These comments by Dr. Dementi constitute his response to Ms Hopkins who requested of him comments on a May 2, 2002 letter of Gladstone N. Jones, III of Jones, Verra and Freiberg, L.L.C., submitted to Administrator Christine Whitman. There is much additional information of great interest in this important letter from Mr. Jones, as well as in Dr. Dementi's response. The principal reason for citing this manuscript in my comments on the draft Malathion Risk Assessment is that information provided therein by Mr. Jones to Administrator Whitman establishes that on storage, malathion rearranges to isomalathion in a time/temperature dependent manner. Isomalathion is much more acutely toxic, cholinergically, than malathion. Thus, on storage of batches of malathion prior to application, the material may acquire unacceptable levels of isomalathion, and consequently violate labeling requirements. The letter of Mr. Jones provided chemical kinetic data on this chemical rearrangement. There is much more of substantial interest in this submission to the Agency. Being concerned about the revelations in this law firm letter, Dr. Dementi elected to copy Administrator Whitman in his response to Ms Hopkins. He also copied Assistant Administrator for enforcement, J.P. Suarez, and advocated sampling batches of malathion for quality assurance prior to application. I cannot over emphasize the importance of this and other information provided to the Agency in this very revealing letter from Mr. Jones. See the related **Attachment XX**, below.

Attachment XII) Memorandum of J. William Hirzy, Ph.D. to EPA's Walker Smith and Ann Pontius concerning a pesticide enforcement issue, where Dr. Hirzy's enquiry, in reference to Dr. Dementi's 9/26/02 memorandum to Yvette Hopkins (**Attachment XI**), reads in part as follows: "Dr. Dementi has received no direct response to his message of 9/26/02 from either the Office of Enforcement and Compliance Assurance (OECA) or the Office of Pesticide Programs. An indirect response is inferred by the union and Dr. Dementi insofar as Dr. Dementi was removed as (*from the*) malathion project about six weeks after the 9/26/02 email. He filed a claim for whistleblower protection with the Administrator on November 29, 2002."

"This message to you is an enquiry as to whether OECA has undertaken any investigation of the matters about which Dr. Dementi expressed concern in his 9/26/02 email."

"Given the ongoing use of malathion in the southern United States (and elsewhere), where high storage temperatures may be causing enhanced toxicity of malathion to humans, the union and Dr. Dementi feel that EPA has a duty to address the possible public health implications of the 9/26/02 email."

Appended to Dr. Hirzy's memorandum (**Attachment XII)** as an exhibit is Dr. Dementi's 9/26/02 memorandum to Yvette Hopkins.

I should advise that following a grievance, Dr. Dementi, having performed his duty admirably on

this action, was reestablished as malathion project toxicologist.

Attachment XIIa) Memorandum of Brian Dementi, Ph.D., DABT, Senior Toxicologist, and William Hirzy, Ph.D., NTEU Representative, to Michael Leavitt, EPA Administrator (June 22, 2004). To this memorandum is append Dr. Dementi's 9/26/02 memorandum to Ms Yvette Hopkins mentioned in **Attachments XI & XII** above, and notes here that while in the 9/26/02 memorandum Christine Whitman, Administrator, and J.P. Suarez, Assistant Administrator, were copy recipients, there has been no acknowledgement. The absence of such acknowledgement, left uncertainty that the issue was either ignored, or that its importance was not fully recognized. Such uncertainty prompted additional correspondence from Dr. Hirzy to Mr Suarez (7/25/03) (appended), which again met with no acknowledgement. So, this 6/22/04 memorandum to Mr Leavitt notes: "The principal concern is the possible increase in the acute toxicity of malathion on storage for extended periods at elevated temperatures prior to application of the pesticide, where there may be direct human exposure, such as in medfly, mosquito and boll weevil control, for example. Now given this concern, my NTEU representative, Dr. William Hirzy, and I elected to copy Mr. Suarez in on the September 26 correspondence in the hope that efforts would be pursued to secure the end result that malathion composition conforms with labeling, certainly just prior to any public use." Hence, via this June 22 correspondence to Mr Leavitt, assurances were sought from the Administrator that this issue has been appreciated and addressed. By my recollection, there still (yet) has been no acknowledgement to those of us identifying this concern.

Attachment XIII) Memorandum of Brian Dementi, Ph.D., DABT, Senior Toxicologist, to Michael Leavitt, Administrator, U.S. Environmental Protection Agency (September 19, 2004), with accompanying memorandum of endorsement by NTEU of the same date, also addressed to the Administrator, signed by J. William Hirzy, Ph.D., Vice-President. This memorandum of Dr. Dementi, some 16 pages, was cited in his 6/13/05 comments on the draft Malathion Risk Assessment as supporting argument/evidence ".....over possible subtle effects on behavior of low level exposures to cholinesterase inhibitors, including malathion. The paper I was developing on this subject, and referred to Mr. Leavitt, entitled 'Cognitive Effects of Cholinesterase Inhibition', though incomplete, deserves its expression in the risk assessment as consonant with the low dose level behavioral effects (no NOEL) seen in the malathion DNT study." (p. 47) This paper raises many issues with respect to the cognitive effects of cholinesterase inhibition, and of how the young may be more susceptible than adults to the effects of cholinesterase inhibitors. The paper indicates that: "Regulatory endpoints are of highly questionable validity if they are derived from flawed cholinesterase data, i.e., inadequate numbers of animals, only whole brain (as opposed to brain regional) cholinesterase assays, no data on offspring, no histochemical procedures verification of neural cholinesterase inhibition NOAELs, etc.", all of which issues are developed/discussed in the text.

This memorandum (**Attachment XIII)**, and its exhibits, are too lengthy to summarize here, but must be readily available to anyone wishing to examine them. **There are some eleven exhibits (each important unto itself), identified as follows**: ***Exhibit 1)*** Memorandum of Peter W. Preuss, Chairman, Risk Assessment Forum, to Vaun A. Newill, Assistant Administrator for Research and Development (September 12, 1988): "Research Needs Relating to Cholinesterase Inhibition", which among other items, references the attached letter of Brian Dementi, Ph.D., Toxicology Branch to Judith S. Bellin, Ph.D., Science Coordinator, Risk Assessment Forum (July 15, 1988); ***Exhibit 2)*** Memorandum of Brian Dementi, Ph.D., D.A.B.T., Senior

Toxicologist, Toxicology Branch/HED, to Marcia Mulkey, Director, Office of Pesticide Programs (May 10, 2000), concerns the developing Agency cholinesterase policy, and many cholinesterase issues; ***Exhibit 3)*** Article by Karen L. Werner, The Bureau of National Affairs, Inc., Washington D.C. (No. 30, Wednesday, February 13, 2002): "Pesticides, Dissenting Agency Scientist Says Review Of Cumulative Risks Not Protecting Children", in which Ms Warner cites, among other matters: ".....Dementi's written comments *(those of Jan. 30)* on the assessment *(meaning a preliminary EPA assessment of cumulative risks posed by the organophosphate pesticides)* was not done in a way that would ensure protection of infants and children,.....";
Exhibit 4) Memorandum of Kevin M. Crofton, Acting Chief, Neurobehavioral Toxicology Branch, Neurotoxicology Division, ORD/RTP, to Brian Dementi, Ph.D., Health Effects Division, OPP and Margaret Stasikowski, Director, Health Effects Division, OPP (January 14, 2002): "This memo summarizes our review of the manuscript entitled 'Cognitive Effects of Cholinesterase Inhibition' by Dr. Brian Dementi", in which Dr. Crofton proceeds in every way imaginable to denigrate the draft paper being developed by its author. I should advise that before this draft paper was submitted to ORD/RTP, I had sought agreement to submit the paper to experts outside the Agency, not so much for review, but for consultation. Nonetheless, without seeking my concurrence, HED's director sent it (or had it sent) to ORD/RTP, as it it were a finished work.

Please note that Dr. Dementi responds to this ORD review in the text of **Attachment XIII** to Administrator Leavitt, namely at the section: "Critique of ORD Review of the draft Cognitive Effects of Cholinesterase Inhibition paper" (pp. 6-16); ***Exhibit 5)*** Brian Dementi, Ph.D., D.A.B.T., Health Effects Division/OPP (December 11, 2001), draft manuscript "Cognitive Effects of Cholinesterase Inhibition". A manuscript of some 67 pages developing the title subject, wherein many parameters and literature references are presented. A most important component of the manuscript for ready insight into the manuscript's content would be the Recommendations section, listing some 15 recommendations (pp. 57-58); ***Exhibit 6)*** Dr. Brian Dementi (Lead), Dr. Mike Ioannou (Sponsor), Health Effects Division FY 2000 Work Plan (November 22, 2000): "Title: Cognitive Effects of Cholinesterase Inhibition", setting forth the objective of this project, before it was entered into, with a projected completion date of March 1, 2000; ***Exhibit 7)*** Memorandum of Brian Dementi, Ph.D., D.A.B.T., Senior Toxicologist, Toxicology Branch/HED/OPP, to Dr. Mike Ioannou, Chief, Toxicology Branch, Health Effects Division, OPP (November 28, 2001), a manuscript providing history and background material of importance with reference to the Cognitive Effects of Cholinesterase Inhibition paper, a very important paper attesting to the legitimate need and worthiness of such a paper within OPP, given the Agency's responsibility to regulate so many cholinesterase inhibiting compounds;
Exhibit 8) Memorandum of Leonid Kopylev, Mathematical Statistician, Engineering and Analysis Division, Office of Science and Technology, Office of Water, to Susan Makris, M.S., Acting Branch Chief; and Brian Dementi, Ph.D., DABT, Toxicology Branch, Health Effects Division, Office of Pesticide Programs (June 25, 2004): "Design and statistical analysis of cholinesterase measures from the malathion range-finding and comparative cholinesterase studies in rats". This statistical analysis of two studies submitted by the malathion registrant, concluded that deficiencies existed: 1) "Inadequate number of animals in each group in the comparative cholinesterase studies resulting in low statistical power of the tests" and 2) "inappropriate treatment of outliers". This is a very important statistics memorandum addressing a recurrent problem within HED/OPP, which is the fundamental weakness of cholinesterase data and its analysis. The entire memorandum requires reading; ***Exhibit 9)*** Article in Pediatric

Perspective, by Dr. Darshak Sanghavi (appearing in the Boston Globe, May 25, 2004): "Lead poisoning still a major problem", an article suggesting lead affects I.Q. in children at such low doses that the Centers for Disease Control (CDC) should lower the allowable blood level to yet lower levels, and cites the work of Dr. Herbert Needleman (whom I would note was OPP SAP panelist appointed there as representative for children's interests under FQPA). Dr. Needleman is mentioned in Dr. Dementi's June 13, 2005 comments on the draft Malathion Risk Assessment and in his **Attachment VII**); ***Exhibit 10)*** Memorandum of Penelope Fenner-Crisp (April 24, 1991), duplicate of **Attachment IX**, above; ***Exhibit 11)*** Memorandum of J. William Hirzy, Ph.D., V. P. NTEU Chapter 280, to Brian Dementi, USEPA (August 19, 2004), conveying a letter to NY Times editor from Barbara Rubin, Cos Cob, Ct, concerning cholinesterase inhibitors, says at one point: "It is time for us to stop denying the dangers of commonly used toxic chemicals and address this widespread problem in civilians as well as in our war heroes, where the title of the NY times article evidently was: "'Chemicals Sickened '91 Gulf War Veterans Latest Study Finds.', by S. Shane".

Obviously, there is much important information in this September 19, 2004 memorandum to Michael Leavitt , which must be readily available for public scrutiny as I was promised by HED/OPP it would be so available.

Attachment XIV) Memorandum of Brian Dementi to Louis Scarano, USEPA (December 2, 2004): Dr. Dementi's comments on the malathion human cholinesterase study (MIRD 45125602) taken under advisement by the council *(HSPOC)* on Monday, 11/29/04. This memorandum is cited in Dr. Dementi's 6/13/05 comments on the draft Malathion Risk Assessment, as setting forth reasons why he is opposed to the recognition and use of this human study. Those reasons essentially being that, after first discounting rationale presented in a November 23, 2004 data package to the HSPOC that illegitimately discredited the Moeller and Rider (1962) human study, used for years as the basis for the malathion RfD, Dr. Dementi explained regarding the new human study: 1) The study did not proceed in dosing to a dose which even minimally inhibited cholinesterase by assay procedures employed, and thus did not illustrate the assay methodology as even capable of detecting cholinesterase inhibition in humans. He wrote: "We have no way of determining whether the study would have detected cholinesterase inhibition at some dose level in man (let alone at what dose)....." Further he wrote: "This was not a Guideline study, nor a published work, and seemingly was narrowly constructed solely to leverage a more comfortable acute RfD for the registrant's benefit. Since when has the Agency, commissioned as the guardian of public health, relaxed its standards to the point, or to the verge I might say, of accepting such a useless study to establish a less protective public health regulatory end point, namely the acute RfD?"; 2) While this study was a single dose study, dosing rationale was evidently based only upon results from multiple dose studies; 3) Lack of comparisons of ".....human to rat in the same study might not be so imperative had rat sensitivity not been shown to be so extremely disparate across studies." In other words, in which ball park of methodologies, shown to be so variable in sensitivity in detecting rat cholinesterase inhibition, did the methodology for detecting human cholinesterase inhibition lie? To be useful, one must show it was at least equally as sensitive as the most sensitive methodology used in the rat across studies, if data obtained in humans is to replace the most sensitive rat data. Such question was not answerable; 4) the registrant did not consult with the Agency on the conduct of the human study before performing it; 5) Dr. Dementi says: "As I indicated at Monday's HSPOC meeting, to affirm comparative malathion purity as being say 94-96% across studies, as claimed, provides little assurance of continuity of

cholinergic toxicity across test materials, as it is the precise composition of the remaining 4-6% that may make all the difference in toxicity." Yet more discussion is presented by Dr. Dementi in this memorandum that would invalidate the human study, from which the above was derived in presenting partial expression of his concerns. This 12/2/04 memorandum has a number of exhibits appended.

Attachment XV) Comments of Brian Dementi, Ph.D., D.A.B.T., Toxicologist, Toxicology Branch, HED/OPP, directed to the August 21, 2002 Malathion Draft Risk Assessment Entitled: Malathion: Updated Revised Phase 6 Human Health Risk Assessment for the Interim Reregistration Eligibility Decision (IRED) Document. Chemical No. 057701. Case No. 0248. Barcode Dxxxxxx", as Received from Paula Deschamp, Reregistration Branch 2, with request to comment. (September 17, 2002) These comments (some 13 pages) were sent to Marcia Mulkey, OPP director via Email on September 17, 2002. This memorandum embraces some 43 enumerated comments, all of which are very notable, but time/space do not permit their recapitulation here. Many of these, but not all, find their repeated expression in Dr. Dementi's 6/13/05 comments on the draft Malathion Risk Assessment. Lack of summary here, detailed or even partial, should not be viewed in any way as indicating the comments to be less important than those in other attachments.

Attachment XVI) Memorandum of Kerry L. Dearfield, Ph.D., Executive Secretary, Peer Review Committee, Science Analysis and Coordination Branch, Health Effects Division, to Joanne Edwards, Review Manager, Special Review and Registration Division (April 12, 1990): Peer Review of Malathion (27 pages). This important manuscript records the results of: "The Health Effects Division Peer Review Committee that met on February 7, 1990 to discuss and evaluate the weight-of-the-evidence on malathion with particular reference to its carcinogenic potential. The Committee agreed to classify malathion as a group D carcinogen; that is, malathion is not classifiable as to human carcinogenicity. This decision was based on the inadequacy of the available studies to make a definitive determination of the carcinogenicity of malathion. The Committee reaffirmed the requirements of the Malathion Registration Standard that the registrant perform/submit an additional mouse carcinogenicity study with malathion and an additional rat carcinogenicity study with malaoxon. The Committee also determined that the Reregistration Standard recommendation to perform a carcinogenicity study in combination with the required rat chronic study on malathion be made into a requirement that both be performed." It should be noted that this particular "Peer Review Committee", that evaluated the carcinogenicity studies on malathion, principally those studies performed during 1978-1979 on malathion and malaoxon at the National Cancer Institute (NCI) (later NTP), was the designated HED Committee that evaluated carcinogenicity studies before this role was officially undertaken by HED's "Carcinogen Assessment Review Committee" (CARC). Thus, one might regard the role of "Peer Review Committee" on malathion as continuing at a later date by CARC. Many (or most) of the members of the Peer Review Committee continued on as members of the CARC. So, when HED's CARC undertook the role of evaluation malathion carcinogenicity, including the newer studies post 1990, it represented the work of the same staff who knew well the prior carcinogenicity and other historic issues on malathion.

This HED peer review report is cited in Dr. Dementi's 6/13/05 comments on the draft Malathion Risk Assessment as a way of establishing the importance of the malathion NCI carcinogenicity bioassays that were not referenced/acknowledged in the risk assessment, as they should have been, in Table 4.1b: "Subchronic, Chronic, and Other Information Relevant to the Toxicity of

Malathion" [(pp. 32-36), page numbers corresponding to those of the draft Malathion Risk Assessment laden with Dr. Dementi's comments]. *The absence from this table (4.1b) of these important NCI carcinogen bioassays on malathion/malaoxon is illustrative of the lack of candor that permeates this malathion risk assessment.*

I should note at this point that Dr. Dementi was *both* author of the referenced Malathion Registration Standard and the presenter of the carcinogenicity data base to the Peer Review Committee convened on 2/7/90. I disagreed vehemently with the Group "D" classification at this meeting, arguing in favor of at least a "C" carcinogen, which I am confident was a view silently shared by some/many Committee members present at the meeting. Dr. Adrian Gross, an Agency Senior Executive Service pathologist, whose independent assessments of the 1978-1979 NCI studies **(copied here as Attachment XVIII)**, shared with me at the time his views that malathion should be classified as a "B2" carcinogen ("Probable Human Carcinogen") under EPA's Guidelines for Carcinogen Assessment in effects in 1990. This report on the Peer Review of Malathion contains important information to keep in mind when evaluating the subsequent bioassays required by the Committee. The NCI studies, not referenced in Table 4.1b, clearly supplement/embellish evidence of carcinogenicity in the newer carcinogen bioassays performed in the mid-1990s on malathion/malaoxon. The evidence of carcinogenicity from the NCI studies and the newer studies must be unencumbered in their composite (mutual) expressions of carcinogenicity.

Attachment XVII) Memorandum of Brian Dementi, Ph.D., Toxicologist, Toxicology Branch/HED to William Miller, PM-16, Registration Division (July 30, 1987): "Malathion, Toxicology Chapter of the Registration Standard", some 69 pages, including a summary of overall toxicology, plus Data Evaluation Records of a number of Guideline toxicology study requirements. This Toxicology Chapter is cited in Dr. Dementi's comments on the draft Malathion Risk Assessment as a way of providing added discussion of the NCI carcinogen bioassays. "These carcinogenicity bioassays, and their review, are all important elements in the weight-of-the-evidence of carcinogenicity of malathion and to the historic record of that assessment, that cannot be ignored." (p. 36), or down-played.

Attachment XVIII) Memorandum of Dr. M. Adrian Gross, Senior Science Advisor, BUD, to Kevin Keaney, Office of Pesticide Products (April 24, 1984): "Carcinogenicity of Malathion". <u>This manuscript should be characterized as one of the most important in the malathion data base</u>. In my view, from the time of its receipt, this expert analysis has met with much deliberate disregard within the Agency. The manuscript was given to Dr. Dementi by HED's Toxicology Branch Chief sometime around 1986-88, on which occasion Dr. Dementi was asked to incorporate it into his drafting of the Malathion Registration Standard. It was my understanding that the Agency held the manuscript until or after Dr. Gross made it known that his work was being ignored. A prodding of HED apparently by an outside person resulted in its being considered, as evidenced by its transfer to Dr. Dementi for evaluation, and inclusion in the Malathion Registration Standard.

This memorandum by Dr. Gross is referenced in Dr. Dementi's comments on the draft Malathion Risk Assessment as a way of emphasizing the importance (and historic record) of the 1978-79 NCI carcinogen bioassays on malathion/malaoxon to the weight-of-the-evidence of carcinogenicity of malathion, which studies the draft Malathion Risk Assessment appears to purposefully neglect to acknowledge in its' Table 4.1b

There is much that could be summarized here regarding Dr. Gross' memorandum, however the entire manuscript itself serves best to convey its content and character to an audience interested in malathion carcinogenicity, and other matters pertinent to HED procedures and the use of this organophosphate. The manuscript's viewing is highly recommended.

Certainly a central theme in the author's twenty-two page manuscript is the re-evaluation of evidence of carcinogenicity in the earlier malathion and malaoxon carcinogenicity bioassays in the rat and mouse conducted by the National Cancer Institute (NCI) during the late nineteen-seventies. Dr. Gross identified certain neoplastic responses apparently not identified in the NCI's reviews of its own studies. Notably, Dr. Gross identified: for *malathion* [tumors of the parafollicular or C cells and/or of the follicular cells of the thyroid gland (both sexes) in Osborne Mendel rats; pheochromocytomas of the adrenal gland (medulla) in Fisher rats (males); and liver carcinoma and carcinoma and/or neoplastic nodules in B6C3F1 mice (males)], and for *malaoxon* [parafollicular (C) cells of the thyroid gland and benign tumors of the mammary gland (*females*) and pheochromocytomas of the adrenal gland (males) in the Fisher rat].

I should note that this memorandum of Dr. Gross is dated April 24, 1984, and disclosed various neoplastic responses. One of those responses was that of thyroid C-cell cancer among females in the malaoxon Fisher rat study. As it turns out, a PWG reassessment of the same NCI malaoxon study,[Huff et al (1985)], mentioned as **Attachment VIII**, above, uncovered the same neoplastic response, but in this latter case among both sexes. It should be noted that in Gross (1984), in discussing this response among (*males*), Dr. Gross emphasizes the strong dose-related increase of hyperplasia of C-cells, while he says: "As for outright tumors of the parafollicular or C cells of the thyroid, these were also increased in incidence with the level of exposure amongst those animals, but only to a borderline significant degree." He then goes on to offer further rationale as to why the borderline assessment he first rendered, may be "...of more than merely 'borderline ' significance." (pp. 14-15) Further, though Dr. Gross reported borderline significance of frank tumors among male rats, it is noteworthy that under the Agency's more recent Carcinogen Assessment Guidelines (e. g. 1999), when both tumors and precursor events (so-called "key events") (in this case, hyperplasia) are present, the incidences of tumors and hyperplasia ("key events") can/should be combined, which in this case logically should yield an unquestionably positive response for neoplasia of thyroid C-cells among *males*. So both Gross (1984) and Huff, et al (1985) independently identified, and reported separately, i.e. in different manuscripts, neoplastic thyroid C-cell responses among Fisher rats in the malaoxon study, evidently missed or not fully appreciated by NCI in its own evaluation.

I should note further, that while writing the Malathion Registration Standard, and considering such studies as Gross (1984), Huff, et al (1985), and many others, I was attending one of EPA's symposia at the main EPA office (Waterside) where an expert individual in carcinogen assessment discussed ways of evaluating carcinogenicity bioassays. After the symposia, I introduced myself, and requested that he comment on the Huff et al (1985) findings in males/females on thyroid C-cell neoplastic response (i.e., data from p.168 of Huff, et al.). I avoided mentioning the name of the test material. This expert immediately responded, in unequivocal manner, "that's B2 data", meaning, of course, animal testing data supporting a classification as "probable human carcinogen", a designated carcinogen classification terminology employed under the Agency Carcinogen Assessment Guidelines in effect at that time. Unfortunately, I do not remember the name of the speaker at this symposium.

Again, there is much additional substantive material in Dr. Gross' very inciteful paper that merits the independent review of interested persons.

Attachment XIX) Memorandum of Brian Dementi, Ph.D., D.A.B.T. to "Whom It May Concern" (May 6, 2002). This manuscript contains comments directed to the April 29, 2002 draft Benchmark Dose (BMD) analysis of malathion offspring cholinesterase data, in which the author presents rationale disputing as appropriate the use of the indicated (BMD) methodology as a means of setting regulatory endpoints that get around (or fly in the face of) actual rat offspring cholinesterase inhibition data obtained experimentally at lower doses. As quoted from his comments on the draft Malathion Risk Assessment in citing **Attachment XIX**, Dr. Dementi says: "The bottom line is that I disagree with employing the BMD approach to malathion offspring cholinesterase data. Estimates of offspring versus adult sensitivity by other comparisons of the cholinesterase data reveal sensitivity to be 90-fold, or could be even higher, if more data had been obtained in the study. The inappropriateness of the BMD in this case was confirmed in the HIARC report of January 28, 2003 (Topic C, pp. 71-72)." (emphasis added) (p. 40 from Dr. Dementi's June 13, 2005 comments on the draft Malathion Risk Assessment). The BMD methodology used on this data with rat offspring is clearly misleading as to the understanding of actual low dose effects of malathion on inhibition of cholinesterase, where one is searching, as EPA should be, for true NOELs. Where offspring effects are sought, cholinesterase inhibition was not the only effect seen across all doses. So, if by use of this erroneous BMD approach, one circumvents the true LOEL in this study derived from cholinesterase data, there yet remain offspring behavioral effects and morphometric effects on the corpus callosum, in the same study, across all doses (effects one might add are commensurate with cholinesterase inhibition across all doses), yet still leaving no NOEL for malathion effects on offspring.

It is imperative that interested persons read this May 6, 2002 memorandum, and Dr. Dementi's comments on the risk assessment to fully appreciate the meaning of this memorandum, and the attempt being made by authors of the risk assessment to circumvent actual effects at the lowest dose on rat offspring, a clear disservice toward EPA's role of protecting public health, in this case the health of those among the Nation's most vulnerable, namely infants/children.

Attachment XX) Memorandum (Email) of Brian Dementi to William Hirzy (November 23, 2004), forwarding a November 18, 2004 briefing for the OPP Director. This information serves to bring to light the fact that malathion used in public spraying operations may well have fallen out of certified limits (with respect to isomalathion content, for example) on storage, especially so at elevated temperatures, prior to application. And it is questioned whether "adulteration of malathion can be addressed" (emphasis added), suggesting a historical lack of certainty about malathion composition when being applied over populace areas to control medfly, for example, while "public safety was pronounced without reservations". This attachment refers to Dr. Dementi's 9/26/02 Email, which is his memorandum to Yvette Hopkins, and rendered above as **Attachment XI**. This is a very important public health issue, referable to many public place uses of malathion, while uncertainty existed as to the product's composition, and possible content of toxic impurities that may arise from high temperature/long term storage prior to use.

Attachment XXI) Letter of Deborah Bechtel, 54 Brentford Ct., Camarillo, CA 93010, to Lynn Goldman, M.D., Assistant Administrator, Pesticides and Toxic Substances, 401 M St. S.W., U.S. EPA, Washington, D.C. 20460 (March 25, 1995), in which Ms Bechtel says in her opening

sentence: "Why is there no one from the US EPA in California monitoring the health effects of the aerial malathion spray program of urban areas?", and goes on to state the adverse health effects people claim to experience, while setting forth her various questions regarding the procedure. Dr. Dementi cites this attachment as a way of documenting in his comments to the draft Malathion Risk Assessment, that people in malathion spray zones do claim adverse health effects, often or usually are ignored, and who seriously question aspects of the process. The letter itself serves as its own best testimony.

This letter was designated as "Controlled Correspondence" in an Agency 4/12/95 cover sheet ("Request for Review").

Attachment XXII) Memorandum of Brian Dementi to Marcia Mulkey (July 9, 2002): "General Comments on Malathion June 13, 2002 HIARC Report". This is a lengthy set of comments (some 23 issues spanning 21 pages) directed to the indicated HIARC report. It is a meritous document within itself, addressing (or dissenting with respect to) many aspects presented in the 6/13/02 HIARC report.

However, it is cited in Dr. Dementi's comments on the draft Malathion Risk Assessment as means of indicating the need for a full External Peer Review on the entire malathion mutagenicity data base, and also is cited as bringing into question HIARC's decision to discount a *Mutation Research* publication [Amer, et al (2002)] revealing mutagenicity of malathion treated wheat grain (pp. 16-17). The HIARC report (p. 52) actually concluded the assay was positive for mutagenicity, but discounted the assay as useful due the the uncertainty of the purity of the malathion involved. Stored wheat grain is widely treated with malathion, and thus this mutagenicity assay, appearing in a widely respected journal, has great relevance where human exposure may be concerned. There should be ways of affirming/refuting the work, as opposed to setting it aside.

Attachment XXIII) Memorandum (Email) of Joseph Bailey to Brian Dementi (December 15, 1999): "List of References". In this memorandum, Mr. Bailey, who I believe was at that time Special Assistant to Ms Marcia Mulkey, OPP Director, says: "Brian, Sorry for the delay, but attached is my listing of the references attached to the HIARC and the CARC reports for malathion. Please let me know if there are any additional references that you believe are not reflected in this listing. Joe Bailey". Now one will observe from Mr. Bailey's attached list of diverse "Malathion Documents", numerous ones that were authored by Dr. Dementi. The presence of the memoranda authored by Dr. Dementi on this list serves as a testimonial of those efforts/intentions in OPP to include and retain Dr. Dementi's dissenting opinions, that he expected would follow from the commitment of Ms Mulkey to retain the same on the record for public inspection. This memorandum of Mr. Bailey is cited in Dr. Dementi's June 13, 2005 comments on the draft Malathion Risk Assessment, where he says in part: "My efforts to have as attachments my views (dissenting opinions) was made possible by OPP's Director, Marcia Mulkey. As testimony to this effort I would cite here, for example: 1) the December 15, 1999 memorandum of OPP's Joseph Bailey (**Attachment XXIII**) listing references of my work appended to CARC and HIARC reports.....", etc. (p. 117). Though this memorandum by Mr. Bailey contains but a partial listing of Dr. Dementi's many dissenting memoranda, it does attest to the effort being made in OPP to catalogue, and thus make publically available his memoranda.

Attachment XXIV) Memorandum (Email) of Brian Dementi to William Hirzy conveying Dr. Dementi's January 28, 2003 and December 11, 2002 memoranda to OPP's John Carley,

concerning the disposition of written dissents to HIARC and risk assessment documents. So, as with the previous **Attachment XXIII**, this correspondence also serves to illustrate the ongoing efforts within OPP to catalogue or index (make permanent) Dr. Dementi's dissenting opinions. To this end, Dr. Dementi's 1/28/03 memorandum to Mr. Carley says at one point, in reference to the January 28, 2003 HIARC report: "Since this HIARC report (*meaning that of 1/28/03*) (qualifying comment added) could replace the June 13, 2002 HIARC, to which you so ably appended my former dissenting views as attachments, I would like to make it certain that my comments to the former report do not loose their promised representation. Therefore I would like to emphasize that in order to secure full presentation of my views, the reader of the HIARC report (s) should have freely availed to him copies of both the June 13, 2002 HIARC report as well as the January, 2003 report...." (I should note that the "January 2003" report ultimately had the 1/28/03 date.) This HIARC report of 1/28/03 met with an inexplicable deletion from the list of HIARC reports in this draft risk assessment (pp.122-124, where HIARC reports find their citations in chronological order, yet the last one listed is that of 6/13/02).

The January 28, 2003 HIARC report *with all its conclusions and notable attachments ,* including those of Dr. Dementi, merits its full expression, both science-wise, and in finding its' proper citation among all HIARC reports.

The January 28, 2003 HIARC report was mentioned previously here under **Attachment XIX**, above.

Attachment XXV) Memorandum (Email) of Brian Dementi to John Carley, Special Assistant to the Director, Office of Pesticide Programs (December 22, 2004): "Additional attachments of dissent to malathion risk assessment document". Among various submitted memoranda of scientific information/dissent, and again illustrating the character of conveyance to the public record of my alternative/dissenting opinions as appended, this document says in reference to the developing malathion risk assessment: "Since last submitting documents to you (and to the risk assessment) for inclusion there, I have a certain few additional expressions of my views that I am requesting be appended to the risk assessment. Included among these are two articles by outside experts. I consider Ms Marcia Mulkey's decision to permit my views of expression to remain viable to that end. At the moment, my retirement from the Agency appears imminent, so in part my intent here is to leave behind 'an orderly account' of that which has transpired." This **Attachment XXV** is introduced as further evidence that OPP retained my various memoranda of dissent, as a source of information available in the public record for review by others.

Attachment XXVI) Memorandum (Email) of Brian Dementi to John Carley (February 29, 2000): "Summary of HIARC issues", having appended Dr. Dementi's 2/28/00 memorandum (some nine pages, containing much important scientific content) to Mr. Carley, which says at the outset: "In my letter to you of January 27, 2000, I provided comments on matters pertaining to malathion being considered by HED's Cancer Assessment Review Committee (CARC) as agreed to at the January 13 meeting. In the present letter I shall attempt to present a similar assessment of non-cancer issues reviewed by HED's Hazard Identification Assessment Review Committee (HIARC), also as agreed to at the January 13 meeting." This memorandum seeks to differentiate, or classify, numerous of Dr. Dementi's memoranda into issues of "substance" and "process", as requested by Mr. Carley, as an aid in his formalizing their retention as appended to HIARC reports. All of the submitted memoranda of Dr. Dementi should find their formal retention on the many HIARC meeting (reports) at which Dr. Dementi presented his views, orally and in writing.

Again, this **Attachment XXVI** serves to document the extensive efforts of Mr. Carley, with Dr. Dementi's assistance, in gaining for the memoranda of dissent an enduring and visible presence on HIARC reports, and thereby made readily available for public inspection/review as part of the HIARC reports.

Attachment XXVII) Memorandum of Brian Dementi, Ph.D., DABT, Toxicologist, HED, to Clark Swentzel, Chairman, Hazard Identification Assessment Review Committee, Health Effects Division (January 29, 1999): "Re: Malathion - December 22, 1998 HIARC Report on the External Peer Review Process". The External Peer Review in this case involved obtaining toxicology perspectives (conclusions) on various malathion toxicology issues/questions presented by HED to the panel. **The panel consisted of three notable experts in toxicology, namely Drs. Rolf Hartung, Walter Decker and Michael Douerson. This external review was pursued in lieu of a FIRFA SAP hearing, the results of which (*including issues/questions presented to the external experts, and their actual individual responses*) should be clearly set forth in this Malathion Risk Assessment, i.e. made readily available for review by outsiders. *However, I believe this condition has not been met in the risk assessment* .**

This is a very important memorandum serving to *rebut the many aberrant conclusions render by the HIARC in its December 22, 1998 report on the committee's evaluation of conclusions rendered by members of the External Peer Review*. Many toxicology issues, and HIARC's mishandling of these, constitute the subject(s) of this 1/29/99 memorandum, that time does not permit advancing in this summary. As stated in Dr. Dementi's comments (again, 6/13/05) on the draft Malathion Risk Assessment: "I wish to cite here my letter of January 29, 1999 (**Attachment XXVII**) to Clark Swentzel, Chairman of the HIARC, containing my alternative views to the December 22, 1998 HIARC report of the meeting which considered the External Peer Review. In my view, after submitting significant questions to the external reviewing toxicologists, the follow-up 1998 HIARC largely disowned the toxicologist's recommendations without reasoned rationale." (p. 59)

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