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 1

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 “malaoxon 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 “NOAELs 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: "Malathion 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