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NRDC COMMENTS ON EPA REVISED HUMAN HEALTH RISK ASSESSMENT FOR MALATHION, 2005

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These comments refer to the Malathion: Updated Revised Human Health Risk Assessment for the Reregistration Eligibility Decision Document (RED). September 13, 2005. (referred to here as rHHRA)

NRDC has submitted considerably detailed comments to EPA on malathion (incorporated herein by reference), including: February 12, 2001. Malathion, Docket OPP-34223 (Referred to here as NRDC 2001)

PRODUCT SUMMARY:

Malathion (registrant is Cheminova A/S) is used on a variety of agricultural commodities, home ornamentals, vegetable gardens and lawns, and for wide area treatments such as public health mosquito control, fruit fly control, and boll weevil eradication programs. Malathion also is used as a head lice treatment. EPA's latest analysis of malathion toxicity data received since 2000 required changes to the Agency's human health risk assessment for that chemical.

Cheminova provided the following market share information: 59-61% is used on USDA Boll Weevil and other special programs, 16-20% is used in general agriculture, 8-15% is used for public health, and 10% is used for home and garden uses (rHHRA at 12). The most predominant agriculture use is cotton (33%), followed by cereal grains (11%) and alfalfa (15%).

This assessment does not address any existing product labels permitting indoor uses, direct animal (pet and livestock) treatments, and other market uses that Cheminova is not supporting for reregistration (Cheminova letters March 1998, March 2002) (rHHRA at 12).

SUMMARY of EPA REVISED HUMAN HEALTH RISK ASSESSMENT 2005 (rHHRA):

The following summary points are discussed in detail in the same numerical order.

1. The use of malathion as a pediculicide for head lice is considered by EPA to be a non-FIFRA use, and EPA will therefore incorporate the FDA analysis of this use in the IRED as a supplementary assessment.
2. EPA considers the toxicology database for malathion to be "substantially complete and of acceptable quality" to assess the potential hazards, including special sensitivity of infants and children (rHHRA at 6).
3. Malathion is considered by EPA to be of low acute toxicity (Category III or IV) (rHHRA at 6)
4. From the full complement of neurotoxicity studies there was evidence of quantitative differences in susceptibility between adults and young in the developmental neurotoxicity study(DNT) and its companion comparative cholinesterease (ChE) study (rHHRA at 7).
5. Malathion has been classified as "suggestive evidence of carcinogenicity" consistent with the 1999 Draft Cancer guidelines (rHHRA at 7).
6. EPA has published a data call-in (DCI) for a comparative cholinesterase inhibition (ChEI) study of malaoxon dosed adult and juvenile rats. However, there is adequate data for EPA to develop a toxicity adjustment factor (TAF) of 77X (calculated from oral studies) to adjust for the relatively increased potency of malaoxon. This TAF is also used for inhalation and dermal exposures, in the absence of malaoxon-specific data on these routes of entry (rHHRA at 7).
7. EPA (HED) recommends retaining the 10X FQPA hazard-based adjustment factor to adjust for the susceptibility ratio between adults and young using the benchmark dose (BMD) analysis of the comparative ChE assay in rats (rHHRA at 7).
8. The acute reference dose[1] (aRfD)is based on a BMD analysis of red blood cell (RBC) ChEI data from a comparative cholinesterase study in rat pups. An uncertainty factor

[1] The PAD is expressed as a percentage of a maximum acceptable dose (i.e. the dose that will result in no unreasonable adverse health effect). It is derived from the Reference Dose (RfD) divided by the FQPA safety factor. EPA is concerned when the dietary risk exceeds 100% of the PAD.

(UF) of 100X was applied (10X for interspecies, 10X for intraspecies extrapolation). The 10X FQPA was NOT used because the studies were from young rodents (11-days) (rHHRA at 8). The chronic RfD (cRfD) was based on RBC ChEI in female rats over 3 mos of a 2-yr study. A 1000X uncertainty factor was applied;10X for inter- and 10X for intraspecies, and 10X FQPA for juvenile susceptibility (rHHRA at 8).

9. The residential incidental oral endpoint was based on the repeat-dose portion of the comparative ChE study and a benchmark dose was estimated. The lower BMD (BMDL)[2] is the lower 10% confidence limit on the RBC ChEI 10% effect level. An UF of 100X is used (10X for inter- and 10X for intra species extrapolation), with no FQPA factor, because the data is based on juvenile rats.

10. The short-term dermal and inhalation endpoints are based on a 21-day rabbit dermal study and a 90-day rodent inhalation study respectively. For the dermal endpoint, a UF of 100X is used for adults, and 1000X for children. For inhalation, an UF of 1000X is used for both because of lesions observed at doses lower than those that resulted in ChEI (rHHRA at 8)

11. Surface water levels of malathion and malaoxon were estimated using the EFED PRZM/EXAMS model and an interim rice paddy model (rHHRA at 9). Dietary risk assessments were conducted using the DEEM model and CSFII residue data, with the TAF of 77X to adjust for malaoxon residues (rHHRA at 9).

12. Some residential uses alone exceeded HED's level of concern. Combining dermal and inhalation exposures for residential risks indicate that the total risks do not exceed HED's level of concern for any scenario (rHHRA at 9). Public health uses assessed separately do not exceed HED's level of concern (rHHRA at 10).

13. Aggregated acute dietary risks for malathion and malaoxon (for food and water) exceed HED's level of concern for 9 of 26 scenarios, primarily attributable to the water exposure (rHHRA at 11).

14. The aggregate chronic dietary risks estimates include average exposures to combined residues of malathion and malaoxon in food and water. Exposures from food alone did not exceed HED's level of concern, but aggregate risks for food and water are of concern for all population subgroups and for the US general population (rHHRA at 11).

15. Occupational exposures may occur to both handlers and postapplication workers (rHHRA at 11). Most mixer/loader scenarios exceed HED's level of concern assuming baseline clothing (long pants, long-sleeved shirt, shoes and socks). Most scenarios are no longer of concern with the additional use of gloves, except for those involving high application rates, large areas of treatment, or wettable powder formulations (rHHRA at 11). For postapplication activities, most reached a Margin of Exposure (MOE)[3] of 100 or above, considered by EPA to be acceptable, within 0-4 days. An interim restricted entry interval

[2] The BMDL is defined as the lower limit of a 90% confidence interval. In other words, there is a 95% certainty that the true value for a 10% decrease in red blood cell cholinesterase activity lies between 13.6 (the lower limit) and an upper limit value. It is considered protective/conservative to use the lower limit on this confidence interval since the true value is likely to be higher.

[3] MOE. Margin of Exposure determines how close the occupational exposure comes to a no-observed-adverse-effect-level (NOAEL), usually derived from animal studies.

(REI)[4] of 12 hrs is established under the Worker Protection Standard (WPS) (rHHRA at 11).

DETAILED COMMENTS ON THE ABOVE SUMMARY POINTS:

1. Work with FDA to cancel the use of malathion as a pediculicide. EPA states that it does not consider the use of malathion as a pediculicide for head lice to be a "FIFRA use." However, the agency has failed to grapple with its legal obligation to consider the pediculicide use (and all other uses for which there is human exposure) in completing its aggregate risk assessment for malathion under FFDCA §408—which in turn must be incorporated into EPA's decisions under the risk standard in FIFRA §2(bb). Of course, the massive human exposure, particularly to children, through the pediculicide use of malathion is likely to dwarf most other routes of exposure, and therefore malathion's pediculicide use should be cancelled. If the pediculicide use of malathion is not cancelled, the malathion risk cup (and in fact the whole organophosphate cumulative risk cup) will be overflowing, and EPA will not be able to approve any tolerances or uses of malathion that lead to any exposure through food.

EPA says it will incorporate the FDA analysis of this use in the IRED as a supplementary assessment. For the reasons noted above, as a legal matter this is insufficient to meet EPA's statutory obligations under FFDCA and FIFRA. In addition, as a scientific matter, this is clearly inadequate to protect health. For example, in addition to the overwhelming likelihood that malathion's pediculicide use causes dermal and other exposures far in excess of safety margins, a case study has shown fetal deformities following maternal exposure to malathion as a head lice shampoo (Lindhout and Hageman, 1997), suggesting, along with other incident reports and literature, that this is an exposure route of very great concern. There are safer and more effective alternatives that can replace malathion as a pediculicide, including effective non-toxic treatments.[5] Alternatives to pesticide treatments include dry-on, suffocation-based pediculicide and mechanical lice removal tools such as the licemeister.

The EPA Assessment reports that this is a non-FIFRA use of malathion, and that the analysis of the Food and Drug Administration (FDA) will be included in the Agency's IRED for malathion (rHHRA at 6, 13). Since pharmaceutical approval requires a determination of both safety and efficacy, one would expect that FDA had already conducted its own risk assessment. We continue to recommend that EPA work with FDA to ban the use of malathion as a pediculicide, and additionally that EPA must estimate or represent this use in its aggregate risk assessment. If no data are available, EPA should adjust for this risk with an additional uncertainty factor as appropriate (NRDC 2001 at 5).

2. The toxicology database is misrepresented in some cases, and is incomplete. EPA considers the toxicology database for malathion to be "substantially complete and of acceptable quality" to assess the potential hazards, including special sensitivity of infants and children (rHHRA at 6). However, EPA notes the paucity of malaoxon toxicity and monitoring data, and also expresses a need for immunotoxicity data on malation (rHHRA at 23). The assessment notes

[4] REI. A restricted entry level is the period of time following a pesticide application before EPA considers it is safe to reenter a treated area to perform normal work actions.

[5] Pearlman DL. A simple treatment for head lice: dry-on, suffocation-based pediculicide. Pediatrics 114: 275-279.

that a comparative ChE study with malaoxon is being conducted by the registrant, but has not yet been received (rHHRA at 23). We encourage EPA to consider these data, as well as additional data in the open literature as it emerges.

We agree that there are sufficient data for EPA to develop and assessment of the risks of malathion, but disagree with the data interpretation and assessment that EPA has presented here. Some of these data are discussed here:

We applaud the EPA for including the two-generation reproduction study with Sprague-Dawley rats (MRID 41583401) in its assessment (rHHRA at 29), whereas this study had been ignored in the previous assessment (2000). This study determined the parental systemic toxicity NOAL to be 5000 ppm (394/451 mg/kg/day in M/F) and the LOEL to be 7500 ppm (612/703 mg/kg/day in M/F), based on decreased body weight. For offspring toxicity, the NOAL was 1700 ppm (131/135 mg/kg/day in M/F), and the LOEL was 5000 ppm (394/451 mg/kg/day in M/F), based on decreased body weight. Thus, the offspring NOEL was one-third the parental NOEL in this study. This study suggests that a likely route of exposure to juveniles, and also to human babies, is through breast milk. Has EPA fully considered this exposure pathway, and the resulting risks to breastfeeding infants during their most susceptible period of development? As with the animals, nursing humans face a likely scenario of being exposed to malathion in both mother's milk and food/their environment during the course of their early years. Such a "double dosing" scenario is not developed by EPA in its setting of safe levels for malathion. This exposure pathway may be significant for premature babies, newborns, and infants. This is not considered in EPA's assessment. Because there are no robust data on breast milk levels, the use of an UF is supported by the data from this rodent study.

In an acute delayed neurotoxicity study (MRID 40939301), hens were given two doses of malathion, administered by gavage. The first dose was 1.3X the oral LD50 (775 mg/kg), and the second dose was 1.5X LD50 (852.5 mg/kg). This study is utterly inadequate to properly assess neurotoxicity end points of concern when evaluating the protection of human health. The doses are so high, mortality would preclude any evidence of toxicity. EPA determined that this study was, "negative for any evidence of acute delayed neurotoxicity" and did not reveal any, "treatment-related effects" (rHHRA at 31). In contrast, the study claims that the only observed clinical effects were due to inhibition of cholinesterase, which is considered a treatment-effect. The study claims that no further treatment-related effects were observed by either necropsy nor histopathology. This is hard to believe, since only 14/60 hens survived the study! What did the other 46 hens die of, if it wasn't treatment-related? Embarrassment at having been included in this poorly-designed and poorly-interpreted study? And, were no abnormal behavioral signs observed, prior to the 46/60 hens dying? How does EPA scientifically justify its conclusions of "no treatment related effects" from a study in which only ¼ of the study subjects survived? This study should not be considered "acceptable" by EPA, and therefore this remains a datagap.

We applaud the EPA's successful efforts since its last assessment (2000) to strengthen its malathion database with the addition of a subchronic inhalation study and a developmental neurotoxicity study. However, and importantly, a comparative cholinesterase study of immature versus adult animals is not available, and would be of great value. We encourage the EPA to develop these data.

3. Malathion is inaccurately classified by EPA as low acute toxicity. Malathion is considered by EPA to be of low acute toxicity (Category III or IV) (rHHRA at 6, 24). We disagree with this determination. EPA asserts that the term is used to describe lethality only, and that this is a convention in toxicology and risk assessment. This is not a convention in modern toxicology, and is inconsistent with cutting edge toxicology that moves beyond the crude and often uninformative

endpoint of lethality, instead developing an impressive understanding of mechanisms of toxicity. In modern toxicology the word "acute" refers to an endpoint with rapid onset, and often short but severe course of action. This describes the ChEI effects of malathion following acute exposures (single dose) to young rats (EPA response to Dementi, September 21, 2005). We request that EPA re-consider its fallback position on outdated and uninformative toxicological approaches, and reassess the toxicity of malathion with appropriate consideration of these critical acute toxicity data.

4. The data supports an FQPA of at least 30X. From the full complement of neurotoxicity studies there was evidence of quantitative differences in susceptibility between adults and young in the developmental neurotoxicity study(DNT) and its companion comparative cholinesterase (ChE) study (rHHRA at 7, 25-26, 36-39). While we support EPA's retention of the 10X FQPA (it had been eliminated in the previous assessment in 2000), we suggest that the data support a factor much greater than 10. This is advocated by EPA's senior toxicologist in his letter to EPA, but dismissed by EPA[6]. Dr. Dementi's position is well supported by the available data. Registrant studies of ChEI submitted to the Agency demonstrate differences in inhibition ranging from 2-fold to over 20-fold, between adults and pups given equivalent doses of malathion[7]. In one study, two hours after a single oral dose of technical grade malathion was administered to young adult rats and PND11 pups, the adult brain cholinesterase levels were inhibited 3-4% (male and female), compared with controls. However, brain cholinesterase activity was inhibited in the pups by 81-84% (female and male; 450 mg/kg/day), compared with controls, a 20-fold difference compared with the adult response. Most importantly, this study failed to determine a no-effect level (NOEL) for RBC ChEI in pups, even at the lowest dose tested (5 mg/kg/day), where no effects on ChEI were seen in adults. Following a single dose at 5 mg/kg/day, male pups had a 16% RBC ChEI, and females had a 7% RBC ChEI (data from adults is not reported). Following 11 days of oral malathion treatment with 5 mg/kg/day, pups had 17% and 15% RBC ChEI (males and females respectively), whereas adults had 4% and 2% (males and females respectively). These results were reported as statistically significant compared with controls.[8] These results indicate that at an acute or subchronic exposure, the lowest dose, 5 mg/kg/day is associated with significant ChEI for immature animals (day 11), but is a no-effect level for adults. These data support an FQPA adjustment factor of at least 20X, and a pup LOAEL of 5 mg/kg/day with no identifiable NOAEL.

We support EPA's assessment of a concern for pre- and/or postnatal toxicity, and its identification of several studies that report susceptibility for immature animals (rHHRA at 37-39). We note also that often there are severe qualitative differences in the responses of juvenile animals versus adults. In the developmental neurotoxicity studies the young rats displayed neurobehavioral and neuropathological effects at levels where the adults showed no effects (MRID 45646401). In the prenatal developmental study in rabbits the maternal NOAEL was based on body weight gains (LOAEL of 50 mg/kg/day) whereas the fetal endpoint was increased death at the same dose (MRID 00152569). EPA reports that the range in pup-to-adult sensitivity

[6] U.S. EPA response to Dr. Brian Dementi's dissenting opinion. September 21, 2005.

[7] letter from Cheminova, submitted by Jellinek, Schwartz, and Connolly, Inc. Re: Malathion: Preliminary data from a developmental neurotoxicity study. February 13, 2001. EPA LIN#L0000617. Obtained by NRDC, Jennifer Sass, by FOIA RIN-0283-02

[8] letter from Cheminova, submitted by Jellinek, Schwartz, and Connolly, Inc. Re: Malathion: Preliminary data from a developmental neurotoxicity study. February 13, 2001. EPA LIN#L0000617. Obtained by NRDC, Jennifer Sass, by FOIA RIN-0283-02

is 0.5-30 fold (rHHRA at 39). Why has EPA not used an FQPA adjustment of 30X, based on its own assessment of the data? How can EPA be confident that its selection of a 10X is appropriately protective when the data support a factor of at least 30X? (see critique of BMD analysis in point#7).

5. The data support classifying malathion as a likely human carcinogen using the 2005 Cancer Guidelines. Malathion has been classified as "suggestive evidence of carcinogenicity" consistent with the 1999 Draft Cancer guidelines (rHHRA at 7, 27, 54-55). This classification is based primarily on studies by Cheminova. These studies showed that malathion caused liver tumors in both laboratory animals studies (rats and mice), but at doses that EPA considered to be excessive. The mouse study (MRID43407201) showed incidences of hepatocellular tumors were increased in treated mice of both genders. Statistically significant increases in liver carcinomas, and combined adenomas/carcinomas in male mice were seen at 100 and 8000 ppm in males, and at 8000 and 16,000 ppm in females (CARC1[9], p. 3). Most concerning is that the mouse study in question did not progress for the full two years standard under EPA protocol, but was truncated at 18-months. Adenomas often progress to carcinomas over time. Further, a 1978 NCI study reported increased incidences of liver tumors in male mice at 16000 ppm malathion (CARC2[10], p. 12), suggesting that the progression from adenoma to carcinoma in these animals is to be expected. It is reasonable to presume that bona fide adenomas would have progressed to carcinomas over an additional six months. These concerns were pointed out to the panel in comments by Dr. Dementi (Jan 18, 2001), and California EPA, but were disregarded.

We have additional concerns about EPA's decision to overlook liver tumor increases in male and female mice at the doses of 8000 and 16000 ppm malathion exposure. Although CARC2[11] discounted these tumors because they occurred in "the presence of severe toxicity", this was defined as severe cholinesterase inhibition (CARC2, 2000, p. 12). This argument was <u>not</u> accepted by the 2000 SAP, which stated that, "using AchE levels to define an excessive dose has no biological basis".[12] Moreover, 23% of the combined adenoma/carcinomas in mice treated with malathion were observed in the lower two doses. These data support the classification of malathion as a likely human carcinogen.

Similar arguments about excessive dose were made by EPA to dismiss evidence of increased incidence of liver tumors observed in the F344 Rat study, (MRID 43942901). That is, tumors are seen only at excessive doses. However, 38% of adenomas occurred in the lower dose range. This was pointed out to EPA in comments by Dr. Dementi (Jan. 18, 2001; 17/OPP#00670-1), and was supported by CARC1. The CARC1 Committee "concluded that the

[9] Cancer Assessment Document. Evaluation of the carcinogenic potential of malathion. Final report. Cancer Assessment Review Committee Health Effects Division, Office of Pesticide Programs. February 2, 2000.

[10] Cancer Assessment Document #2. Report of the 12-April-2000 meeting. Evaluation of the carcinogenic potential of malathion. Cancer Assessment Review Committee Health Effects Division, Office of Pesticide Programs. April 28, 2000.

[11] Cancer Assessment Document #2. Report of the 12-April-2000 meeting. Evaluation of the carcinogenic potential of malathion. Cancer Assessment Review Committee Health Effects Division, Office of Pesticide Programs. April 28, 2000.

[12] SAP Report No. 2000-04. Report. FIFRA Scientific Advisory Panel Meeting, August 17-18, 2000. Set of scientific issues being considered by the Environmental Protection Agency regarding: A consultation on the EPA Health Effect Division's proposed classification on the human carcinogenic potential of malathion. December 14, 2000.

incidence of liver tumors at the 50 and 500 ppm dose levels provide suggestive evidence of carcinogenicity and cannot be discounted. The Committee also concluded that the liver tumor incidences at 6000 ppm and at 12,000 ppm (although considered excessive doses) provide positive evidence of carcinogenicity" [13]. These data support the classification of malathion as a likely human carcinogen.

EPA dismissed nasal tumors that were observed in rats (MRID 44782301). EPA questioned whether these tumors were a result of malathion exposure or an artifact. The SAP's conclusion "while it is unlikely that these two tumors were related to malathion treatment, it cannot be unequivocally ruled out"[14] warns against dismissing these data. For neoplastic findings, the reviewers find that the study is considered positive at high doses based upon the finding of rare nasal tissue neoplasms, and extensive nasal histopathology. The study is considered positive at all doses attributable to rare neoplastic findings, two of which occurred at the 100/50 ppm dose level, one each in rats of each sex. These data are supported by evidence of a dose response for the same rare findings at 6000 and 12000 ppm in males. These data are supported by evidence of nasal non-neoplastic histopathology in the rat subchronic inhalation study (MRID 43266601). It is especially relevant that these effects were seen after only 13 weeks and occurred at all test concentrations.

As reviewed by the Northwest Coalition for Alternatives to Pesticides[15], in addition to the above discussed studies from Cheminova, a 2001 study done by scientists at Columbia University and the Universities of Tarapaca and Concepcion (Chili) found that the malathion insecticide Fyfanon increased the incidence of breast cancer in rats[16]. In a Canadian 2001 study men from six provinces diagnosed with non-Hodgkin's lymphoma were almost twice as likely as healthy men to have been exposed to malathion.[17]

Data from the Agriculture Health Study of the National Cancer Institute reported in 2005 that husband's malathion use is associated with an increased relative risk of breast cancer among wives who never used pesticides (Iowa RR=1.4, 95%CI 0.9-2.2; N. Carolina RR=1.5, 95%CI 0.8-2.7). Among post-menopausal women the association was even stronger (RR=1.5, 95%CI 1.0-2.3).[18]

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[13] Cancer Assessment Document. Evaluation of the carcinogenic potential of malathion. Final report. Cancer Assessment Review Committee Health Effects Division, Office of Pesticide Programs. February 2, 2000.

[14] SAP Report No. 2000-04. Report. FIFRA Scientific Advisory Panel Meeting, August 17-18, 2000. Set of scientific issues being considered by the Environmental Protection Agency regarding: A consultation on the EPA Health Effect Division's proposed classification on the human carcinogenic potential of malathion. December 14, 2000.

[15] Data is discussed in: Cox, C. 2003. Malathion factsheet. Journal of Pesticide Reform, 23(4).

[16] Cabello, G. et al. 2001. A rat mammary tumormodel induced by the organophosphorus pesticides parathion and malathion, possibly through acetylcholinesterase inhibition. Environ Health Perspect, 109:471-479

[17] McDuffie, HH et al. 2001. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev, 10:1155-1163

[18] Engel LS, Hill DA, Hoppin JA, Lubin JH, Lynch CF, Pierce J, Samanic C, Sandler DP, Blair A, Alavanja MC. 2005. Pesticide Use and Breast Cancer Risk among Farmers' Wives in the Agricultural Health Study. Am J Epidemiol. 2005 Jan 15;161(2):121-35
http://aghealth.org/engel_tables.html

The 2005 Cancer Guidelines provide a framework for judging whether available data support a mode of carcinogenic action hypothesized for an agent. This framework incorporates the criteria for causality used in epidemiological studies, as stated by Bradford Hill (1965), with subsequent modifications. Each criterion support the determination of causality, and the more criteria that are satisfied, the stronger the evidence for causality. However, it is not necessary, and not likely, that all criteria are satisfied to demonstrate causality. A classification of *"Likely to Be Carcinogenic to Humans"* is strengthened for: a) An agent with some evidence of an association between human exposure and cancer, with or without evidence of carcinogenicity in animals. This criterion is fulfilled by the evidence from the Agriculture Health study, the Canadian study, and the Chilean study discussed above. b) An agent that has tested positive in more than one species, sex strain, site, or exposure route, with or without evidence of carcinogenicity in humans. This criterion is fulfilled by the evidence from the mouse and rat studies discussed above. c) A positive study that indicates a highly significant result, for example, an uncommon tumor, a high degree of malignancy, or an early age at onset. This criterion is fulfilled by the nasal tumors seen in the 2-yr feeding and 13-wk inhalation rodent studies discussed above. There is also evidence of mutagenicity that is not discussed in the EPA assessment. The National Institute for Occupational Safety and Health (NIOSH) describes malathion as a mutagen, based on the genetic damage it caused in 29 laboratory studies published between 1978 and 1995.These studies included tests of bacteria, fruit flies, mice, hamsters, fish, and human cell cultures.[19] These in vitro data are consistent with a 2002 study from India reporting that malathion given orally caused genetic damage in laboratory mice.[20]

The classification of malathion as a likely human carcinogen is supported by the 2005 Cancer Guidelines criteria. Why has EPA not discussed and referenced these data, or considered their impact on the cancer classification of malathion? Does EPA feel that its total reliance on Cheminova data is appropriate, when published independent data support cancer risks? How does EPA support its assessment when so much data has seemingly been overlooked?

6. Malaoxon toxicity is likely more than 77X more potent than malathion. EPA has published a data call-in (DCI) for a comparative cholinesterase inhibition (ChEI) study of malaoxon dosed adult and juvenile rats. However, there is adequate data for EPA to develop a toxicity adjustment factor (TAF) of 77X (calculated from oral studies) to adjust for the relatively increased potency of malaoxon. This TAF is also used for inhalation and dermal exposures, in the absence of malaoxon-specific data on these routes of entry (rHHRA at 7, 50-51). It is based on male RBC cholinesterase in a 14-day rat study (MRID 46080001) and a 2-year chronic rat study (MRID 43975201), with upper and lower confidence limits of 127 and 46. It's not clear why EPA has not chosen a value closer to the upper confidence limit, to better capture the high risk tail of the data. Moreover, malaoxon has been shown to inhibit acetylcholinesterase about 1,000–fold more strongly than does malathion.[21] These data suggest that the TAF that EPA has chosen does not reflect all the available data, and is not likely to be sufficiently protective. Has EPA reviewed these data and fully considered the potency of malaoxon?

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[19] Data is discussed in: Cox, C. 2003. Malathion factsheet. Journal of Pesticide Reform, 23(4).

[20] Giri, S. et al. 2002. Genotoxic effects of malathion: an organophosphorus insecticide, using three mammalian bioassays in vivo. Mut Res, 514:223-231. Data is discussed in: Cox, C. 2003. Malathion factsheet. Journal of Pesticide Reform, 23(4).

[21] Rodriguez OP, Muth GW, Berkman CE, Kim K, Thompson CM. Inhibition of various cholinesterases with the enantiomers of malaoxon. Bull Environ Contam Toxicol 1997;58(2):171-176

7. The benchmark dose analysis is weak and poorly supported by the data. EPA (HED) recommends retaining the 10X FQPA hazard-based adjustment factor to adjust for the susceptibility ratio between adults and young using the benchmark dose (BMD) analysis of the comparative ChE assay in rats (rHHRA at 7, 34). The available data support an FQPA factor of 20X or higher, as discussed in point #4 of these comments and in the comments from Dr. Dementi. Unfortunately, EPA attempts to make these and other supporting data go away through its preference of a BMDL analysis[22] (see detailed discussion in point #7 of these comments). A model is only as good as the underlying data and assumptions it rests on. Since EPA lacks reliable data at the low dose range, the BMD analysis is mostly extrapolation rather than data-driven. The estimate of BMD_{10} would be more reliable when there are a number of doses close to the BMD_{10}, below and above. In the case of malathion and most cholinesterase inhibitors it is difficult to make accurate measures of ChE inhibition at doses below BMD_{10}. Adding doses much higher than BMD_{10}, as EPA has done in this case, may give a fit that looks good on paper, but it will not substantially improve an inherently weak and unreliable estimate of the BMD10. This view is held by Dr. Dementi in his letters to EPA[23], and by the expert Scientific Advisory Panel (SAP) in its review of the dimethoate BMD analysis[24] that suffered from similar weaknesses as this malathion BMD analysis. The dimethoate SAP also pointed out that relying on a BMD analysis goodness-of-fit test, as EPA has done here with malathion, is problematic. The null hypothesis for a goodness-of-fit test is that the model explains a large fraction of response variability. Unlike experimental hypotheses tests where one hopes to reject the null hypothesis, in goodness-of-fit tests one hopes to not reject the null hypothesis and thus conclude adequate model fit. In situations where there are few data points at the relevant doses, as for malathion, and large experimental error, the goodness-of-fit test is not very powerful, and hence the probability of not rejecting the null hypothesis when the alternative is true is quite high. The conclusion of an adequate model fit does not necessarily imply that the model form used is the best and the low power of this test increases the uncertainty in BMDL10 estimates that are derived from the model. [25]

We encourage EPA to incorporate the data that supports an FQPA of greater than 10X and at least 30X (rHHRA at 39), and discourage attempts to make that data go away in lieu of a BMD analysis that is poorly supported by data at the relevant dose range.

8. The acute and chronic reference dose is not supported by available data and should be 2-3 fold more protective. The acute reference dose[26] (aRfD; 0.14 mg/kg/day)is based on a BMD analysis of red blood cell (RBC) ChEI data from a comparative cholinesterase study in rat pups (MRID 45566201; BMDL=13.6 mg/kg/day). An uncertainty factor (UF) of 100X was applied (10X for interspecies, 10X for intraspecies extrapolation) (aRfD=13.6/100=0.14 mg/kg/day). The

[22] U.S. EPA response to Dr. Brian Dementi's dissenting opinion. September 21, 2005.

[23] Dementi, B. Comments directed to the April 29, 2002 draft BMD analysis of malathion cholinesterase data. May 6, 2002.

[24] SAP minutes No. 2005-01. Dimethoate: issues related to hazard and dose-response assessment. November 30 and December 1, 2004.

[25] SAP minutes No. 2005-01. Dimethoate: issues related to hazard and dose-response assessment. November 30 and December 1, 2004.

[26] The PAD is expressed as a percentage of a maximum acceptable dose (i.e. the dose that will result in no unreasonable adverse health effect). It is derived from the Reference Dose (RfD) divided by the FQPA safety factor. EPA is concerned when the dietary risk exceeds 100% of the PAD.

10X FQPA was NOT used because the studies were from young rodents (11-days) (rHHRA at 8, 42-43). The chronic RfD (cRfD; 0.003 mg/kg/day) was based on RBC ChEI in female rats over 3 mos of a 2-yr study (MRID 43942901; NOAEL=3 mg/kg/day). A 1000X uncertainty factor was applied;10X for inter- and 10X for intraspecies, and 10X FQPA for juvenile susceptibility (cRfD=3/1000=0.003 mg/kg/day) (rHHRA at 8, 43-46).

We are concerned by the use of a BMDL for the acute RfD, where it has not been robustly supported by data at the relevant dose range (point #7). In addition, we are concerned that EPA has failed to use any FQPA adjustment for the acute RfD, saying this is because it is based on data from immature animals (PND 11). We have discussed data that demonstrates that the comparative ChE study used by EPA to support the aRfD actually reports effects in pup RBC ChEI at the lowest dose tested, 5 mg/kg/day (point #4 and rHHRA at 42-43), and that no NOAEL could be identified. Therefore, the BMDL of 13.5 used by EPA is significantly higher and unsupported by the underlying data. Instead of a BMDL of 13.5, we believe that the data supports a LOAEL of 5 mg/kg/day and an UF adjustment of 3X for lack of a true NOAEL. Thus, the aRfD should be (5/[100x3])=0.016 mg/kg/day, instead of 0.14 mg/kg/day. This recommended aRfD is over 2-fold more protective, and is supported by the available data. The aRfD that EPA has calculated is not supported by data and therefore may not be adequately protective.

Based on detailed comments already discussed, the data that is available to EPA supports an FQPA adjustment of at least 30X, and not the 10X used by EPA for the chronic RfD (point #4). Therefore, the cRfD should be (3/[100x30])=0.001 mg/kg/day, instead of 0.003 mg/kg/day. This recommended cRfD is 3-fold more protective, and is supported by the available data. The cRfD that EPA has calculated is not supported by data and therefore may not be adequately protective.

9. The residential oral exposure risk is not supported by available data and should be over 400-fold more protective. The residential incidental oral endpoint was based on the repeat-dose portion of the comparative ChE study and a benchmark dose was estimated (rHHRA at 46-47). The lower BMD (BMDL)[27] is the lower 10% confidence limit on the RBC ChEI 10% effect level. An UF of 100X is used (10X for inter- and 10X for intra species extrapolation), with no FQPA factor, because the data is based on juvenile rats (MRID 45566201). We are concerned by the use of a BMDL for the residential oral exposure, where it has not been robustly supported by data at the relevant dose range (point #7). In addition, we are concerned that EPA has failed to use any FQPA adjustment for the residential oral exposure, saying this is because it is based on data from immature animals (rHHRA at 47). Following 11 days of oral malathion treatment with 5 mg/kg/day, pups had 17% and 15% RBC ChEI (males and females respectively), whereas adults had 4% and 2% (males and females respectively). These results were reported as statistically significant compared with controls.[28] EPA reports that, "in pups, RBC effects were noted at 5 mg/kg in both sexes after repeated exposures" (rHHRA at 47). It is not clear then why EPA has not used these data to support a pup LOAEL of 5 mg/kg/day with no identifiable NOAEL. Instead, EPA has used these same data to support a BMDL of 7.1 mg/kg/day. Instead of a BMDL

[27] The BMDL is defined as the lower limit of a 90% confidence interval. In other words, there is a 95% certainty that the true value for a 10% decrease in red blood cell cholinesterase activity lies between 13.6 (the lower limit) and an upper limit value. It is considered protective/conservative to use the lower limit on this confidence interval since the true value is likely to be higher.

[28] letter from Cheminova, submitted by Jellinek, Schwartz, and Connolly, Inc. Re: Malathion: Preliminary data from a developmental neurotoxicity study. February 13, 2001. EPA LIN#L0000617. Obtained by NRDC, Jennifer Sass, by FOIA RIN-0283-02

of 7.1, we believe that the data supports a LOAEL of 5 mg/kg/day and an UF adjustment of 3X for lack of a true NOAEL. Therefore, the residential oral exposure endpoint for risk assessment should be (5/[100x3])=0.016 mg/kg/day, instead of 7.1 mg/kg/day. This recommended exposure estimate is over 400-fold more protective, and is supported by the available data. The BMDL for residential oral exposure that EPA has calculated is not supported by data and therefore may not be adequately protective.

10. The dermal and inhalation exposure assessments have not included an FQPA of at least 30X based on available data. The short-term dermal and inhalation endpoints are based on a 21-day rabbit dermal study (MRID 41054201) and a 90-day rodent inhalation study (MRID 43266601) respectively. For the dermal endpoint, a UF of 100X is used for adults, and 1000X for children (10X each for intra- and inter-species variation, and 10X FQPA). EPA reports that the range in pup-to-adult sensitivity to malathion is 0.5-30 fold (rHHRA at 39). Why has EPA not used an FQPA adjustment of 30X, based on its own assessment of the data?

For inhalation, an UF of 1000X is used for both because of lesions observed at doses lower than those that resulted in ChEI (rHHRA at 8, 48-50). We support EPA's use of a 10X for the lack of a NOAEL, but recommend that an additional UF be used to adjust for the severity of the effects seen at the LOAEL, lesions of the nasal cavity and larynx. In addition, we are concerned that EPA has not used any FQPA adjustment factor for inhalation exposure. Why did EPA not use any FQPA for this endpoint? EPA reports that the range in pup-to-adult sensitivity to malathion is 0.5-30 fold (rHHRA at 39). Why has EPA not used an FQPA adjustment of 30X, based on its own assessment of the data?

11. Estimated food residues and drinking water concentrations generally reflect monitoring data. Surface water levels of malathion and malaoxon were estimated using the EFED PRZM/EXAMS model and an interim rice paddy model (rHHRA at 9, 69-70). Dietary risk assessments were conducted using the DEEM model and CSFII residue data, with the TAF of 77X to adjust for malaoxon residues (rHHRA at 9).

We ask EPA to consider data suggesting that the TAF that EPA has chosen does not reflect all the available data, and is not likely to be sufficiently protective (point #6). The highest detected malathion concentration in ground water was 3 ppb. Malaoxon was not examined. EPA EFED (Environmental Fate and Effects Division) recommended conservative ground water estimates of 3 ppb for each of malathion and malaoxon based on the assumption that the concentration of malaoxon will not exceed malathion. Drinking water concentrations in this assessment presume 100% conversion to malaoxon, which is expected during chlorination. These estimates, which reasonably reflect real-world monitoring data, exceed EPA's acute and chronic reference dose. We generally support EPA's approach for estimating drinking water and dietary exposure. However, we encourage the EPA to solicit monitoring data for malaoxon.

12. Some residential scenarios are of concern. Some residential uses alone exceeded HED's level of concern. For residential mosquito spraying, EPA recommends that final label directions for perimeter house treatments should specifically require the treatment to only include structural foundations and wood piles, and the 2-ft wide path surrounding this area (rHHRA at 78). EPA suggests that this language would avoid the problem of phytotoxicity, as well as eliminating unintended broadcast turf exposure. While we appreciate EPA's suggestions, these are likely to be inadequately heeded. EPA notes that an informal assessment to residues on turf wide-swath

residential building perimeter treatment resulted in excessive risks (rHHRA at 79). How does EPA intend to eliminate this risk? How will EPA reduce exposures beyond label language?

EPA has recognized that spray drift is always a potential source of exposure to residents nearby spraying operations (rHHRA at 82). We concur, and encourage the EPA to incorporate these additional exposure scenarios, and consider broad mitigation measures to eliminate these risks.

In its public health mosquito control uses, we are encouraged that EPA notes in its assessment that it has avoided the use of proprietary data from the industry-dominated Spray Drift Task Force in this assessment (rHHRA at 83). We encourage EPA to continue to rely on public and independent data, including its own in-house experts. EPA reports that an assessment of dermal, inhalation and incidental oral exposure from malathion public health spraying did not exceed EPA's level of concern (rHHRA at 10, 84). However, we encourage EPA to consider replacement of malathion with reduced-risk and non-toxic integrated pest management (IPM) strategies for mosquito spray, boll weevil eradication uses (rHHRA at 85), and medfly control (rHHRA at 90). The supporters of these comments would be eager to work closely with EPA to identify successful IPM programs and strategies to protect the public from both pests and toxic chemical exposures.

13. Aggregate acute dietary exposures from food and water are unacceptably excessive for the US population, and particularly for infants and young children. The aggregate exposure (food, drinking water, residential exposure) was performed using a Lifeline Model and DEEM. Aggregated acute dietary risks for malathion and malaoxon (for food and water) exceed HED's level of concern for 9 of 26 scenarios, primarily attributable to the water exposure (rHHRA at 11, 107, Table 7.1.3). Exposures from food and water alone exceeded HED's level of concern. The acute dietary exposure estimates for food and drinking water using the worst-case crop scenario (FL citrus) at the 99.9th percentile exceeds the acute Population Adjusted Dose[29] (aPAD; 0.14 mg/kg/day) for all populations. The U.S. general population is 155% aPAD. Infants under 1 yr are 540% aPAD, over 5-fold higher than the generally acceptable safe exposure level. Children 1-2 yrs are at 237% aPAD, and Children 3-5 yrs are at 214% aPAD (rHHRA at 105-106, Table 7.1.1).

Here EPA has presumed that the aRfD=aPAD. Neither of these values incorporates an FQPA adjustment (see point #8). However, as discussed earlier, we recommend that the aRfD should be 0.016 mg/kg/day. Since the aPAD= RfD/FQPA, then our recommended aPAD would be 0.016/30X=0.0005. Using this re-calculated aPAD, the US population would be (exposure/PAD=0.217/0.0005) 434% aPAD, and infants under 1 yr would be (0.756/0.0005) 1,500% aPAD. Thus, infants exceed the acceptable exposure level by 15-fold, using the worst-case crop scenario. However, even using the less-risky Oregon apple crop scenario (rHHRA at 106, Table 7.1.2), infants would be (0.060/0.0005) 120% aPAD, and children 1-2 yrs would be (0.064/0.0005)128% aPAD.

Whether one uses the EPA aPAD or our recommended aPAD that incorporates a 30X FQPA, it is clear that acute dietary exposures from food and water are unacceptably excessive for the US population, and particularly for infants and young children. It is not clear how EPA intends to reduce these unsafe exposures to this known neurotoxic and teratogenic agent.

[29] The Population Adjusted Dose (PAD) is expressed as a percentage of a maximum acceptable dose (i.e. the dose that will result in no unreasonable adverse health effect). It is derived from the Reference Dose (RfD) divided by the FQPA safety factor. EPA is concerned when the dietary risk exceeds 100% of the PAD.

14. Aggregate chronic dietary exposures from food and water are unacceptably excessive for the US population, and particularly for infants and young children. The aggregate chronic dietary risks estimates include average exposures to combined residues of malathion and malaoxon in food and water. Exposures from food alone did not exceed HED's level of concern, but aggregate risks for food and water are of concern for all population subgroups and for the US general population (rHHRA at 11, 108-109). EPA presents data calculated using two models, the DEEM-FCID and the Lifeline. Using the worst-case scenario (FL citrus) for drinking water, these data indicate that the US population is 149-104% cPAD (DEEM and Lifeline, respectively), infants under 1 yr are 472-385% cPAD, and children 1-2 yrs are 234-228% cPAD. These levels are unacceptably excessive.

Here EPA has presumed that the cRfD=cPAD. We provide data supporting a cRfD of 0.001 mg/kg/day, instead of 0.003 mg/kg/day (point #8). This would mean that using the worst-case scenario (FL citrus) for drinking water and approximate calculations, the US population is 375% cPAD, infants under 1 yr are 1,200% cPAD, and children 1-2 yrs are 675% cPAD. These levels are unacceptably excessive.

Whether one uses the EPA cPAD or our recommended cPAD that is 3X more protective, it is clear that chronic dietary exposures from food and water are unacceptably excessive for the US population, and particularly for infants and young children. It is not clear how EPA intends to reduce these unsafe exposures to this known neurotoxic and teratogenic agent.

15. Workers are inadequately protected. Occupational exposures may occur to both handlers and postapplication workers (rHHRA at 11). Most mixer/loader scenarios exceed HED's level of concern assuming baseline clothing (long pants, long-sleeved shirt, shoes and socks). Most scenarios are no longer of concern with the additional use of gloves, except for those involving high application rates, large areas of treatment, or wettable powder formulations (rHHRA at 11). For postapplication activities, most reached a Margin of Exposure (MOE)[30] of 100 or above, considered by EPA to be acceptable, within 0-4 days. An interim restricted entry interval (REI)[31] of 12 hrs is established under the Worker Protection Standard (WPS) (rHHRA at 11). These exposure assessments are inadequately protective because they fail to take into consideration that both handlers and postapplication workers frequently work more than 8 hours per day. The EPA itself recognized this fact when it permitted glove liners to be worn by workers for 10 hours per day (or a single shift). In addition, the EPA's estimates are not adequately protective because they fail to take into account that handlers and postapplication workers are frequently exposed to malathion in mixtures with other pesticides – organophosphates or other classes – which can have additive or synergistic effects. In addition, the risk assessment for postapplication workers is marred by the inclusion of data from the Agricultural Re-entry Task Force (ARTF) which has not as yet been subjected to independent peer review or public notice and comment. We recommend that these ARTF data undergo rigorous independent review, and that EPA re-assess worker exposures to better capture the reality of field conditions for many workers.

RECOMMENDATIONS:

[30] MOE. Margin of Exposure determines how close the occupational exposure comes to a no-observed-adverse-effect-level (NOAEL), usually derived from animal studies.

[31] REI. A restricted entry level is the period of time following a pesticide application before EPA considers it is safe to reenter a treated area to perform normal work actions.

- The toxicity database is inadequate and deficient on a number of critical studies. An additional uncertainty factor of at least 10X is reasonable and supported by the failure of key studies to identify a systemic no-effect level.
- The FQPA adjustment factor of 10X is inadequate, and an FQPA adjustment of at least 30X is supported by available data. It is standard practice to add another factor of 3-10X for the lack of a true no-effect level for the relevant endpoint, cholinesterase depression.
- EPA should work with FDA to cancel uses of malathion as a pediculicide. At a minimum, these uses of malathion should be incorporated into the aggregate assessment.
- The acute and chronic RfD should be 2-3X more protective, based on available data regarding the FQPA adjustment and lack of a true no-effect level in immature animals.
- The cancer classification of malathion is too weak, and should be re-classified as a likely human carcinogen, consistent with the 2005 Cancer Guidelines.
- Residential exposures for numerous scenarios are unacceptably excessive.
- The exposure from drinking water and aggregate exposure exceed the EPA level of concern by 4-5 fold, using EPA's calculations, and may be as high as 10-15 fold using more protective RfD values. These exposures are unacceptably excessive.
- EPA has not demonstrated that it can reduce or eliminate malathion uses so as to protect the population from unsafe exposures.
- The exposure to workers, in some cases even with protective equipment, is excessive and unsafe. At a minimum, all worker scenarios must be reassessed based on a 10-hr work day, and without reliance on ARTF data.
- In addition to non-chemical and reduced use alternatives, numerous integrated pest management (IPM) strategies and reduced-risk chemicals are effective replacements for malathion.
- In light of the health risks to the general population, to children, and to workers, and given the availability of less toxic alternatives, the registrant cannot meet its burden of showing that the pesticide does not pose an unreasonable risk of adverse effects, when considering the risks and benefits of its use.

Respectfully,

Jennifer Sass