Appendix F. Reviews of ECOTOX Papers Included in Assessment

A total of 20 references were identified for ODM in a search of ECOTOX conducted in February 2007. Of these, no studies contained toxicity endpoints that were more sensitive than those provided by registrant-submitted data. Information from Sanders (1969 and 1972, ECOTOX reference #885 and #887), Hill et al. (1975, ECOTOX reference # 35243) and Mayer and Ellersieck (1986, ECOTOX reference #6797) provided additional acute toxicity endpoints for guideline and non-guideline species; but they were not more sensitive than endpoints. They are included, but since they are referenced frequently in EFED documents, they are not reviewed independently below. In addition, eight studies provide qualitative information that was used to determine no effects to plants, as well as information that characterizes sublethal effects to animals. Reprints for each of these studies were reviewed to determine their quality. Below is a brief description of each of the studies along with any uncertainties that were identified during the review. The bolded number preceding each of the citations represents the ECOTOX reference number.

ECOTOX Record Number and Citation: 88987 Clemens, G. R., R. E. Hartnagel, J. J. Bare, and J. H. Thyssen. 1990. Teratological, neurochemical, and postnatal neurobehavioral assessment of Metasystox-R, an organophosphate pesticide in the rat. Fundam. Appl. Toxicol. 14:131-143.

Purpose of Review (DP Barcode or Litigation): Litigation

Date of Review: July 30, 2007

Summary of Study Findings: This study demonstrated few effects of ODM with repeated oral exposure during gestation in female laboratory rats. In a one-generation reproduction study, the authors dosed female rats with 0.0 to 4.5 mg/kg of ODM (90.6% purity) orally from Days 6 to 16 of gestation. Females were studied from Day 16 of gestation through Day 21 postpartum to observe body weight, food consumption, and blood and brain ChE activity. Abnormalities were observed in fetuses, and offspring that were delivered were observed for neurobehavioral function with a series of behavioral challenges (e.g., time to righting after being dropped from 38 cm, degree of negative geotaxis, reaction to auditory startle, performance in a maze, activity in an open field, olfactory discrimination, and visual placing). Tremor and reduced food consumption was observed in dams at the highest test dose, but reproductive parameters were not affected. Brain AChE activity was significantly affected in all test groups, and in the two highest test groups brain AChE was depressed to >50% on Day 16 and in the highest test group on Day 20. No significant effects were observed in the offspring. The authors conclude that limited effects occurred as a result of repeated exposures during gestation; however, the AChE effects observed in the brain indicate the potential for sublethal effects and mortality to occur.

Description of Use in Document (QUAL, QUAN, INV): Qualitative

Rationale for Use: The study provides useful qualitative information for sublethal effects.

Limitations of Study: The study was only a one-generation study that followed the offspring for up to 35 days post partum.

Primary Reviewer: Shannon Borges, Biologist
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ECOTOX Record Number and Citation: 88896 Kumari, J., N. B. Krishnamurthy, and V. Vasudev. 1995. Mutagenicity studies with Metasystox-R in mice. Cell Chromosome Res. 18:79-85.

Purpose of Review (DP Barcode or Litigation): Litigation

Date of Review: July 30, 2007

Summary of Study Findings: The investigators administered sublethal doses of 28, 56, and 80 mg/kg Metasystox-R orally to Swiss albino mice (7-8 weeks old). Observations of mutagenicity based on chromosomal aberration and abonormal sperm cells are reported. The authors also note induction of micronuclei, potentially indicating DNA damage. The data from this study requires a revised analysis, but does demonstrate the potential for sublethal mutagenic effects that may affect fertility and reproductive success in mammals.

Description of Use in Document (QUAL, QUAN, INV): Qualitative

Rationale for Use: The study provides useful qualitative information for sublethal effects.

Limitations of Study: The study reports effects based on statistical significance; however, the significance may be misleading because of batches of cells from multiple animals were combined and each cell was considered to be the experimental unit. This results in pseudoreplication.

Primary Reviewer: Shannon Borges, Biologist

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ECOTOX Record Number and Citation: 88893 Lenselink, D. R., J. E. Midtling, and G. L. Kolesari. 1993. Teratogenesis associated with oxydemeton-methyl in the stage 12 chick embryo. Teratology 48:207-211. ECOTOX

Purpose of Review (DP Barcode or Litigation): Litigation

Date of Review: July 30, 2007

Summary of Study Findings: This is a teratogenicity study with domestic chickens (*Gallus domesticus*) in which chick embryos were exposed to ODM (technical grade, 89% purity) at doses ranging from 0.01 mg to 2.00 mg via direct injection into the egg. Survival to later stages was significantly reduced at 0.50 mg and higher doses ($p<0.001$), with none of the embryos surviving at the highest dose level of 2.00 mg. The percentage of animals showing developmental anomalies was significantly greater at dose levels ≥ 0.05; however they did not show a clear dose-response relationship as the 1.00 mg dose group did not show a significant percentage of affected animals. These included the musculoskeletal effects of wry neck, absent or malformed limbs, eye abnormalities, and thoracogastroschisis; and cardiovascular effects such as ventricular septal defects and aortic arch anomalies. This study does demonstrate that ODM has the potential to affect birds during development within the egg. How this may apply to amphibians is unknown, but may indicate some potential for teratogenicity.

Description of Use in Document (QUAL, QUAN, INV): Qualitative

Rationale for Use: The study provides useful qualitative information for sublethal effects.

Limitations of Study: The study does not report whether the dose values used in the study are corrected for percentage of active ingredient, so these values may be lower. Whether the observed effects occur in wild birds is questionable because it is not known whether injection into the egg represents potential exposure that would occur in the field.

Primary Reviewer: Shannon Borges, Biologist

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ECOTOX Record Number and Citation: 12184 Moses, G., K. Ramamurthy, M. J. Chroistopher, and K. J. Rao. 1985. Toxicity evaluation of Heptachlor and Metasystox on freshwater edible fish, *Tilapia mossambica*. Geobios 12:104-107.

Purpose of Review (DP Barcode or Litigation): Litigation

Date of Review: July 30, 2007

Summary of Study Findings: Study provides a 96-hour LC50 value for Metasystox-R, a 25% ai formulated product for tilapia (*Tilapia mossambica*). The value is 6.85 ppm.

Description of Use in Document (QUAL, QUAN, INV): Qualitative.

Rationale for Use: The study provides a point of reference for toxicity in other species that are not typically tested. If there were any need to use toxicity values for formulated products, this study would provide the most sensitive value for this formulation.

Limitations of Study: The study does not report whether the LC50 was adjusted for the percentage of ai contained in the formulated product.

Primary Reviewer: Shannon Borges, Biologist

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ECOTOX Record Number and Citation: 89003 Panda, B. 1983. Effect of the insecticides oxydemeton methyl and thiodemeton on the mitotic and meiotic chromosomes of barley. Environ. Exp. Botany 23:293-296.

Purpose of Review (DP Barcode or Litigation): Litigation

Date of Review: July 30, 2007

Summary of Study Findings: Barley seeds soaked in water containing 100 ppm ai ODM for 6 hours did not demonstrate significant decreases in germination rate compared to controls. This time is approximately at the DNA-synthetic stage of germination. Germination and growth were not affected at the 100 ppm ai concentration. A NOAEC value for growth was determined to be 1500 ppm ai in this study based on seedling height after one week.

Description of Use in Document (QUAL, QUAN, INV): Qualitative.

Rationale for Use: The study provides information demonstrating lack of effects of ODM on plants.

Limitations of Study: The test does not necessarily represent the exposure that would occur in the field, nor does it represent the exposure required by guideline seedling germination and vegetative vigor tests.

Primary Reviewer: Shannon Borges, Biologist

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ECOTOX Record Number and Citation: 89002 Pandita, T. K. 1986. Mutagenic studies on the insecticide Metasystox-R with *Allium cepa*. Cytologia 51:387-392.

Purpose of Review (DP Barcode or Litigation): Litigation

Date of Review: July 30, 2007

Summary of Study Findings: Methods were similar to those used above in the Panda (1983) study. This study using onion showed a NOAEC for seed germination rate of 2000 ppm ai. Chromosomal aberrations were observed and a decrease in pollen fertility was observed, but was not significant at concentrations below 3000 ppm ai.

Description of Use in Document (QUAL, QUAN, INV): Qualitative.

Rationale for Use: The study provides information demonstrating lack of effects of ODM on plants at levels that are applied in the field.

Limitations of Study: The test does not necessarily represent the exposure that would occur in the field, nor does it represent the exposure required by guideline seedling germination and vegetative vigor tests.

Primary Reviewer: Shannon Borges, Biologist

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ECOTOX Record Number and Citation: 89143 Raizada, R. B., M. K. Srivastava, R. P. Singh, R. A. Kaushal, K. P. Gupta, and T. S. S. Dikshith. 1993. Interaction of technical hexachlorocyclohexane and oxydemeton methyl 25 EC to female rats after dermal application. Indian J. Exp. Biol. 31:142-146.

Purpose of Review (DP Barcode or Litigation): Litigation

Date of Review: July 30, 2007

Summary of Study Findings: Female laboratory rats were exposed dermally to ODM as Metasystox-R, Raizada et al. (1993) alone and in combination with hexachlorocyclohexane (lindane), which is a broad-spectrum insecticide. Rats were exposed dermally to 125 mg/kg-bw/day ODM alone and in combination with 100 mg/kg-bw/day HCH for 7, 15, and 30 days (the study does not report whether the dose is corrected for percentage ai in the test material). Mortality was observed in all test groups, but further details are not provided. Exposure to ODM alone for 30 days produced severe sublethal effects, including tremor, dyspnea, salivation, convulsion, and diarrhea. ODM also produced severe necrosis in liver cells and changes in the granular and molecular layer of the cerebellum. Further, significant reductions in brain AChE activity occurred by 15 and 30 days of exposure in the ODM group. The degree of inhibition was >20% in all cases, indicating sufficient AChE depression to cause sublethal effects and behavioral changes. Inhibition was also observed in erythrocyte ChE on all days examined. Effects observed in the ODM-only group were more pronounced in the group receiving the combination of pesticides. This study demonstrates that severe sublethal effects and some mortality may result from dermal exposure to ODM in the field.

Description of Use in Document (QUAL, QUAN, INV): Qualitative.

Rationale for Use: The study provides information on sublethal effects and effects that may occur as a result of the dermal route of exposure.

Limitations of Study: It is not known how this study represents levels of actual exposure. Rats were not tested at different concentrations. Rather they were tested at the same concentration for varying lengths of time. Currently there is no methodology that adequately quantifies dermal exposure, so how well this study represents effects that would be observed in the field is not known.

Primary Reviewer: Shannon Borges, Biologist

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ECOTOX Record Number and Citation: 89144 Tayyaba, K., M. Hasan, F. Islam, and N. H. Khan. 1981. Organophosphate pesticide Metasystox-induced regional alterations in brain nucleic acid metabolism. Indian J. Exp. Biol. 19:688-690.

Purpose of Review (DP Barcode or Litigation): Litigation

Date of Review: July 30, 2007

Summary of Study Findings: **N**ucleic acid metabolism alterations were studied in the brain of laboratory rats as a result of exposure to Metasystox-R (25% ODM). Injections of 4 mg/kg-bw were given to the rats daily for 10 days. Mortality was not observed in any of the rats; however, sublethal effects that were observed included unconsciousness, muscular fasciculations, hyperexcitability to tactile stimuli, convulsions, and ataxia. Further, the authors found that the test material altered the concentration of nucleic acids in the brain and also the functional activity of lysosomal enzymes in the brain. This study provides some additional information on sublethal effects of ODM in mammals.

Description of Use in Document (QUAL, QUAN, INV): Qualitative.

Rationale for Use: The study provides information on sublethal effects.

Limitations of Study: The exposure route in the study is not necessarily relevant to a field situation.

Primary Reviewer: Shannon Borges, Biologist

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