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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

3/5/99

MEMORANDUM

SUBJECT: **Fenthion. Revised Human Health Risk Assessment.** P.C.Code 053301. Case No. 0290. DP Barcode D253930.

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Background

This memorandum serves to revise HED's preliminary human health risk assessment for **Fenthion** (W. Hazel, 4/29/98) by reconsidering the human study used heretofore as the source of dose/endpoint and by addressing comments submitted by Bayer Corporation, Agricultural Division to the Docket in response to the preliminary assessment. Note that no other public comments applied specifically to the human health risk assessment for fenthion; consequently, these will not be addressed here. In the preliminary assessment, acute dietary, chronic dietary, occupational, and residential risks were found to be above the Agency's level of concern. Bayer's comments on the preliminary risk assessment included statements that voluntary cancellation of a bird control product and two granular products is being pursued, that a proposal to prohibit human flaggers will be submitted, and that EPA made an error in the calculation of average aerial application rate; these comments have been addressed in the 1/7/99 W. Hazel memorandum responding to public comments.

Fenthion is an organophosphate insecticide. Cumulative risk assessment considering risks from

other pesticides having a common mechanism of toxicity was not addressed in the preliminary assessment and is not addressed in this document.

Fenthion is formulated as soluble concentrates, ready-to-use products, and impregnated material (ear tag) for livestock direct animal treatments and wide area mosquito (adulticide) control. There are no homeowner uses of fenthion although there is residential exposure resulting from the mosquito abatement use.

Technical fenthion is classified as Toxicity Category II for oral, dermal, and inhalation toxicity, Category III for eye irritation, and Category IV for dermal irritation. Cholinesterase inhibition, with or without attendant cholinergic signs, was the principal toxic effect associated with all risk assessment endpoints. Doses and endpoints for all exposure scenarios were derived from an oral 2-year monkey study. Results of the 28-day human oral dosing study support use of the endpoint from the 2-year monkey study for risk assessment purposes. Recently submitted acute and subchronic neurotoxicity studies (rat) have satisfied earlier deficiencies and have, in conjunction with developmental toxicity studies, obviated the need for a developmental neurotoxicity study. Also, because new developmental toxicity and neurotoxicity studies did not demonstrate an increased sensitivity to infants and children, HED's Hazard Identification Assessment Review Committee (HIARC) and HED's FQPA Safety Factor Committee determined that the 10x FQPA uncertainty factor should be removed taking hazard **and** exposure considerations into account. There was no evidence of carcinogenicity in any fenthion study. A new dominant lethal mutagenicity study is required to confirm the negative results of an older study.

REEVALUATION OF THE HUMAN STUDY

In response to internal and external concerns, HED is systematically reevaluating any toxicology studies making use of humans as subjects if such studies are used, directly or supportively, as the source of dose and endpoint for a human health risk assessment. An *ad hoc* group of HED toxicologists selected a nonhuman study in lieu of the human study: the 2-year monkey study was chosen for all risk assessments (J. Rowland; 12/1/98). HIARC (2/19/99) determined that the 28-day human study previously used for risk assessment purposes should be classified as "supplemental" because it only included male subjects and it had limited test power; thus, it is not considered rigorous enough for risk assessment purposes except in a supplemental way (memorandum forthcoming). Further, HIARC determined the appropriate Uncertainty Factors to assign to each dose to be used for human health risk assessment. Note that MOE denotes "Margin of Exposure." The outcome is presented in Table 1.

Table 1. Human vs. Animal Endpoints and Uncertainty Factor Assignment.

Exposure period	Use of human study (preliminary risk assessment)	Use of animal study (this revised risk assessment)	Comments re: animal study endpoint/dose/UF
Acute dietary	NOAEL = 0.07 mg/kg UF = 10 aRfD = 0.007 mg/kg	NOAEL = 0.07 mg/kg UF = 30 **aRfD = 0.002 mg/kg**	True NOAEL in monkey during first week. Supported by human. Interspecies 10x reduced to 3x.
Chronic dietary	NOAEL/ LOAEL = 0.02 mg/kg/day UF = 30 RfD = 0.0007 mg/kg/day	NOAEL/LOAEL = 0.02 mg/kg/day UF = 300 **RfD = 0.00007 mg/kg/day**	Threshold dose used. UF: 10x interspecies, 10x intraspecies, 3x for lack of a true NOAEL
Short-term dermal	Oral NOAEL = 0.07 mg/kg/day MOE = 10	Oral NOAEL = 0.07 mg/kg/day MOE = 30 (20% dermal absorption)	True NOAEL in monkey during first week. Supported by human. Interspecies 10x reduced to 3x.
Intermediate-term dermal	Oral NOAEL/LOAEL = 0.02 mg/kg/day MOE = 30	Oral NOAEL/LOAEL = 0.02 mg/kg/day MOE = 300 (20% dermal absorption)	Threshold dose used. UF: 10x interspecies, 10x intraspecies, 3x for lack of a true NOAEL
Short-term inhalation	Not applicable	Oral NOAEL = 0.07 mg/kg/day MOE = 30 (100% absorption; convert to equivalent oral dose.)	True NOAEL in monkey during first week. Supported by human. Interspecies 10x reduced to 3x.
Intermediate-term inhalation	Not applicable	Oral NOAEL/LOAEL = 0.02 mg/kg/day MOE = 300 (100% absorption; convert to equivalent oral dose.)	Threshold dose used. UF: 10x interspecies, 10x intraspecies, 3x for lack of a true NOAEL

OCCUPATIONAL RISK

PRELIMINARY RISK ASSESSMENT. Significant occupational exposure to fenthion was determined to be likely based on surrogate exposure estimates using the Pesticide Handler Exposure Database (PHED). Dermal and inhalation exposures were combined because inhalation exposures were quite small compared to those associated with the dermal route of exposure. For short- and intermediate-term risk assessment, the doses used were 0.07 and 0.02 mg/kg/day, respectively, from the 28-day human oral study in which plasma cholinesterase inhibition was the endpoint (threshold NOAEL/LOAEL was 0.02 mg/kg/day). Dermal absorption was assumed to be 20% based on a comparison of rabbit oral and dermal toxicity studies. Inhalation absorption was assumed to be the default level of 100% compared to absorption via the oral route of administration. Calculation of combined dermal and inhalation risks resulted in short-term MOEs of <6 for occupational scenarios involving mixing/loading and applying liquids aerially even after application of engineering controls (closed mixing or closed cockpit); short-term risks were considered adequately protective (MOE >10) for other exposure scenarios utilizing engineering controls. Intermediate-term risks to all occupational scenarios using engineering controls were unacceptable (MOEs of 1-29 when 30 was considered protective) except in the case of the granular loading scenario for aerial applications which was acceptable using engineering controls.

REVISED RISK ASSESSMENT. The exposure values and the NOAELs used to calculate short-term and intermediate-term occupational risk have not changed since the preliminary risk assessment. However, the increases in the uncertainty factor (UF) associated with interspecies variability (previously set at 1x) has resulted in corresponding increases in EPA's levels of concern (MOE considered to be protective) from 10 to 30 for short-term and from 30 to 300 for intermediate-term risk assessments due to the use of an animal, rather than human, toxicity study (see Table 1). As a result, exposures associated with two additional short-term occupational scenarios, also assuming use of engineering controls, now result in MOEs less than 30 which is the Agency's level of concern: the MOE is 13 for ground ULV applicators and 26 for flaggers. Recall that Bayer intends to propose a prohibition against use of human flaggers. Although the intermediate-term MOEs remain 1-29, these risks must now be considered in relation to the increased level of concern (MOE = 300) for this duration of exposure, rendering occupational risks for this exposure duration well above the Agency's level of concern.

ACUTE DIETARY RISK

PRELIMINARY RISK ASSESSMENT. In order to refine dietary exposure, anticipated residue data were generated; because all crop uses of fenthion and use on poultry are not being supported, these anticipated residues represent only milk and tissues of cattle. Tolerance level residues were used for swine tissues. In the case of fenthion, the magnitude of residue data for milk and the meat, fat, and meat by-products of cattle do not represent the label directions for direct animal treatments in terms of application rate or preslaughter interval. As a result, data from the existing livestock dermal metabolism studies were extrapolated to reflect current label directions to estimate upper bound residues in milk and cattle tissues. It was assumed that 100% of livestock were treated. In the case of all cattle tissues, these residues represented an increase over the current tolerance levels.

The preliminary risk assessment revealed an acute dietary risk concern for fenthion. The endpoint used for acute dietary risk assessment was plasma cholinesterase inhibition observed at the 24-hour interval in the 28-day human oral dosing study; the dose used for risk assessment was 0.07 mg/kg/day. MOEs from an acute DRES run, conducted 9/23/97, were 5 for non-nursing infants (<1 year) and children (1-6 years) and 7 for the general U.S. population and males and females (13 plus). An MOE of 10 was considered protective for the preliminary acute dietary risk assessments.

REVISED RISK ASSESSMENT. This revised risk assessment reflects the following: (i) use of the same upper bound estimates of fenthion residue levels in cattle tissues and milk used in the preliminary risk assessment; (ii) use of the dose, endpoint, and uncertainty factor recently selected based on an animal (monkey) oral dosing study (Table 1); (iii) use of estimated maximum percent livestock treated figures provided by OPP's Biological and Economic Analysis Division (A. Halvorson, 2/4/99); and (iv) use of the DEEM™ software to generate acute dietary risk figures based on the variables listed above and the distribution of consumption from the USDA 1989-92 CSFII. The percent livestock treated are as follows: 12% of beef cattle, 4% of dairy cattle, and 9% of swine. We note that the figure for swine is based on a 1994 Nebraska State University survey and, consequently, that it may be a conservative estimate not accurately representing national usage of fenthion on swine; the Agency will use this figure until such time as national usage is known.

Acute risks have been recalculated as described above. Risks to various population subgroups are presented in Table 2 as both MOEs and as % Acute RfD (aRfD) as per the 2/23/99 C. Swartz memorandum. Note that an MOE of 30 is considered to be protective (aRfD = 0.002 mg/kg).

Table 2. Revised Acute Dietary (99.9th percentile) and Chronic Dietary Risks.

Population subgroup	Acute dietary MOE (30 is the level of concern)	Acute dietary risk (%aRfD)	Chronic dietary risk (%RfD)
U.S. population	21	165	134
All infants (<1 year)	16	207	58
Nursing infants (<1 year)	21	165	51
Non-nursing infants (<1 year)	16	215	61
Children (1-6 years)	12	284	268
Children (7-12 years)	18	186	194
Females (13-50 years)	29	119	104
Males (20+ years)	27	126	125

Beef meat and fat are the highest contributors to the chronic dietary risk for all population subgroups. However, this is not predictive of major contributors to the acute dietary risk. We stress that the exposure values used were upper bound and were obtained via extrapolation of nonrepresentative residue data. Therefore, we expect that the required livestock dermal/eartag treatment studies will permit potentially significant refinement of the risk estimates. Also, national swine usage figures may permit additional refinement although, compared to beef meat and fat, it is likely that pork commodities do not contribute as significantly to the acute dietary risk.

In order to better understand the acute dietary risk contributors and the risk distributions within potentially exposed population subgroups, the Agency determined: (i) the percentiles of exposure at which risk fell below our level of concern (≤aRfD) and (ii) acute risks calculated without the consumption of milk; this information is presented in Table 3 (C. Swartz; 3/99; in preparation).

Table 3. Revised acute dietary risk: percentiles of exposure and risk contribution due to milk.

Population subgroup	%aRfD at 99.9th percentile (all foods)	Percentile of all-food exposure at which %aRfD is ≤100 (%aRfD at that percentile)	%aRfD at 99.9th percentile (excluding milk)
U.S. population	165	99.5th (99)	165
All infants (<1 year)	207	99th-99.5th (70-105)	202
Nursing infants (<1 year)	165	99th-99.5th (72-131)	159
Non-nursing infants (<1 year)	215	99.5th (101)	214
Children (1-6 years)	284	97.5th (97)	284
Children (7-12 years)	186	99th (98)	187
Females (13-50 years)	119	99.75th (92)	120
Males (20+ years)	126	99.75th (99)	125

Based on the information in Table 3, acute dietary risks are the same or very similar whether or not milk is included in the diet. It is apparent, therefore, that milk is not a significant contributor to acute dietary risk for any population subgroup, including infants and children. Also presented in Table 3, the percentiles of exposure at which the acute dietary risk rises above/drops below the Agency's level of concern (aRfD) are all below the 99.9th percentile considered appropriate for this probabilistic assessment. Note that, except in the case of children (1-6 years), risk becomes acceptable at or above the 99th percentile.

CHRONIC DIETARY RISK

PRELIMINARY RISK ASSESSMENT. A chronic DRES run was conducted 9/23/97. The RfD of 0.0007 mg/kg/day was used for risk calculations; this was based on an uncertainty factor of 30 and a LOAEL of 0.02 mg/kg/day for the threshold effect of plasma cholinesterase inhibition observed in the 28-day human oral dosing study supported by the 2-year oral monkey study. Chronic dietary risks were calculated using the same upper bound exposure estimates described above for the acute dietary risk assessment. Chronic dietary risks were unacceptable for all population subgroups except nursing infants (<1 year). The chronic risks were generally 150-250% of the RfD; we will specifically note the following: U.S. population (209%), non-nursing infants <1 year (201%), children 1-6 years (387%), and children 7-12 years (300%). As the anticipated livestock residue levels are quite conservative (yet not refinable at this time), we expect that the required livestock magnitude of the residue studies will permit refinement and a much higher level of confidence in the database.

REVISED RISK ASSESSMENT. This revised risk assessment reflects the following: (i) use of the same upper bound estimates of fenthion residue levels in cattle tissues and milk used in the preliminary risk assessment; (ii) use of the dose, endpoint, and uncertainty factor recently selected based on an animal (monkey) oral dosing study (Table 1); (iii) use of estimated maximum percent livestock treated figures provided by OPP's Biological and Economic Analysis Division (A. Halvorson, 2/4/99); and (iv) use of the DEEM™ software to generate chronic dietary risk figures based on the variables listed above and the dietary consumption figures from the USDA 1989-92 CSFII. The percent livestock treated are as follows: 12% of beef cattle, 4% of dairy cattle, and 9% of swine. We note that the figure for swine is based on a 1994 Nebraska State University survey and, consequently, that it may be a conservative estimate not accurately representing national usage of fenthion on swine; the Agency will use this figure until such time as national usage is known.

Chronic dietary risks have been recalculated as described above. Risks to various population subgroups are presented in Table 2 as % chronic RfD as per the 2/23/99 C. Swartz memorandum. Note that the chronic risks have declined somewhat compared to the preliminary assessment, i.e., they are generally 50-150% RfD as opposed to the 150-250% RfD in the preliminary risk assessment. Particularly notable changes include the three infant subpopulations for which risk is now below the Agency's level of concern (51-61% RfD); this is likely due to the low (4%) percent dairy cattle treated, the fairly low (0.005 ppm) fenthion residue level in milk, and the lower consumption of beef meat and fat by these subgroups compared to other groups. It appears as though the tenfold increase in the uncertainty factor for interspecies variability has largely offset the use of percent livestock treated data in this revised chronic dietary risk assessment for all groups except infants.

RESIDENTIAL RISK

PRELIMINARY RISK ASSESSMENT. Although there are no homeowner uses, residential exposure assessments were conducted to permit risk calculations reflecting the use of fenthion as a residential wide area mosquito adulticide. The AgDRIFT model was used to estimate deposition of residues following aerial and ULV applications whereas published studies were used to calculate residue deposition following ground-applied ULV treatments. The Residential SOPs were used to calculate dermal exposures and subsequent risks associated therefrom. Short-term residential risks to toddlers and adults were acceptable (MOE >10) on the day of treatment: MOEs were >11 following aerial ULV and >90 reflecting ground-based ULV applications. Short-term risks declined thereafter (MOEs increasing with time, reaching >500 by day 30). In the case of intermediate-term risk, residential MOEs were 80-300, i.e., above the protective level of 30 following ground ULV applications. Residential exposure to aerial ULV applications (typical rates) resulted in acceptable risk (MOE of 38) to adults; risks to toddlers (exposed to typical or maximum rates) and adults (maximum rate only) were unacceptable (MOEs of 10-20) reflecting aerial ULV mosquito abatement treatments.

REVISED RISK ASSESSMENT. Residential risks have been refined to reflect the following: (i) use of the corrected average aerial application rate (11% reduction in residential exposure following aerial mosquitocide applications) discussed in the 1/7/99 W. Hazel response to public comments and (ii) comparison of MOEs with the new EPA levels of concern for short-term and intermediate-term duration risk assessments brought about by the selection of the animal study to replace the 28-day human study as the source of dose and endpoint for use in risk assessment (see Table 1). The MOEs for regulatory purposes are typically based upon the maximum label rate which is 0.1 lb ai/A for aerial and 0.03 lb ai/A for ground applications. Therefore, the small changes in MOEs reflecting the average aerial rate correction are of minor regulatory concern. The increased uncertainty factor **is** a significant change incorporated into this revised risk assessment. As a result, **short-term risks** are now above EPA's level of concern, i.e. MOE <30, at the maximum aerial label rate until 3 days posttreatment for adults and until 10 days posttreatment for toddlers. Even at the corrected typical/average aerial rate, the toddler risk does not fall below our level of concern until day 3 posttreatment. **Intermediate-term risks** to both toddlers and adults are now of concern (MOE <300) at the 1x label rate (MOEs = 10-20 for aerial and 83-170 for ground). Even at the corrected typical/average rate, MOEs are 20-43 following aerial treatment and 160 (toddlers) or 310 (adults) following ground application.

AGGREGATE RISK

Aggregate exposure to fenthion was not calculated in the preliminary risk assessment and will not be calculated at this time. Acute and chronic dietary risks exceed the Agency's levels of concern. There is no residential use of fenthion; however, residential exposure to fenthion as a result of mosquito abatement programs is expected to result in unacceptable short-term and intermediate-term risks as noted above. GENEEC model estimates of fenthion water concentrations are available but we are not aware of water monitoring data.

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ATTACHMENTS

Attachment 1. J. Rowland/HIARC. 12/1/98. Selection of animal endpoint for fenthion in lieu of the human study.
Attachment 2. J. Rowland/HIARC. 2/19/99. Determination of appropriate uncertainty factors for hazard endpoints for fenthion human health risk assessment.
Attachment 3. C. Swartz. 2/23/99. Revised fenthion chronic and acute dietary exposure and risk analysis (D253503).
Attachment 4. C. Swartz. 3/ /99. Revised acute risk assessment excluding milk and detailing percentiles of exposure at which risk drops below EPA's level of concern (D253964).

cc: W. Hazel (RRB-1), C. Olinger (RRB-1), C. Swartz (RRB-1), J. Dawson (RRB-1), List A file, EFED, LAN files
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