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MEMORANDUM

SUBJECT: **Phosmet.** (Chemical ID No. 059201/List A Reregistration Case No. 0242). HED Review of the Gowan Co. Probabilistic (Monte Carlo) Acute Dietary Exposure and Risk Assessment. MRID Nos. 44771101 and 44771102. DP Barcode No. D254657.

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Background

An acute dietary exposure and risk analysis was completed (C. Swartz, 10/9/98, D250037) in conjunction with the HED preliminary human health risk assessment for phosmet (C. Swartz, 10/30/98, D236026). Although anticipated residues (ARs) for some blended commodities were used in the deterministic analysis, acute dietary exposure and risk greatly exceeded HED's level of concern. The most highly exposed population subgroups were infants and children, with up to 2,000% of the acute reference dose (aRfD) consumed.

In response to the Agency's preliminary risk assessment, Gowan Co. has submitted a probabilistic acute dietary exposure and risk analysis (MRID Nos. 44771101 and 44771102, 3/5/99). The registrant submission is reviewed herein with respect to current HED policies for

conducting acute probabilistic dietary risk assessments. An HED in-house probabilistic analysis will be completed in conjunction with a revised human health risk assessment for phosmet. HED methods for conducting probabilistic acute dietary exposure analyses have changed significantly since the preliminary risk assessment was issued, and subsequent to the Gowan submission. Therefore, the HED in-house assessment will rely heavily on use of monitoring data from the USDA Pesticide Data Program (PDP) and the Food and Drug Administration (FDA). The HED analysis is anticipated to generate a more refined assessment of dietary exposure than the current registrant submission.

Conclusion/Recommendation

The Gowan analysis results in acute dietary risk which is below HED's level of concern. However, the Gowan analysis was not conducted in accordance with HED policies because of the way in which some processing factors were applied and since the weighted average, rather than the estimated maximum, of percent crop treated (%CT) was used. The registrant's probabilistic analysis is not acceptable; however, field trial and processing study data discussed in the Gowan submission have been verified, and can be used in the HED in-house probabilistic acute dietary exposure analysis. A more detailed examination of the residue decline kinetics calculations provided in the submission will be undertaken if necessary for risk mitigation purposes.

DETAILED CONSIDERATIONS

Model/Consumption Data

The registrant probabilistic assessment was conducted using the Dietary Exposure Evaluation Model (DEEM™). The analysis used consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. The specific recipe translations for consumption of food forms used in the phosmet dietary exposure assessment were included in the submission [MRID No. 44771102].

HED Comment

The registrant submission is adequate with respect to documentation of the dietary exposure model and the consumption data used; the model and consumption data used are acceptable.

Hazard Identification

Pending submission of acute and subchronic neurotoxicity studies, the HED preliminary acute dietary exposure analysis was completed using a NOAEL of 1.1 mg/kg/day selected from a rat chronic/oncogenicity study. Uncertainty factors applied to the NOAEL to derive the corresponding acute reference dose (aRfD, 0.0037 mg/kg/day) included 100X for interspecies extrapolation and intraspecies variability and 3X for uncertainty regarding the extra sensitivity to

infants and children.

In the current analysis, the registrant used an acute dietary NOAEL of 4.5 mg/kg/day selected from a rat acute neurotoxicity study which had not been submitted to the Agency when the preliminary risk assessment was completed. The acceptable margin of exposure (MOE, equivalent to the NOAEL/exposure) was cited as >100.

HED Comment

An acute neurotoxicity study in the rat was submitted and found to be acceptable (MRID No. 44673301); plasma, red blood cell and brain cholinesterase inhibition were observed at the LOAEL of 22.5 mg/kg/day (K. Raffaele, 2/3/99, D250525). In meetings held 7/8/99 and 7/15/99, the HED Hazard Identification Assessment Review Committee (HIARC) selected the NOAEL of 4.5 mg/kg/day from the acute neurotoxicity study for acute dietary risk assessment. The HIARC recommended the additional safety factor required by the Food Quality Protection Act (FQPA, 1996), previously reduced to 3X for phosmet pending submission of required neurotoxicity studies, be removed (reduced to 1X). In a meeting held 7/12/99 and in subsequent communications, the HED FQPA Safety Factor Committee considered the quality and depth of the exposure database in conjunction with HIARC recommendations, and removed (reduced to 1X) the FQPA Safety Factor (memo, B. Tarplee, 7/21/99).

In current HED risk assessments, acute dietary exposure is referred to in terms of the percent of the acute population adjusted dose (aPAD) consumed. The aPAD is defined as an acute reference dose (aRfD) which includes the FQPA safety factor (1X, 3X or 10X). For phosmet, acute dietary exposure should be compared to the aPAD of 0.045 mg/kg/day, which is equivalent to the acute RfD. For the purpose of comparison with the Gowan assessment, the corresponding acceptable MOE is >100. Therefore, HED concludes that the dose/endpoint used in the registrant submission is acceptable.

Use of % Crop Treated (%CT)

The Gowan summary stated that weighted average %CT estimates generated by BEAD/OPP and cited in the 8/1/96 D. Hrdy memo (D224581, D226330) were used in the analysis. The registrant generated residue distribution files (RDFs) for many commodities, but used a single point estimate for kiwi and nuts. In the RDFs generated using field trial data, the adjustment for %CT was made by adding residues of 0 ppm corresponding to the % of the crop not treated. However, for nuts and kiwi, the %CT was entered into DEEM™ as adjustment factor 2, which was applied in the analysis.

HED Comment

The registrant stated that use of estimated maximum %CT for every crop results in a conservative estimate of exposure; in addition, the registrant stated that since weighted average

%CT estimates rely more heavily on recent years of usage data, they are more realistic. However, current HED policy dictates that weighted average %CT can only be used in chronic dietary exposure analyses. The estimated maximum is appropriate for use in acute dietary exposure analyses, which reflect the maximum exposure that could occur on a single day. The registrant's use of the weighted average %CT in the probabilistic acute dietary exposure analysis is not in accordance with current Agency guidelines, and is therefore unacceptable.

The application of the %CT as adjustment factor 2 in acute analyses conducted using the DEEM™ software is only appropriate for blended commodities. Currently, kiwi fruit are considered to be not-blended, and the registrant's application of the %CT as adjustment factor 2 in the analysis is inappropriate. A residue distribution file should have been prepared from field trial data.

Application of Processing Factors

The registrant cited several processing studies which were used to derive processing factors (PFs) for the analysis. The specific processing studies were discussed, and the submission included a detailed table of the PFs used as adjustment factor 1 in the analysis.

Apple processing data (MRID No. 41840401) were summarized in previous Agency memoranda (D. Hrdy, 8/1/96, P. A. Deschamp, 4/7/92), and were deemed acceptable for the purpose of risk assessment. In the Gowan analysis, the PF for canned apples (0.028X) was used as a surrogate for all cooked apples; in addition, certain PFs were multiplied, i.e. $PF_{dried\ apples}$ x $PF_{canned\ apples}$ = $PF_{cooked\ dried\ apples}$. The apple processing factors were used for relevant apple and pear food forms:

Table 1. Apple Processing Factors (MRID No. 41840401).

Food Form	Phosmet (ppm)	Phosmet oxon (ppm)	Total Residue (ppm)	Processing Factor
Raw apples	12.85	0.05	12.9	n/a
Peeled apples	1.05	0.05	1.1	0.085271
Canned apples	0.32	0.05	0.37	0.028682
Applesauce	0.95	0.05	1.00	0.077519
Unclarified juice	5.3	0.05	1.45	0.414729
Clarified juice	1.4	0.05	1.45	0.112403
Dried apples	1.22	0.05	1.27	0.09845

The peach processing study (41836701) was summarized in the Gowan submission:

Table 2. Peach Processing Factors (MRID No. 41836701).[1]

Food Form	Phosmet (ppm)	Phosmet oxon (ppm)	Total Residue (ppm)	Processing Factor
Raw peaches	13.1, 10	0.082, 0.072	13.182, 10.072 (11.627)	n/a
Washed peaches	10.6	0.202	10.802	0.929044
Peeled peaches	0.182	0.05	0.232	0.019954
Canned peaches	0.075	0.05	0.125	0.010751
Dried peaches	0.392, 0.3	0.05, 0.05	0.422, 0.35	0.038015, 0.034059 (0.036037)

[1] Raw and dried peaches were analyzed in duplicate. The duplicate residue values are presented, along with the (average).

Peach processing factors were translated to other stone fruits and berries (other than grapes and cherries). The canned peach PF was used for cooked peaches, and the peeled peach PF was used for peach juice/nectar. Certain PFs were multiplied, as was the case with apples.

Two grape processing studies were summarized in the registrant submission [MRID Nos. 43391801 (raisins) and 00037175 (juice)]. The PFs from these studies were used for grape and cherry food forms, as well as for berry juice. The average PFs were 0.68 (juice) and 0.92 (raisins).

A prune processing study (MRID No. 43391802) was cited in which a PF of 0.32 was determined. A potato processing study (MRID No. 43401301) was used to generate PFs for potato food forms. The mean total residue of 0.099 ppm in tubers processed into chips, wet peel and granules resulted in PFs of <0.5051 (chips), 0.9596 (wet peel), and <0.5051 (granules). The registrant's DEEM™ analysis used a PF of 0.5 for raw potatoes, based on the PF of 0.5 for granules. A cooking factor of 0.05 was applied to all cooked potato, sweet potato and pea food forms, based on the apple and peach processing studies, which yielded cooking factors of 0.028 and 0.011, respectively. The cooking factor of 0.05 assumed for potatoes and other commodities was deemed conservative by the registrant, based on the results of these studies. For cooked potatoes, the granule PF was multiplied by the cooking factor.

The registrant cited a peeling factor of 0.1 for kiwi fruit, based on the finding that residues in the fruit are generally 2.9% of the total residue; the MRID citation for this factor was not included in the discussion of the data. The PF of 0.1 was deemed to be conservative by the registrant.

HED Comment

The apple, grape and prune processing data were used in the HED deterministic acute dietary exposure analysis. The peach processing data were not used in the previous HED analysis, but are acceptable for use in dietary exposure and risk assessments.

In general, the Agency discourages multiplication of processing factors (as described above for cooked dried apples) without specific knowledge of the exact nature of typical commercial processing procedures. This practice may result in "double counting" the reduction or concentration of residues during processing. HED has specifically advised against using a 0.1 PF for kiwi fruit, since there are no data supporting the assumption that all kiwi are peeled prior to consumption (8/1/96 D. Hrdy memo).

As noted above, Gowan translated the canned apple PF to all cooked apples; however, the canned apple PF should not be translated to all cooked apples (i.e., cooked, baked and fried), since the processing method (including removal of the skin) and length, time and temperature of cooking methods may affect residues in these food forms. The average PF of 0.053010 (0.05) for canned apple food forms, based on the average PF from canned apples and applesauce should be applied to all canned food forms, as well as cooked and boiled food forms.

Similarly, the 0.05 PF, considered by Gowan to be an upper-bound estimate of a cooking factor based on the canned apple/peach PFs, should not be used for all cooked food forms of potato, sweet potato and peas. The registrant did not provide the rationale or justification for translating peach PFs to berries.

The registrant used PFs of essentially 0 (i.e. <0.001x) for the following food forms: dried apples (cooked, baked, cooked:dried, and frozen:cooked); dried pears (baked, boiled, and cooked:dried); dried apricots (cooked, baked and cooked:dried), dried peaches (baked and cooked:dried); plums/prune-juice (baked and canned:cooked); peaches-juice (canned:cooked and canned:baked); and pears-nectar (canned:cooked and canned:baked). These PFs were generated through multiplication of cooking/drying PFs, which is inappropriate due to translation of the peach and apple canning factors to all other cooked food forms for pome and stone fruit. The use of these PFs results in exposure to these commodities being excluded from the analysis.

HED notes that the PF determined for potato granules was used for raw peeled potatoes, which is not appropriate. Use of the granule PF for dried potatoes is appropriate, but not when combined with the 0.05 PF for cooked potatoes (see above).

In summary, while the registrant relied on acceptable data for generation of the PFs used in the analysis, application of certain factors and combinations of factors were not justified.

Monitoring Data

The registrant incorporated monitoring data generated by the USDA PDP during 1994-1996, which were used for blended food forms of the following RACs: apples (1994-1996); apple juice (1996); grapes (1994-1996); peaches (1994-1996); and sweet potatoes (1996). Apple data were translated to all relevant blended pear food forms. The data were incorporated into RDFs consisting of the detected residues and non-detects at ½ the limit of detection (LOD).

HED Comment

The registrant's use of the monitoring data was appropriate at the time the analysis was completed. However, current HED policy allows for use of PDP composite residue data in acute dietary exposure analyses following statistical generation of single unit residue values for "single serving" commodities (i.e. an apple or pear).

Field Trial Data

The registrant used field trial residue data to complete the probabilistic analysis. Since numerous commodities had a limited number of trials conducted at 1X (with respect to both rate, number of applications and PHI), a detailed justification was provided for calculating 1X residues from other data based on the purported linearity of the decline in residues. A discussion of residue decline kinetics for phosmet was included in the submission. Data from the dislodgeable foliar residue studies submitted for occupational and residential exposure assessments were cited as support for this approach.

The registrant indicated that West coast apples are treated at higher rates for codling moth control (4 lb ai/A), while East coast apple application rates are 2.7 times lower (1.5 lb ai/A). Therefore, two separate dietary exposure assessments were completed, based on both empirical and extrapolated field trial data, to allow for the difference in apple application rates.

HED Comment

Since the current HED approach to completing probabilistic acute dietary exposure analyses using monitoring data permits significant refinement over the use of field trial data, commodity-specific field trial data have not been presented in great detail. There are certain commodities for which use of field trial data may be necessary; these data will be discussed in more detail in the HED in-house assessment. A more detailed examination of the residue decline kinetics calculations provided in the submission will be undertaken if necessary for risk mitigation purposes.

HED notes that PDP monitoring data are collected to reflect an appropriate regional distribution of production, and therefore the difference in apple use patterns should be accounted for in the range of residues found in the monitoring data.

Results

There were no significant differences between the results conducted based on East vs. West coast application rates for apples. The MOEs determined by the registrant are presented in Table 3.

Table 3. Summary of Gown Dietary Risk Estimates for Phosmet.[1]

Population Subgroup	East Coast Apple Rate		West Coast Apple Rate	
	Exposure (mg/kg/day)	MOE	Exposure (mg/kg/day)	MOE
General US Pop.	0.017951	251	0.018997	237
Infants (nursing)	0.026574	169	0.029032	155
Infants (non-nursing)	0.001994	2257	0.002039	2207
Children (1-6 years)	0.035018	129	0.036285	124
Children (1-7 years)	0.024377	185	0.025563	176
Females (13-19 years)	0.011826	381	0.012578	358
Females (20+ years)	0.012672	355	0.012808	351
Males (13-19 years)	0.010410	432	0.010445	431
Males (20+ years)	0.010664	422	0.010899	413

[1] Results in the table reflect the 99.9th percentile of exposure. An acceptable MOE is considered to be greater than 100.

HED Comment

The Gowan analysis results in acute dietary risk which is below HED's level of concern. Although the apple application rate and concomitant residues in the RDF for West coast apples were higher, the estimated dietary exposure and risk were lower than those generated using the East coast apple rate and residue data. Upon further examination of the residue inputs, HED noted that in the West coast apple analysis, the field trial data for cranberries were based on a 7-day PHI, while in the East coast analysis, the cranberry residue data from a 21-day PHI were used. This may account for the slightly higher exposure estimates in the East coast analysis. In both analyses, the most highly exposed population subgroup was children, 1-6 years old.

cc: Reviewer (C. Swartz), List A File, SF, DRES File.
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Dietary Exposure SAC Review:7/20/99