

Office of Environmental Health Hazard Assessment



Agency Secretary

Joan E. Denton, Ph.D., Director

Headquarters • 1001 I Street • Sacramento, California 95814

Mailing Address: P.O. Box 4010 • Sacramento, California 95812-4010

Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612



Arnold Schwarzenegger
Governor

MEMORANDUM

TO: Gary T. Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
830 K Street
Sacramento, California 95814-3510

FROM: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section

DATE: April 9, 2003

SUBJECT: COMMENTS AND RECOMMENDATIONS ON THE DRAFT METAM
SODIUM RISK CHARACTERIZATION DOCUMENT PREPARED BY THE
DEPARTMENT OF PESTICIDE REGULATION

Thank you for the opportunity to review the draft risk characterization document (RCD) for metam sodium prepared by the Department of Pesticide Regulation (DPR). The Office of Environmental Health Hazard Assessment (OEHHA) reviews risk assessments prepared by DPR under the general authority of the Health and Safety Code, Section 59004, and also under the Food and Agricultural Code (FAC), Section 13129, in which OEHHA has the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticide active ingredients.

In general, we believe the draft RCD includes the important studies of concern and the bases for the determinations made in the document are thoughtful and clearly presented. We have organized our comments into the following categories: 1) non-cancer endpoints, 2) cancer endpoint, 3) exposure assessment, and 4) specific comments.

California Environmental Protection Agency

The energy challenge facing California is real. Every Californian needs to take immediate action to reduce energy consumption.



Printed on Recycled Paper

1) *Non-cancer Endpoint Selection and Selection of Uncertainty Factors*

A. Rat developmental toxicity

A rat developmental toxicity study (Zeneca) is discussed on pages 55 to 57 of the draft RCD. In this study, the low dose level (5.0 mg/kg-day) is selected as the developmental no-observed-adverse-effect level (NOAEL) based on increased incidences of delayed skeletal ossification and decreased mean fetal weight at the mid dose level (20 mg/kg-day). However, delayed fetal ossification was also observed in the low dose group. The draft RCD concludes that the ossification delays in the low dose group were not test article-related because:

- (i) The reduction in mean fetal weight ($p > 0.05$) in the low dose group was not statistically significant.
- (ii) The incidences of fetal ossification delay (both 2nd centrum and calcaneum) in the low dose group were below the mean incidences for ten historical control groups, and within the historical ranges.

On the other hand, OEHHA staff determines that the following evidence suggests that these ossification delays in the low dose animals are test article-related:

- (iii) The delays in ossification were statistically significant compared to the concurrent control; at the $p = 0.05$ level for the 2nd centrum and at the $p = 0.01$ level for the calcaneum (refer to Table 19 in the draft RCD).
- (iv) Both delays exhibited a dose-response over the entire dose range.
- (v) Maternal toxicity was also observed in the low dose group in the form of reduced maternal weight gain ($p < 0.05$) and decreased food consumption ($p < 0.01$), possibly contributing to the ossification delays in the low dose fetus.

There are two important points to consider when interpreting these data. The first is that if delayed ossification can be induced by the test article at doses below those that result in decreased fetal body weight, then conclusion (i) made in the draft RCD is not relevant. Secondly, with regard to the use of historical controls compared to the use of concurrent controls, it should be noted that the concurrent control values for unossified 2nd centrum (16.9 percent) and unossified calcaneum (43.3 percent) are in the low ends of the ranges for historical controls (draft RCD, Table 19), suggesting that the concurrent control value

is not an “outlier” and that the low dose ossification data have meaning in relation to the concurrent control. The Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991; Federal Register. Vol 56, No. 234: 63798-63826) recommend “Comparison of data from treated animals with concurrent study controls should always take precedence over comparisons with historical control data.” This would be especially important to do if the historical control incidences of delayed ossification were found to decrease over time, as could result from such factors as genetic drift in the test animal population or even improvements in methodology.

Based on our review of the data, we recommend using the concurrent control incidences rather than the historical control mean incidences to evaluate the ossification delays in the low dose group. This confers statistical significance to the ossification delays in the 2nd centrum and calcaneum, and along with the other factors discussed above (dose-response and concurrent maternal toxicity) supports the designation of 5.0 mg/kg-day as a lowest-observed-adverse-effect level (LOAEL) rather than a NOAEL. If 5.0 mg/kg-day were identified as a LOAEL, then an additional uncertainty factor of three to ten should be applied to account for LOAEL to NOAEL conversion. The use of an additional three or ten-fold uncertainty factor will result in lower margins of exposures (MOEs) for developmental effects (page 104 of the draft RCD).

B. Rabbit developmental toxicity

Regarding the rabbit developmental toxicity study (BASF), the draft RCD (page 58) states, “Resorptions were induced at 30 and 100 mg/kg/day. Though statistical significance was not attained at 30 mg/kg/day, the effect was considered due to metam sodium exposure because of the trend to even higher resorption values at 100 mg/kg/day (Table 20).” However, this trend extends over the entire dose range for both total resorptions and the proportion of litters with resorptions (Table 20). Therefore, by this criterion (a trend towards higher resorption values at higher dose levels), 10 mg/kg-day should be identified as a LOAEL, rather than a NOAEL for this study.

We recommend a trend test be performed using the raw data (both total resorptions and percent litters with resorptions) in order to determine whether the trend for increased resorptions is significant at 10 mg/kg-day. If it is, we recommend designating 10 mg/kg-day a LOAEL and applying an additional uncertainty factor of three to ten to account for LOAEL to NOAEL conversion. The use of an additional three or ten-fold uncertainty factor would result in lower MOEs for developmental effects (page 104 of the draft RCD).

C. Selection of uncertainty factor for subchronic toxicity

We recommend that the RCD include an expanded discussion supporting the selection of an uncertainty factor of three to adjust the LOAEL to a NOAEL for subchronic toxicity. Without adequate scientific justification, the more standard (and health-protective) practice of applying a factor of ten should be followed.

From our review of the data, we determine that frank liver toxicity was observed in one of four female dogs dosed at 1.0 mg/kg-day in the subchronic study. Similar liver toxicity was observed at a dose level of 1.0 mg/kg-day in one of four female dogs in a chronic study. In both dog studies, liver toxicity exhibited a dose-response. These data indicate that the livers of female dogs are consistently sensitive to metam administered at a dose level of 1.0 mg/kg-day. Estimating a NOAEL from the subchronic data depends on the shape of the dose response curve; if the curve is steep, a factor of three might be sufficient. However, there is no discussion of the steepness of the dose response curve in the draft RCD.

The use of an uncertainty factor of three for estimating a NOAEL from a LOAEL is discussed on pages 34 and 35 of the draft RCD. In summary, the basis for the selection of a factor of three is the finding that liver toxicity was observed in only one of four female dogs dosed at 1.0 mg/kg-day because “the toxicologic significance of this occurrence in a single animal was unclear.” On page 98, the argument for a factor of three rather than ten is expanded to include “the apparent mildness of the response at that [1.0 mg/kg/day] dose.” Since only four dogs/dose level/sex were used in this study, toxicity in a single animal must be given greater weight than toxicity in a single animal in a subchronic toxicity study with ten or more animals per dose level per sex. Furthermore, the activity of plasma alanine transaminase (ALT) in one of four low dose females in the subchronic dog study increased approximately 15-fold. This was greater than the mean increase for all females in the high dose group, indicating that the response of the single low dose female may be more than mild.

2) *Cancer Endpoint*

The sections relating to the carcinogenicity of metam are well written and contain the information and data most appropriate for making a determination that there should be a concern for carcinogenicity from exposure to metam. Some areas with suggested revision or areas of concern are identified below:

- (i) Add text to the “quantitative assessment” section that describes the assumptions made in calculating the dose used for the estimation of the cancer potency. For example, the conversion from mg/mL drinking water to mg/kg-day dose appears to be consistent with the U.S. Environmental Protection Agency’s (U.S. EPA) calculations, but this is not stated in the draft RCD.
- (ii) The selection of the sensitive endpoint (angiosarcoma in male mice) is appropriate and the calculation of the carcinogenic potency has been verified by OEHHA, although our calculation of the potency is slightly higher than that presented in the draft RCD [95 percent upper bound: $0.195 \text{ (mg/kg-day)}^{-1}$ vs. $0.185 \text{ (mg/kg-day)}^{-1}$]. This difference may be due to rounding.
- (iii) We recommend some clarification in the wording describing the modeling of the cancer dose-response data (see specific comments below). It is important to include a statement that the software Global 86 was used to calculate the cancer potency as several programs are available which use different algorithms to optimize the fit of the linearized multistage model to cancer incidence data (ToxRisk, MSTAGE, U.S. EPA’s Benchmark Dose software).
- (iv) There is a slight discrepancy between the tumor incidence denominators presented in Table 12 of the draft RCD and those presented by the U.S. EPA Peer Review of the mouse drinking water studies¹. We recommend adding clarification whether this is because of slight differences between the definitions of “at risk” animals (surviving 52 weeks vs. 48 weeks), or whether there is an error in the denominator.
- (v) The discussion of the possible influence of caloric/weight restriction on the tumor incidence of hemangiosarcomas in rats seems speculative, although a conclusive statement was (appropriately) not made because of the conflicting data at another site. We recommend presenting any available data that support this hypothesis specifically (it is not clear whether Tannenbaum looked at this endpoint). If no such support can be located, we recommend removing the sentences to avoid the implication that dietary restriction is known to reduce hemangiosarcoma in rats.

¹ U.S. EPA (1995). Metam sodium qualitative risk assessment based on Hsd/Ola:Wistar tox rat and C57BL/10JfCD-1/Alpk mouse drinking water studies. Memorandum from Lori Brunsman to Timothy McMahon, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, February 1, 1995.

3) Exposure Assessment

The draft RCD (pages 86 and 107) considers that worker exposure to metam sodium occurs “exclusively via the dermal route.” The Exposure Assessment elaborates on pages 22 and 26, postulating that, “inhaling metam-sodium was assumed to be insignificant compared to dermal exposure.” The basis for this conclusion is, “because metam-sodium end-use products have very low vapor pressure of 21 mm Hg at 77°F/25°C (OR-CAL, 1987; Myers and Johnson, 1985).” However, 21 mm of Hg at 25°C is not low compared to other pesticides considered to be volatile, such as chloropicrin (24 mm at 25°C).

We recommend that a quantitative estimate of the fraction of metam exposure that is due to the inhalation route, compared to the dermal route, be included in the RCD in the exposure assessment section. Depending on the response, we might also recommend that the aggregate exposure (dermal plus inhalation) and associated risk be considered in the risk appraisal.

4) Specific Comments

The following specific comments are organized roughly into three categories, specific comments that relate to: 1) the document as a whole, 2) the cancer risk assessment, and 3) the exposure assessment. These comments augment the issues and recommendations we provide above.

A. Document as a whole

Summary section at front of the draft RCD: Some studies are discussed without reference to the species. Recommendation: cite the species.

Page 1, second to last paragraph: An LC₅₀ value is presented without mention of the duration of exposure. Recommendation: add the duration of exposure.

Page 2, top paragraph: “included suppression fetal body weights.” Suspect a typographic error. Recommendation: add “of.”

Page 9, second and third paragraphs: An estimate is made of 9.2 million pounds of methyl isothiocyanate (MITC) released per year from 1995-1999, but by our calculation it should read 9.8 million. Recommendation: check calculation.

Page 12: Recommend checking the structural formula for metam sodium.

Pages 15-16 discussion of “plant residue/metabolites”: Recommendation: Add a brief conclusion as to whether or not these reported levels of metam residues on food crops are considered to be toxicologically significant.

Page 17, first paragraph: The section designations (as letters) do not correspond to the rest of the document (numerals used for sections). Recommend harmonizing.

Page 17, second paragraph: Recommend designating the atom(s) in the metam sodium molecule that were radiolabeled.

Page 17, second paragraph: Expired air was collected for up to seven days, not three.

Page 17, third paragraph: “absorbed fecal fractions” is vague. Recommend rephrasing into something like, “absorbed into the body from the GI tract followed by excretion via the feces.”

Page 17, fourth paragraph: Recommend providing the tissue values. Also, recommend deleting the “on” that follows “highest in the thyroid.”

Table 4: The horizontal line separating “Amount absorbed” from “Feces” is missing. Recommend adding it to help indicate that levels in the feces were not included in the amount absorbed.

Page 23, last paragraph: “The lowest LOEL was 1.9 mg/L in the metam sodium technical study (Holbert, 1989)” However, the lowest lowest-observed-effect level (LOEL) listed in Table 5c is 1.23 mg/L for the Jackson and Hardy (1992) study.

Footnote on pages 31-31: The key metam degradation rates used to calculate the doses received by the animals (68 percent, 38.3 percent and 29.1 percent) are spread throughout this long footnote. Recommend putting these three values in one sentence, so as to make it clear which degradation rate was applied to which starting concentration of metam.

Page 32, about midway down the page: “Alterations in urine volume, pH, specific gravity or protein content were variably present in both sexes at 0.089 or 0.443 mg/ml. The former 3 changes were likely secondary to the reduction in water intake.” The terms “alterations” and “changes” are vague. Recommend stating whether each parameter increased or decreased.

Page 33, top paragraph: Recommend changing “is 0.018” to “at 0.018.”

Page 33, second paragraph: “Adjusted terminal liver weights were significantly increased in both sexes at the top 3 doses” On page 82 it is stated that liver weights were increased at all dose levels. Recommendation: show the liver data, since increases at all dose levels may support designating 0.018 mg/mL a LOAEL, rather than a NOAEL.

Page 34, last sentence: “a minimal to slight increase in the number of mitoses of urinary bladder epithelial cells in several animals....” Recommend supplying the values, if possible.

Page 42, discussion of rat combined study: There is no mention of tumor incidence in females. Recommend either briefly summarizing the female data, or showing it in Table 11.

Page 43, last sentence: “cytoplasmic” is misspelled.

Page 50, first paragraph: Should read Table 15, not Table 14. Also, recommend adding that besides being clastogenic (breaks chromosome), the data indicate that metam sodium also induces polyploidy (changes number of chromosomes).

Page 50, fourth paragraph: Recommend specifying the cell type used for detecting chromosome aberrations. Also, recommend discussing whether the induction of polyploidy exhibited a dose response.

Page 50, fifth paragraph: For the study by Gelbke and Engelhardt (1987a), recommend specifying the magnitude of the increase in aberration frequency.

Table 15: (Engelhardt, 1987) should read Engelhardt (1987a) and Engelhardt (1987b). For the Engelhardt (1987b) study in CHO cells, the dose in the text is in “mg,” suggesting that the “ μg ” designation in Table 15 is incorrect. The dose for the Gelbke and Engelhardt (1987b) study in SPF cells should read mg/kg, not mg/ml.

Page 53, rat reproductive toxicity study: The NOAEL (0.01 mg/mL) is based on decreased water consumption at the two highest dose levels. However, as pointed out in the discussion of this study, water consumption was also significantly decreased at the low dose level. Recommendation: provide the rationale for why decreased water



Office of Environmental Health Hazard Assessment



Joan E. Denton, Ph.D., Director

Headquarters • 1001 I Street • Sacramento, California 95814

Mailing Address: P.O. Box 4010 • Sacramento, California 95812-4010

Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612

Agency Secretary

Arnold Schwarzenegger
Governor

consumption at the lowest dose level was not considered toxicologically significant, compared to decreased water consumption at the mid and high dose levels.

California Environmental Protection Agency

The energy challenge facing California is real. Every Californian needs to take immediate action to reduce energy consumption.



Printed on Recycled Paper

Page 57, legend to Table 19: The incidences of non-ossified 2nd centrum and calcaneum from the Tinston (1993) study are not means, contrary to what is indicated in the legend (in contrast, the historical control incidences are means). Recommend omitting the word “mean.”

Page 59: Recommend providing some description of the skeletal variations observed, as this would help the reader understand the developmental effects and selection of the developmental NOAEL.

Page 64, rat acute neurotoxicity range-finding study: The dose level 100 mg/kg is not listed in the first sentence along with the other dose levels.

Page 67, first paragraph under immunotoxicity: Recommend listing the dose levels used in the study.

Page 70, second paragraph: “The air concentration NOEL of 220 ppb was the critical NOEL used for evaluation of potential short-term risk to residents and bystanders (adults and children) from exposure to airborne MITC.” Recommend citing the publication, which describes this study.

Page 70, last paragraph: “A default uncertainty factor of 3 was then used to calculate an estimated critical subchronic NOEL of 100 ppb.” Since the usual default is 10, recommend discussing why a factor of three was used in this instance.

Page 70, last paragraph: “A NOEL of 0.7 mg/kg/day was established in a 3-month mouse oral gavage study based on reduced body weight gain and increased liver weight at 1 mg/kg/day.” These dose levels are very close. Recommend checking to be sure they are correct.

Page 71, last paragraph: The first “a” in the last sentence should be removed.

Page 81, third paragraph: “As these growth effects were considered to be functions of the acute maternal growth effects, they too were considered likely to be acute in nature.” The suppression of fetal bodyweights and delayed ossification were caesarean data, collected at the end of the dosing period. Recommend providing justification for why these effects should be considered acute (also discussed on page 107, first paragraph).

Page 82, last paragraph: “available using a 42.7% formulation” On page 38 this value is given as 42.4 percent.

Page 82, last sentence: “systemic dermal effects” is ambiguous. Recommend rephrasing into something like “systemic effects due to dermal exposure.”

Pages 84-85: Recommend the table numbers be coordinated.

Page 86, second paragraph: Recommend providing a citation for the decision to scale according to bodyweight raised to this particular exponent.

Table 26 has five footnotes indicated in the table but only four in the legend.

Page 96, second to last paragraph: The Tinston citation should be 1993, not 1979.

Page 103, third paragraph: Not sure about the meaning of “ve.” This may be a typographical error.

B. Cancer assessment

Page 4, fourth paragraph: Recommend replacing the text in this paragraph with the following text:

“Incidence of angiosarcoma, a malignant vascular tumor, at all sites following exposure of male mice to metam sodium in the drinking water for 2 years was 7/53, 12/53, 12/55, and 27/53 at internal doses of 0, 1.9, 7.2, and 28.9 mg/kg/day, respectively. The increase in angiosarcoma incidence at all sites was highly significant at the high dose compared to controls ($p < 0.001$, Fisher Exact Test). Likewise, the increases in angiosarcoma incidence (i.e., liver, spleen, and bone marrow) were significant for angiosarcoma. The dose-response curve was also positive for trend ($p < 0.001$, Cochran-Armitage trend test). The incidence of angiosarcoma (all sites) in females was 4/55, 2/55, 6/46, and 10/52 at internal doses of 0, 2.6, 9.6, and 31.2 mg/kg/day, respectively. While Fisher Exact tests in females were not significant at any dose ($p > 0.05$) when angiosarcomas at all sites were evaluated, the increase in incidence of this tumor in the spleen was significantly increased in the high dose group relative to the control group and the increase in the liver in the high dose group was marginally significantly increased ($p = 0.055$). The dose-response curve for angiosarcoma (all sites) was significant (positive) in a Cochran-Armitage trend test ($p < 0.01$).”

Page 4, fifth paragraph: Recommend removing the reference to “GLOBAL 86” and correcting the spelling of “Weibull.”

Page 5, last sentence of first paragraph: Recommend that the word “linearized” be deleted.

Page 42, second paragraph: Recommend the following text to replace the existing text:

“The interpretation of the rat data on tumor incidence was ambiguous with respect to hemangiosarcoma induction (Table 11). Although there was a statistically significant increase in hemangiosarcoma incidence in the mid dose relative to controls and all metam treated groups showed a greater incidence than the control group, a clear dose-response relationship was not observed. Further, historical control data are not available [for this strain??] making interpretation of the mid dose increase in incidence difficult. It is possible that decreased caloric intake at the high dose was responsible for the lowered hemangiosarcoma incidence rate at that dose. Partial caloric restriction suppresses the development of many kinds of tumors in laboratory animals (Tannenbaum, 1959). If this was the case, however, one might expect a similar dose profile for hemangioma incidence, which was not observed. Furthermore, when incidences of hemangiomas and hemangiosarcomas were combined as suggested by the NTP (McConnell *et al*, 1986), no increase with dose was evident (Table 11). The incidence of another vascular tumor type, benign meningiomas, did, on the other hand, exhibit biphasic behavior, though the low absolute rates (0/50, 1/50, 3/51, 1/51 at increasing doses) precluded a determination that they were treatment related. Without historical controls, the absence of hemangiosarcomas and meningiomas in the concurrent controls must be accepted as representative of their historical behavior. A final point: the observation in the mouse oncogenicity study (see below) of a metam-induced increase in angiosarcomas (equivalent to hemangiosarcomas) tends to support a metam etiology for vascular tumors in the rat.”

Page 46, Table 12: Recommend removing the word “malignant” which is used as a qualifier for angiosarcoma in the table.

Page 86, last paragraph: Recommend removing the reference to “GLOBAL 86.”

Page 100, last paragraph; page 102, first paragraph; and page 109, fourth paragraph: Recommend removing the word “linearized.”

Page 109, fourth paragraph, first sentence: Recommend adding that the angiosarcomas occurred in multiple organs.

C. Exposure assessment

Page 12, third paragraph: “MITC at a nonirritating concentration of 0.1% has the potential to produce dermal sensitization reactions after the animals were induced with 1% Vapam.” Recommend deleting the word “sensitization.”

Page 14, fourth paragraph: “The dermal absorption value is the sum of the percentage of dose excreted at asymptote (maximum or “A” term) and percent of dose recovered in carcass, blood, air traps, and cage washings.” However, in the first sentence of this paragraph it states that the cage washing is used in the calculation to estimate the asymptote. Recommend checking this explanation to be sure the cage washing is not counted twice.

Page 14, fourth paragraph: Recommend providing a conclusion, based on the data in Table 5, regarding the bioavailability of the bound skin residues. In this regard, if the values in the “Excreted” column in Table 5 were calculated using the equation on the preceding page, recommend indicating this with a footnote in Table 5. Also, if the values in the “Excreted” column are based on extrapolation to infinite time, it is not clear why the entries for 0.1 and 10 $\mu\text{g}/\text{cm}^2$ are less than the 72 hour values from Table 4 for urine+feces+cage wash. Recommend checking the calculations.

Page 16, last paragraph: “Results of the study reveal the absorption of metam-sodium in the rat and human skin is dose dependent.” The data indicate this is true for the “washed skin” data in Table 6. However, if this statement refers to the “absorbed” column in Table 6, the percent absorbed was not dose dependent in the rat. Recommend clarifying to what the term “absorption” refers in the above sentence.

Page 17, first paragraph: “It is likely that the ratio could approach 1.0 when a lower dose level was used, e.g. 8.6 $\mu\text{g}/\text{cm}^2$, which was employed in the *in vivo* dermal absorption study.” This statement is based on only two data points (i.e., 4.1 and 1.4 at two dose levels). Such sparse data make it difficult to predict what would happen at lower dose levels. The ratio might approach 1.0, or the human skin might exhibit even greater absorption than that of the rat. Nonetheless, the use of a ratio of 1.0 seems reasonable since the ratio at the lowest dose tested was 1.4. Rounding 1.4 off to 1.0 appears reasonable, given the absence of data at lower dose levels and the health-protective nature of the rounding (i.e., using a ratio of 1.0 tends to overestimate human absorption compared to using 1.4). Recommend removing the statement that the ratio likely approaches 1.0 at lower dose levels, unless data from similar studies with structurally related compounds can be cited for support.

Gary T. Patterson
April 9, 2003
Page 14

Page 18, third paragraph “absorbed fecal fraction”: This phrase is vague. Recommend adding explanation to the text.

Page 18, last and second to last paragraphs: Recommend providing the values for the different tissue levels of metam-sodium and MITC.

Page 22, third paragraph: “At each site, there were two applicators and one mixer/loader. These workers did not enter the treated area during the application at any of the sites.” It seems contradictory to say that the applicators did not enter the area during application. Recommend giving more details of the application procedure.

Page 25, fourth paragraph: “The estimated workdays of 23 days in a 120-day season for a pest control operator are likely underestimated because metam-sodium is intensively used to treat soil before planting varieties of crops.” The basis for this statement should be presented, and if possible, a more accurate estimate of workdays per season should be made. Any new estimate should be incorporated into the RCD (for example, used in the calculations for Table 25).

Page 25, fifth paragraph: “Results from an *in vitro* dermal absorption study of the rat and human skin do not support a lower human dermal absorption value than 2.5%.” Please see comment above for page 17, first paragraph.

Thank you again for the opportunity to review the draft RCD for metam and to provide comments, advice, and recommendations. If you have any questions, please contact me or Dr. Charles Vidair (510) 622-3170.

cc: Val F. Siebal
Chief Deputy Director
Office of Environmental Health Hazard Assessment

George V. Alexeeff, Ph.D., D.A.B.T.
Deputy Director for Scientific Affairs
Office of Environmental Health Hazard Assessment

Michael J. DiBartolomeis, Ph.D.
Chief, Pesticide and Food Toxicology Unit
Pesticide and Environmental Health Hazard Assessment
Office of Environmental Health Hazard Assessment

Gary T. Patterson
April 9, 2003
Page 15

Charles Vidair, Ph.D.
Staff Toxicologist
Pesticide and Environmental Health Hazard Assessment
Office of Environmental Health Hazard Assessment

bcc: Genevieve L. Vivar