UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **MEFENOXAM.**
PC Code: 113502
Report of the Hazard Identification Assessment Review Committee.

FROM: William F. Sette, PhD. William F Sette 11-03-97
as Executive Secretary,
Hazard Identification Review Committee
Health Effects Division (7509C)

Thru: K. Clark Swentzel, Chairman K. Clark Swentzel 11/4/97
Hazard Identification Review Committee
Health Effects Division (7509C)

To: Donna Davis, Chief
Registration Action Branch I
Health Effects Division (7509C)

PM 21
Fungicide Branch
Registration Division (7505C)

On September 11 and October 7, 1997, the Health Effects Division's Hazard Identification Review Committee met to: determine whether data for **metalaxyl** could be used to satisfy the data requirements for **mefenoxam (CGA 329351)**; and to select toxicological endpoints for **mefenoxam** (CGA 329351) for: acute and chronic dietary risk assessments as well as occupational and residential exposure risk assessments. The Committee also evaluated this chemical with respect to estimating the sensitivity of infants and children to exposures as required by the Food Quality Protection Act of 1996.

Mefenoxam (CGA 329351) is the R-enantiomer of the racemic mixture **metalaxyl** (CGA 48988) which contains about 50 % each of the R- and S-enantiomers. As a result, the Committee evaluated the toxicology data bases of mefenoxam and **metalaxyl** and considered it appropriate for studies using **metalaxyl** to be used to estimate the toxicity of **mefenoxam** ("bridging").

Committee members in attendance at one or both meetings: David Anderson, Karl Baetcke (Senior Science Advisor, HED), William Burnam, Susan Makris, Nancy McCarroll, Melba Morrow, Kathleen Raffaele, John Redden, Jess Rowland (as Executive Secretary, meeting 2), Clark Swentzel (Chairman), and William Sette (as Executive Secretary, meeting 1). Also present at the second meeting was Stephanie Irene (Associate Division Director, HED

Hazard Identification Committee member(s) in absentia for both meetings was George Ghali.

The data was presented by Marion Copley, Registration Action Branch 1.

Data Presentation: Marion Copley 11/3/97
Marion Copley, DVM, DABT

Report Preparation: W F Sette
William F. Sette, Ph.D.

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I. TOXICOLOGY ISSUES

A. BRIDGING DATA FROM Metalaxyl TO MEFENOXAM

Mefenoxam (CGA 329351) is the R-enantiomer of the racemic compound **metalaxyl** (CGA 48988) which contains about 50 % each of the R- and S-enantiomers. Some studies use the old terminology for R- and call it the D-enantiomer. **Metalaxyl** has an extensive toxicity data base and has had an HED chapter for a Reregistration Eligibility Decision document completed on July, 18, 1994. RfD (dated 3/3/94) and TES (dated 5/25/96) Committee reports have been completed for **metalaxyl**.

Ciba-Geigy Corp. submitted acute, subchronic, teratology and mutagenicity studies conducted with **mefenoxam** technical to support bridging to the data base for **metalaxyl**. A comparison of comparable studies from both chemicals is in the following table.

Mefenoxam appears to have similar toxicity to that observed with the racemate, **metalaxyl**. Although the acute oral toxicity category is lower (II) for **mefenoxam** than **metalaxyl** (III), the actual values for these are similar (669 mg/kg/day - ♂ & ♀ and 490 mg/kg/day - ♀ for **metalaxyl** and **mefenoxam**, respectively) and is within the variability expected with this type of test. **Mefenoxam** is more irritating to the eye (I) than **metalaxyl** (II). Both are toxicity category IV for dermal irritation and neither technical is a sensitizer.

In subchronic studies, the toxicity profile is similar for both compounds. Although the NOELs for the side by side **28 day rat gavage studies** are not the same both compounds result in increased hepatocellular hypertrophy and increased liver weight at the similar doses. There is a minimal extramedullary hematopoiesis (EMH) increase only reported in **metalaxyl.** The NOELs for **90 day rat feeding studies** with both compounds are also not the same due to different dose levels tested. Hepatic changes are again seen with both compounds while the decreased food consumption with Metalaxyl occurred at a dose higher than that tested with mefenoxam. The **6 month/3 month (metalaxyl/mefenoxam) dog studies** also indicate a similar toxicity profile with increased serum alkaline phosphatase and an increase in liver weight (abs. and rel.) with the NOELs and LOELs differing due to dose selection.

The only difference in toxicity appears to occur in the **rat developmental studies**. Signs of maternal toxicity at 250 mg/kg/day with **metalaxyl** include ataxia and convulsions (death at higher doses). This was not seen at 150 mg/kg/day in the 28-day rat gavage study with **metalaxyl**. This was also not seen at any dose with **mefenoxam** and in fact, no definitive maternal toxicity was observed at dose levels as high as 250 mg/kg/day. **Metalaxyl** had increased unossified vertebrae at 250 mg/kg/day (HDT), a dose with marked maternal toxicity, while **mefenoxam** had no evidence of developmental toxicity at any dose.

Neither compound is mutagenic for Salmonella - gene mutation tests and chromosomal aberration (in-vitro).

Conclusions: The Committee determined that the toxicity data submitted for **mefenoxam**, when compared to **metalaxyl** toxicity data, support using **metalaxyl** data for registration of **mefenoxam** technical.

COMPARISON OF STUDIES USING METALAXYL AND MEFENOXAM

Study Type	Metalaxyl	MEFENOXAM
Acute oral	LD_{50} (M+F)= 669 (575-868) mg/kg **TOX CAT III**	LD_{50}(M)=1671 (1380-2024) mg/kg LD_{50}(F)=490 (360-666) mg/kg LD_{50}(both)=1269 (737-2187) mg/kg **TOX CAT II**
Acute dermal	LD_{50} > 6000 mg/kg **TOX CAT III**	LD_{50}(M) > 2000 mg/kg LD_{50}(F) > 2000 mg/kg **TOX CAT III**
Acute inhalation	Waived because Metalaxyl could not be adequately prepared.	LC_{50}(M) > 2.29 mg/L LC_{50}(F) > 2.29 mg/L **TOX CAT IV**
Eye irritation	Moderate irritant **TOX CAT II**	severe to corrosive ocular irritant **TOX CAT I**
Dermal irrit	Mild irritant **TOX CAT IV**	slight dermal irritant **TOX CAT IV**
Dermal sensit.	Not a sensitizer	maximization test - not a sensitizer Buehler test - not a sensitizer
Subchronic rat	28 Day - Gavage NOEL = 50 mg/kg/day LOEL = 150 mg/kg/day based on minimal EMH and hepatocellulary hypertrophy. Increased liver weight occurred at 300 mg/kg/day 90 Day - Dietary NOEL = 250 ppm (17 mg/kg/day) LOEL = 1250 ppm (83 mg/kg/day) based on slightly reduced food consumption (m) and minimally increased liver cell hypertrophy (f)	28 Day - Gavage NOEL ≥ 300 mg/kg/day LOEL > 300 mg/kg/day. At 150 mg/kg/day there was hepatocellular hypertrophy. Increased liver weight occurred at 300 mg/kg/day 28 Day - Dietary NOEL ≥ 600 ppm (534.2 mg/kg/day) LOEL > 600 ppm. At 50 ppm (42.68 mg/kg/day - LET) there was increased liver weight and hepatocellular hypertrophy. 90 Day - Dietary NOEL ≥ 1250 ppm (90.5 mg/kg/day) LOEL > 1250 ppm. At 625 ppm (44.8 mg/kg/day) there was minimal hepatocellular hypertrophy.
Subchronic dog	6 Month NOEL = 250 ppm (7.4 mg/kg/day) LOEL = 1000 ppm (32.4 mg/kg/day) based on elevation in serum alkaline phosphatase and an increase in liver weight (abs. and rel/brain).	3 Month NOEL = 250 ppm 7.25 mg/kg/day) LOEL 1250 ppm. Based on slightly increased alk. phos and increased abs and rel liver weights (m&f).
Developmental rat	Maternal NOEL = 50 mg/kg/day Maternal LOEL = 250 mg/kg/day based on ataxia and convulsions. There was mortality at 400 mg/kg/day. Developmental NOEL = 50 mg/kg/day Developmental LOEL = 250 mg/kg/day based on increased incidence of unossified sternebrae.	Maternal NOEL ≥ 250 mg/kg/day Maternal LOEL > not observed (maybe marginal transient changes (BW, Food Consump., Food Efficiency) developmental NOEL ≥ 250 mg/kg/day Developmental LOEL > not observed
Mutagenicity	negative in Ames, gene mutation (L5178Y (TK+/-) line, reverse mutation in yeast, in vivo cytogenetics (CHO), dominant lethal, UDS with primary cultured rat hepatocytes.	negative in Ames and in vitro chromosomal aberration (CHO)

II. TOXICOLOGY PROFILE

A. ACUTE TOXICITY

Acute Toxicity of CGA-329351 (Mefenoxam)

Guideline No.	Study Type	MRID #(S)	Results	Toxicity Category
81-1	Acute Oral	43800383	LD_{50}(M)=1671 (1380-2024) mg/kg LD_{50}(F)=490 (360-666) mg/kg LD_{50}(both)=1269 (737-2187) mg/kg	II
81-2	Acute Dermal	43800384	LD_{50}(M) > 2000 mg/kg LD_{50}(F) > 2000 mg/kg	III
81-3	Acute Inhalation	43800385	LC_{50}(M) > 2.29 mg/L LC_{50}(F) > 2.29 mg/L	IV
81-4	Primary Eye Irritation	43800386	severe to corrosive ocular irritant	I
81-5	Primary Skin Irritation	43800387	slight dermal irritant	IV
81-6	Dermal Sensitization	43800388 43800389	maximization test - not a sensitizer Buehler test - not a sensitizer	NA
81-8	Acute Neurotoxicity	no test		

B. SUBCHRONIC TOXICITY

Adequacy of data base for subchronic toxicity (Series 82): The data base for subchronic toxicity is considered complete. No additional studies are required at this time.

82-2 Repeated Dose Dermal – Rat

A 21-day dermal study was conducted with male and female New Zealand white rabbits. **Metalaxyl** was applied to intact or abraded skin at dose levels of 10, 100, or 1000 mg/kg/day for 6 hours/day, 5 days/week. Endpoints evaluated included body weight, food consumption, hematology, clinical chemistry, organ weights, and histopathology. No treatment-related dermal or systemic effects were observed at any dose level. Therefore, the NOEL for dermal and systemic toxicity was the highest dose tested, 1000 mg/kg/day. (MRID 00072394)

This 21 day dermal toxicity study is classified **acceptable** and satisfies the guideline requirements for a subchronic oral study (82-2) in rats.

82-1b Subchronic Oral Toxicity - Dog

In a subchronic toxicity study (MRID 43800392), **mefenoxam**; (97.1% ai; Lot #OP.4) was administered to four beagle dogs/sex/dose in the diet at dose levels of 50, 125, 250 or 1250 ppm (measured means 1.57, 4.07, 7.25 or 38.60 mg/kg/day, respectively, for males; 1.56, 4.33, 7.93 or 39.46 mg/kg/day, respectively, for females) for 3 months. Dogs in the 1250 ppm treatment groups had increased alkaline phosphatase activity (87-159% at 7 and 13 weeks) and higher absolute and relative liver weights (25-33%) compared to the controls. No other treatment-related responses were observed in the high dose groups. **Mefenoxam** had no effect on food consumption, body weights, ophthalmoscopic, hematological, clinical blood chemistry or urinalysis parameters, organ weights or gross or microscopic postmortem changes in other treatment groups. **The LOEL is 38.6 mg/kg/day (1250 ppm), based on increased alkaline phosphatase activity and increased absolute and relative liver weights for both sexes. The NOEL is 7.25 mg/kg/day (250 ppm).**

This subchronic toxicity study is classified **acceptable** and satisfies the guideline requirements for a subchronic oral study (82-1b) in dogs.

C. CHRONIC TOXICITY

Adequacy of data base for chronic toxicity (Series 83-1): The data base for chronic toxicity is considered complete. No additional studies are required at this time.

83-1b Chronic Oral Toxicity - Dog

A 6-month study was conducted with beagle dogs fed diets containing 0, 50, 250, or 1000 ppm of **metalaxyl**. The diet concentrations were equivalent to chemical intakes of 1.57, 7.8, 30.63 mg/kg/day for males, respectively and 1.71, 7.41 32.36 mg/kg/day for females, respectively. Exposure to the high dose was associated with an elevation in serum alkaline phosphatase and an increase in liver weight (absolute and relative to brain weight). No clinical signs or findings in hematology, urinalysis, or histopathology were related to treatment. The LOEL was 32.4 mg/kg/day and the NOEL was 7.4 mg/kg/day. (MRID 00071598)

D. CARCINOGENICITY

Adequacy of data base for Carcinogenicity (Series 83-2, 83-5): The data base for carcinogenicity is considered complete. No additional studies are required at this time.

In 1985 the EPA (Peer Review of Metalaxyl, 12/31/85) reviewed four major issues concerning the rat and mouse carcinogenicity studies with **metalaxyl**: (1) parafollicular cell adenomas in the thyroid of female rats, (2) adrenal medullary tumors (pheochromocytomas) in male rats, (3) liver tumors in male mice, and (4) use of a maximum tolerated dose. (50 FR 49690)

Concerns about the incidence of thyroid tumors in female rats was mitigated by the following evidence: (1) no progression of adenomas (benign) to carcinomas (malignant), (2) no increase in hyperplastic changes, (3) no dose-response relationship, and (4) two re-evaluations of microscopic slides showing no treatment-related effect. Similar microscopic reassessments of the adrenal gland of male rats and the liver of male mice indicated no compound-related effect on tumor incidence in these organs.

Although the highest dose tested (1250 ppm) was not a maximum tolerated dose (MTD) in either study, the EPA concluded that the rat and mouse studies were sufficient to demonstrate that **metalaxyl** did not have carcinogenic potential in laboratory animals and further testing was unwarranted. The conclusion was supported by the following evidence: (1) the doses in both studies were high enough to produce treatment-related changes in liver weight and/or histology (i.e., increased liver weight and hepatocellular vacuolation in rats; fatty infiltration in the liver of mice), (2) no structural relationship to known carcinogens, (3) no genotoxic activity, and (4) no effect on neoplasm incidence in mice or rats of either sex at any dose level tested.

E. DEVELOPMENTAL TOXICITY

Adequacy of data base for Developmental Toxicity (Series 83-3): The data base for developmental toxicity is considered complete. No additional studies are required at this time.

83-3a Prenatal Developmental Study - Rat

In a developmental toxicity study (MRID 43800393) CGA 329351 (**mefenoxam** 97.1% a.i.) was administered by gavage to 24 female Tif:RAI f (SPF) rats/dose in a 0.5% (w/v) aqueous solution of sodium carboxymethylcellulose at dose levels of 0, 10, 50, or 250 mg/kg/day from days 6 through 15 of gestation. At 250 mg/kg/day, reductions in mean body weight gains were noted on treatment days 6-11 (↓27%, $p \leq 0.01$) and for the overall treatment period (days 6-16, ↓12%, $p \leq 0.05$). However, no rebound effect on body weight gain was apparent during the post-treatment interval. In addition, mean body weights and body weight gains corrected for gravid uterine weights were comparable to the controls. Therefore, the reduction in the uncorrected body weight gain at the high-dose cannot clearly be associated with the administration of the test substance. On treatment days 6-11, statistically significant and dose-dependent reductions in food consumption were noted at 50 mg/kg/day (↓7%, $p \leq 0.05$) and at 250 mg/kg/day (↓16%, $p \leq 0.05$). However, during the 11-16 day treatment interval, reductions on food consumption were not dose dependent as food consumption

was greater for the high-dose group than the mid-dose group. In addition, no rebound effect in food consumption was apparent during the post-treatment interval. Therefore, as the reductions in food consumption at the mid- and high-dose levels were not persistent throughout treatment and did not rebound after treatment, they cannot be considered to represent overt toxicity. When feed efficiency was calculated, there was a decrease in efficiency at the high dose for the 6-11 day time interval (18.8% vs. 16.4% for controls and high dose, respectively). There was an increase in efficiency for the period of days 11-16. The submitted range-finding study confirmed that no overt maternal toxicity is demonstrated at dose levels of ≤ 250 mg/kg/day. There was, however marginal decreases in body weight and food consumption at both 150 and 250 mg/kg/day. When taken together, the data indicate that while the animals could have tolerated higher doses, the high dose approached a toxic level and the study should not be repeated at higher doses at this time. There were no treatment-related effects in developmental parameters at any dose level. **The maternal LOEL and NOEL were greater than 250 mg/kg/day. The developmental LOEL and NOEL were greater than 250 mg/kg/day.**

The submitted developmental study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a developmental study in the rat (83-3a).

83-3b Prenatal Developmental Study - Rabbit

A developmental toxicity study was conducted with Dutch belted rabbits given doses of 0, 30, 150, or 300 mg/kg/day of **metalaxyl** on days 7 through 19 of gestation. Does were sacrificed on day 28 of gestation. The high dose does showed a slight loss in body weight. In a range-finding study, 500 mg/kg/day decreased maternal body weight and 1000 mg/kg/day produced mortality. No treatment-related developmental toxicity was observed at any dose level. The LOEL for maternal toxicity was 300 mg/kg/day and the NOEL was 150 mg/kg/day. The highest dose tested, 300 mg/kg/day, was the NOEL for developmental toxicity. (MRID 00144371 -72, 00148866, 00154938).

The submitted developmental study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a developmental study in the rabbit (83-3b).

F. REPRODUCTIVE TOXICITY

Adequacy of data base for Reproductive Toxicity (Series 83-4): The data base for reproductive toxicity is considered incomplete because the only available reproduction study has been re-evaluated and graded as unacceptable and cannot be upgraded. This is considered a data gap for both **mefenoxam** and **metalaxyl**. However, a new study is not required at this time for **mefenoxam** since the extra 3-fold uncertainty factor on the RfD is considered protective.

83-4 2-generation Reproduction Study in the Rat

A 3-generation reproduction study (MRID 00071600) was conducted with SPF Crl:COBS CD (SD) rats. **Metalaxyl** (93.5 % a.i.) was administered in the diet at concentrations of 0, 50, 250, or 1250 ppm (equivalent to 2.5, 13, and 63 mg/kg/day, respectively). There were no treatment-related effects on parental body weight, food consumption, mating, fertility, gestation length, or macroscopic observations. Pre/post implantation loss, litter size and weight, and incidence of fetal malformations/variations were also unaffected by treatment. **The LOELs for reproductive and parental toxicity were above the highest dose tested, 1250 ppm (63 mg/kg/day). The NOELs for reproductive and parental toxicity were at or above the highest dose tested, 1250 ppm (63 mg/kg/day).**

This study is classified **unacceptable (guideline)** and does not satisfy the guidelines for a 2-generation reproduction study (83-4). This study is not upgradable since adequate dose levels were not tested to achieve either parental or reproductive toxicity.

This study was evaluated by the HED RfD Committee in 1994 (document 4/20/94) and "was considered to be tentatively acceptable. The Committee recommended reevaluation of the study to confirm the findings and conclusions reported in the data evaluation record of this study." This study was not re-evaluated prior to issuance of the Reregistration Eligibility Decision document for **metalaxyl**.

The current (1997) re-evaluation of this study has resulted in the study being downgraded to unacceptable (guideline) and **not satisfactory** to satisfy the guideline requirement for a 2-generation reproduction study. This is justified on the grounds that there is no evidence of any parental or reproductive toxicity at the high dose resulting in the inability to determine sensitivity: 1) to offspring and 2) for reproductive effects as related to parental effects.

The Committee determined that there is no evidence that would suggest that mefenoxam requires a review by HED's Reproduction and Developmental Assessment Review Committee

G. DERMAL ABSORPTION

85-2 Dermal Absorption - Rat

A dermal absorption study (MRID 00161402) was conducted with male and female rats treated with 1 or 10 mg/kg **metalaxyl**. Thirty percent of the dose was absorbed from the skin within 8 hours. The absorption half-times were 12 and 20 hours for males at the low dose and high dose, respectively, and 13 hours for females at both dose levels. Within 72 hours, 70-80% of the applied dose had been excreted. The elimination half-times were 36 and 49 hours for males and 42 and 44 hours for females at the low and high doses, respectively. Females eliminated the majority of the dose in urine whereas males eliminated most in feces.

III. HAZARD IDENTIFICATION

Based on comprehensive evaluation of the toxicology data available on **mefenoxam** and **metalaxyl**, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories indicated below. The HED Toxicology Endpoint Selection Committee (document dated 5/24/94) selected endpoints for acute dietary and short-, intermediate-, and long-term occupational exposure (dermal and inhalation) to **metalaxyl** (mixture which contains 50% **mefenoxam**) Where no appropriate data have been identified for a particular duration or exposure scenario, or if a risk assessment is not warranted, this is noted. **Based on the exposure/use profile for mefenoxam, the Committee evaluated the need for the risk assessments indicated below**.

A. ACUTE DIETARY EXPOSURE (one day)

Study selected: None

MRID No. None

Executive Summary: None

Dose/Endpoint for Risk Assessment: Not applicable

Comments about Study/Endpoint: Toxicity observed in oral studies was not attributable to a single exposure (dose). No developmental toxicity was observed following oral administration of **mefenoxam** to pregnant rats (Developmental NOEL $\geq$ 250 mg/kg/day, the highest dose tested) or **metalaxyl** to pregnant rabbits (Developmental NOEL = 300 mg/kg/day, highest dose tested) (See I. C. Developmental Toxicity) .

This risk assessment is NOT required.

B. CHRONIC DIETARY EXPOSURE (REFERENCE DOSE)

Study selected: 83-1 Six month dog study

MRID No. 00071598

Executive summary: A 6-month study was conducted with beagle dogs fed diets containing 0, 50, 250, or 1000 ppm of **metalaxyl**. The diet concentrations were equivalent to chemical intakes of 1.57, 7.8, 30.63 mg/kg/day for males, respectively and 1.71, 7.41 32.36 mg/kg/day for females, respectively. Exposure to the high dose was associated with an elevation in serum alkaline phosphatase and an increase in liver weight (absolute and relative to brain weight). No clinical signs or findings in hematology, urinalysis, or histopathology were related to treatment. The LOEL was 32.4 mg/kg/day and the NOEL was 7.4 mg/kg/day. (MRID 00071598)

Dose/endpoint for establishing the RfD: NOEL = 7.4 mg/kg/day based on increased alkaline phosphatase and increased absolute and relative liver weights at 32.4 mg/kg/day (LOEL).

Uncertainty factor: An UF of 100 was applied to account for both inter-species (10) and intra-species (10) variability.

Derivation of RfD: $\frac{7.4 \text{ mg/kg /kg (NOEL)}}{100 \text{ (UF)}} = 0.074 \text{ mg/kg/day}$

Comments: The RfD committee (HED 3/3/94; 5/23/86; EPA 7/8/86, 12/8/94) established this RfD of 0.074 mg/kg/day[1] for **metalaxyl.** Based on the comparable toxicity seen from dogs exposed to mefenoxam, summarized in the toxicology section II, this Committee (HIARC) concluded that this RfD should be used for **mefenoxam**

The Hazard Identification Review Committee, based on the comparable toxicity seen from subchronic and chronic toxicity studies in dogs with **mefenoxam** (Sections II.A and B), concluded that the RfD established for **metalaxyl** should be used for **mefenoxam**.

The Committee, however, determined that the **10 x** factor to account for potential increased sensitivity of infants and children (as required by FQPA) **should be reduced to 3 x.** Thus, for chronic dietary risk assessment, **the total UF would be 300** (10 x for inter-species variation, 10 x for intra-species variation and 3 x for FQPA.) and **the RfD for mefenoxam would be 0.025 mg/kg/day**. An UF of 300 is supported by the following factors:

(I) The only available three-generation reproduction study in rats of **metalaxyl** was judged to be unacceptable due to no toxicity at any dose. Thus, there is a lack of an adequate assessment of toxicity to young animals following postnatal exposure, and this limits our ability to evaluate the potential for additional sensitivity to infants and children following exposure to **mefenoxam**.

(ii) Developmental toxicity studies provided no indication of increased sensitivity to fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits for both, **mefenoxam** and **metalaxyl**.

[1] In the RfD meeting of 1986, the NOEL (6.25 mg/kg/day) in the six month dog study was calculated based on a standard conversion food factor. At the 1994 meeting the Committee decided to use the actual food intake to calculate the NOEL in this study. On the basis of actual food intake the NOEL for males was calculated to be 7.8 mg/kg/day and for females 7.4 mg/kg/day.

C. OCCUPATIONAL/RESIDENTIAL EXPOSURES

Dermal Absorption

A dermal absorption study was conducted with male and female rats treated with 1 or 10 mg/kg **Metalaxyl**. **Thirty percent of the dose was absorbed from the skin within 8 hours**. The absorption half-times were 12 and 20 hours for males at the low dose and high dose, respectively, and 13 hours for females at both dose levels. Within 72 hours, 70-80% of the applied dose had been excreted. The elimination half-times were 36 and 49 hours for males and 42 and 44 hours for females at the low and high doses, respectively. Females eliminated the majority of the dose in urine whereas males eliminated most in feces.

Dermal Absorption Factor: 30% at 8 hours. This factor is not applicable for Short- and Intermediate Term dermal exposure since risk assessments for these exposure scenarios are not required. This factor, however, should be applied for chronic dermal risk assessments since an oral dose was selected for this risk assessment.

1. SHORT TERM DERMAL EXPOSURE (1 to 7 days)

Study selected: None

MRID No. None

Executive Summary:- None

Dose/Endpoint for Risk Assessment: Not applicable

Comments about Study/Endpoint: In a 21-day repeated dose dermal toxicity study (MRID 00072394) with **metalaxyl**, there were no signs of dermal or systemic toxicity was seen at dose upto and including 1000 mg/kg/day (Limit-Dose). In oral developmental toxicity studies, developmental effects were observed only at maternally toxic doses.

This risk assessment is NOT required

2. INTERMEDIATE TERM DERMAL EXPOSURE (1 week to several months)

Study selected: None

MRID No. None

Executive Summary - None

Dose/Endpoint for Risk Assessment: Not applicable

Comments about Study/Endpoint: In a 21-day repeated dose dermal toxicity study (MRID 00072394) with **metalaxyl,** there were no signs of dermal or systemic toxicity was seen at doses upto and including 1000 mg/kg/day (Limit-Dose). In oral developmental toxicity study, developmental effects were observed only at maternally toxic doses.

This risk assessment is NOT required

3. CHRONIC DERMAL EXPOSURE (Several Months to Lifetime)

Study selected:	83-1 6 month oral dog study	85-2 rat dermal absorption study
MRID Nos.:	00071598 Dog Study	00161402 Rat Study

Executive summary: A 6-month study was conducted with beagle dogs fed diets containing 0, 50, 250, or 1000 ppm of **metalaxyl**. The diet concentrations were equivalent to chemical intakes of 1.57, 7.8, 30.63 mg/kg/day for males, respectively and 1.71, 7.41 32.36 mg/kg/day for females, respectively. Exposure to the high dose was associated with an elevation in serum alkaline phosphatase and an increase in liver weight (absolute and relative to brain weight). No clinical signs or findings in hematology, urinalysis, or histopathology were related to treatment. The LOEL was 32.4 mg/kg/day and the NOEL was 7.4 mg/kg/day.

Dose/Endpoint for Risk Assessment: NOEL = 7.4 mg/kg/day based on increased alkaline phosphatase and increased absolute and relative liver weights at 32.4 mg/kg/day (LOEL).

Comments about Study/Endpoint: Since this dose is from an oral study, a dermal absorption factor of 30 % should be used in risk assessments. This dose was also used for establishing the RfD for chronic dietary exposure.

This risk assessment is required

4. INHALATION EXPOSURE (Any time period)

Based on the LC_{50} value of 2.29 mg/L, mefenoxam is placed in Toxicity Category IV , indicating low toxicity by this route (MRID 43800385). However, if there is a concern for high exposure via this route, a risk assessment may be required.

The Committee noted that except for an acute inhalation toxicity study, no inhalation toxicity studies are available for selection of a dose and endpoint for inhalation exposure risk assessment. Therefore, the Committee recommended the use of an oral NOEL for this risk assessment.

Study Selected: 6 Month Dog Study Guideline 82-1b

MRID No. 00071598

Executive Summary: See Chronic Dietary exposure section

Dose/Endpoint for Risk Assessment: NOEL = 7.4 mg/kg/day based on increased alkaline phosphatase and increased absolute and relative liver weights at 32.4 mg/kg/day (LOEL).

Comments about Study and/or Endpoint: The above dose was identified if there is chronic inhalation exposure. Since the dose identified for inhalation risk assessment is from an oral study (i.e., an oral NOEL), risk assessment should be as follows:

(i) The inhalation exposure component (i.e., mg/L) using a 100% absorption rate (default value) should be converted to a dose (mg/kg/day).

(ii) The dermal exposure component (i.e., mg/kg/day) using 30% dermal absorption may be combined to this converted dose (mg/kg/day).

(iii) This dose should then be compared to the oral NOEL of 7.4 mg/kg/day to calcutate the Margins of Exposure.

(iv) The dermal MOE and the inhalation MOE cannot be combined since a common toxicological endpoint via these routes was not identified.

This risk assessment is required if there is chronic inhalation exposure.

D. CARCINOGENICITY CLASSIFICATION

The Committee saw no reason to deviate from the E classification that was determined by the HED Cancer Peer Review Committee (1985) (see II. C. TOXICITY PROFILE, CARCINOGENICITY section for additional details).

E. FQPA ASSESSMENT

1. Adequacy of data: An acceptable prenatal toxicity study in rats with mefenoxam and acceptable prenatal developmental toxicity studies in rats and rabbits with metalaxyl have been submitted to the Agency. There are no data gaps for the assessment of the effects of mefenoxam following *in utero* exposure. However, the two-generation reproduction study in rats submitted for metalaxyl is not acceptable due to the lack of parental or offspring toxicity at any dose level. Therefore, for both metalaxyl and mefenoxam, there is insufficient information available to adequately assess the effects to young animals following early postnatal exposure.

2. Susceptibility issues: The data demonstrated no indication of increased sensitivity of rats and/or rabbits to *in utero* exposure to mefenoxam or metalaxyl. The NOELs for maternal toxicity were always less than or equal to the NOELs for fetal toxicity. No assessment could be made of age-related sensitivity following postnatal exposure, since no toxicity was identified in either adults or pups in the two-generation reproduction study in rats.

3. **Uncertainty Factor:** The Committee determined that for mefenoxam the 10-fold uncertainty factor for the protection of infants and children should be reduced to 3-fold. This is based upon the lack of an adequate assessment of toxicity to young animals following postnatal exposure, since the three-generation reproduction study in rats was conducted at insufficiently high dietary dose levels, and upon the inability to adequately evaluate the potential for additional sensitivity to infants and children.

4. **Recommendation for a developmental neurotoxicity study:** Following evaluation of the database, it was noted that there was no evidence that supported requiring a developmental neurotoxicity study with mefenoxam. No evidence of developmental anomalies, including abnormalities in the development of the fetal nervous system, were observed in the prenatal developmental toxicity studies in Tif rats with mefenoxam at doses up to 250 mg/kg/day, nor in COBS rats or Dutch belted rabbits with metalaxyl at doses up to 400 or 300 mg/kg/day. Additionally, no evidence of overt neurotoxicity was observed in the overall database, and neurotoxicity studies were apparently not required.

The three-generation reproduction study in rats did not demonstrate effects in either adults or their offspring with dietary doses up to 63 mg/kg/day, which is over 10-times the NOEL from which the RfD was calculated (6.25 mg/kg/day from the 6-month feeding study in dogs, based upon marginal evidence of toxicity, specifically, increased relative liver weights and increased alkaline phosphatase activity at the LOEL of 25 mg/kg/day). Although the Committee designated the inadequate reproduction study as a data gap, it did not require that a new study be submitted. It is noted, however, that upon submission of an adequate multi-generation reproduction study by the registrant, the Agency can reevaluate the need for the additional 3-fold FQPA uncertainty factor.