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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: FORTRESS (Chlorethoxyphos; DPX-43898; IN 43898). An Organophosphate:

1. Review of Additional Toxicology Studies Submitted to Support the Full Registration of Fortress Technical and Fortress 5G and to Support a Tolerance Petition for the Use of Fortress on Corn (3F04174);

2. Overview of the Fortress Technical and Fortress 5G Toxicological Databases.

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Registration Division (H7505)

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Conclusions

1. The new toxicology studies/data submitted for Fortress and Fortress 5G have been evaluated by Toxicology Branch and Data Evaluation Reports are attached;

2. The toxicology database submitted thus far for Fortress technical and Fortress 5G to support the registration of Fortress technical and Fortress 5G and to support the request for a permanent tolerance on corn is for the most part complete, acceptable, and adequate.

However, some additional data and information are required or reserved as listed below. Once the carcinogenicity issue is satisfactorily addressed, the additional testing requirements need not hold up the registration of Fortress technical or Fortress 5G nor impede the request for a tolerance on corn.

The additional data required or data requirements to be held in reserve are as follows:

i) The registrant has been asked to prepare a response (including the submission of appropriate historical control data) to the finding of a slight increase in kidney tumors in high dose male rats in the 2-year chronic/carcinogenicity study (MRID 417368-37). At the present time, plans have been made to submit this issue for evaluation by the HED Cancer Peer Review Committee; Conclusions about the carcinogenicity aspect of the study and its classification are reserved pending the outcome of the Agency's evaluation;

ii) A new acute neurotoxicity study in the rat is required due to deficiencies in the existing study (MRID 425592-10) which has been classified as Supplementary and not upgradeable (rationale appears later in this memo). The new study should include a histopathology exam, and cholinesterase and body temperature evaluations. The protocol should be submitted in advance;

iii) A neurotoxic esterase (NTE) study in the hen is required (rationale appears later in this memo). The protocol should be submitted in advance;

iv) The submitted subchronic neurotoxicity study in the rat (MRID 425592-17) was also found to be Supplementary and not upgradeable, however, the requirement for a new study (probably by gavage) is Reserved at this time pending receipt and evaluation of the other two neurotoxicity studies;

v) A study to establish a NOEL for plasma, erythrocyte, and brain cholinesterase inhibition following an acute oral dose of Fortress may be required in the future once guidance is available from the Agency;

3. Concerns stated in a previous memo (K. Hamernik to D. Edwards, 4/11/91) about the toxicity of Fortress still apply. Fortress is a highly toxic organophosphate with a steep dose response curve. Females generally appear to be more sensitive than males to its toxic effects. Human exposure to Fortress by any route should be prevented.

4. An RfD has been established for Fortress by the HED RfD Peer Review Committee at 0.0006 mg/kg/day based on an overall NOEL of 2 ppm (0.061 mg/kg/day) from the combined subchronic and chronic

dog studies and an uncertainty factor of 100. The final report is not yet available.

5. The same critical study and effect level of 2 ppm (about 0.06 mg/kg/day) from the 6-Month Ocular Toxicity Study in Dogs is the basis for the Less than Lifetime endpoints for acute dietary and occupational/residential risk assessments.

6. OREB will address worker exposure concerns, DRES will address dietary exposure issues, and HED/CCB/RS will perform any risk assessments.

A. Action Requested

E.I. du Pont de Nemours and Co., Inc. has submitted additional toxicology data for review to support a full Section 3 Registration for Fortress technical and Fortress 5G and to support a tolerance petition for the use of Fortress on corn as follows: corn, field, forage 0.01 ppm; corn, field, fodder, 0.01 ppm; corn, field, silage 0.01 ppm; corn, pop, forage, 0.01 ppm, corn, pop, fodder, 0.01 ppm; corn, grain, 0.01 ppm; corn, sweet (K & CWHR), 0.01 ppm; corn, sweet, forage, 0.01 ppm, 0.01 ppm; and corn, sweet, fodder, 0.01 ppm. The proposed use of Fortress-containing products is to suppress corn rootworm and other soil insect pests of field corn.

B. New Toxicology Data Submissions

The following data have been submitted by du Pont with the current request and were evaluated by Toxicology Branch I. Data Evaluation Reports (DERs) were prepared for these studies (attached):

For Fortress Technical

1. 1-Year Dog Chronic Feeding Study	MRID 417368-33
2. 2-Year Rat Chronic Feeding/Carcinogenicity Study	MRID 417368-37
3. 2-Generation Rat Reproduction Study	MRID 417368-36
4. 18-Month Mouse Carcinogenicity Study	MRID 417368-35
& Supplement	MRID 417368-35
5. Metabolism Study (Rat) (Supplement to Upgrade Previously Submitted Study)	MRID 425592-20
6. 90-Day Rat Feeding Study	MRID 425592-15
7. 6-Month Dog Ocular Toxicity Study	MRID 425592-21
8. Enzyme Inhibition and Recovery Study	MRID 425592-11
& Supplement	MRID 429661-01
9. Acute Neurotoxicity Study (Rat)	MRID 425592-10
10. Subchronic Neurotoxicity Study (Rat)	MRID 425592-17
11. Developmental Toxicity Study (Rabbit) (Supplement Submitted to Upgrade Previously Submitted Study)	MRID 425592-19

For Fortress 5G

1. Acute Dermal (Rabbit)	MRID 425592-07
2. Acute Inhalation (Rat)	MRID 417368-32
3. Primary Dermal Irritation (Rabbit)	MRID 425592-08
4. Dermal Sensitization (Guinea Pig) (Supplement to Upgrade Previously Submitted Study)	MRID 425592-09

Note: Some DERs (new or previously prepared) were augmented or amended for or upon recommendation of the HED RfD Committee. This is reflected in the attached DERs.

Other Supplements:
The registrant prepared comments on some studies performed with Fortress technical which Toxicology Branch I had reviewed previously. Formal DERs were not prepared for these supplements as they did not alter the conclusions of the previous reviews:

1. Commment on previous review of 2-yr Rat Chronic/ Carcinogenicity Study Interim Report (MRID 412906-34)	MRID 425592-18
2. Comment on 6 Week Rat and Mouse Feeding Studies (MRID 412906-32)	MRID 425592-12
3. Comment on Rat 90-Day Feeding and One-Generation Reproduction Study (MRID 412906-27)	MRID 425592-14
4. Comment on Mouse 90-Day Feeding Study (MRID 412906-29)	MRID 425592-16
5. Comment on 6 Week Mouse Feeding Study (MRID 412906-30)	MRID 425592-13

C. Toxicology Branch I Evaluation Of What Data Requirements Have Been Met to Support the Registration of Fortress and Fortress 5G and to Support the Requested Tolerance and the Impact of Additional Testing Requirements

1. A complete summary of the toxicology data required for full Section 3 Registration of Fortress technical and Fortress 5G and the status of each of the studies is listed in TABLE 1 below.

2. The toxicology database submitted to support the registration of Fortress technical and Fortress 5G and to support the requested tolerance on corn is complete, acceptable, and adequate with the following exceptions:

i) With regard to the 2-Year Chronic/Carcinogenicity Feeding study in the rat (MRID 417368-37), the chronic toxicity portion of the study is acceptable and is classified Core Guideline. However, a concern has arisen about a slight increase in kidney tumors in high dose group male rats. The registrant has been informed that more information is required for further evaluation by the Agency (including appropriate

historical control data). Plans have been made at this time to refer the issue to the HED Cancer Peer Review Committee. Therefore, conclusions about the carcinogenicity aspect of the study and its classification are Reserved pending the outcome of the Agency's evaluation.

ii) Both the rat Acute Neurotoxicity study (MRID 425592-10) and the rat Subchronic Neurotoxicity study (MRID 425592-17) are considered to be Supplementary and not upgradeable. A major deficiency in the acute study is the absence of histopathological examinations (following perfusion). In addition there appeared to be a problem with dose solution preparation or verification.

Because of recent concerns about neurotoxicity associated with exposure to the chemical Chlorpyrifos, it is prudent for the Agency to have a reasonable degree of confidence in the neurotoxicity databases associated with other organophosphate chemicals, including Fortress, and to ensure that the databases for these chemicals are as complete as possible under existing guidelines and data requirements.

Therefore, a new acute neurotoxicity study with Fortress technical by the gavage route in the rat is being required which includes a histopathological exam (following perfusion), evaluation of plasma, erythrocyte, and brain cholinesterase activities following a single dose of the test material, and body temperature evaluations. It is recommended that the protocol be submitted to the Agency for comment prior to starting the study.

In addition, an NTE (neurotoxic esterase) study in the hen (including an assay of NTE activity) as per the 1991 Neurotoxicity Guidelines is also being required. It is recommended that the protocol be submitted to the Agency for comment prior to starting the study.

The requirements for a new acute neurotoxicity study and an NTE study in the hen need not hold up registration of Fortress.

Confidence in the results of the rat subchronic neurotoxicity study was reduced because of inconsistences with results in other 90-day rat feeding studies (e.g. mortalities or at least toxic effects would have been anticipated at the highest dose of 12.8 ppm in the subchronic neurotoxicity study but none of these effects were seen).

The requirement for a new subchronic neurotoxicity study in the rat (probably by gavage) is Reserved pending the receipt and evaluation of the new rat acute neurotoxicity study and hen NTE study.

iii) In a previous memo (K. Hamernik to D. Edwards (12/9/92), the registrant was informed that a study designed to establish a NOEL for plasma, erythrocyte, and brain cholinesterase inhibition following an acute oral exposure to Fortress might be required in the future. The possibility for such a requirement still exists. [The registrant had responded in the past that it was amenable to performing the study but preferred to wait until after guidelines or a study design was issued]. Although the registrant may wish to consider incorporating an "acute NOEL" study into the newly required rat acute neurotoxicity study, guidance for this type of study is not available from the Agency at this time.

3. Once the kidney tumor issue has been satisfactorily resolved, none of the additional testing requirements for Fortress technical need hold up registration of the chemical nor impede the tolerance request.

D. Toxicology Branch I Evaluation of the Toxicological Database for Fortress and Fortress 5G

1. A complete summary of the toxicology assessment for Fortress technical and Fortress 5G is provided in the attached TABLE 2.

2. Toxicology Branch I has stated concerns about the toxicity of Fortress in a previous memo (K. Hamernik to D. Edwards, 4/11/91, HED Document 08330). These concerns still apply. Human exposure to Fortress by any route (air, oral, dermal) should be prevented.

Fortress is a highly toxic, potent organophosphate with a steep dose response curve. In animal studies, females have been generally more sensitive to the cholinesterase inhibiting properties of Fortress than have males but males are also very susceptible. Fortress technical is in Toxicity Category I for exposure by the oral, dermal, inhalation, and ocular instillation route (both sexes) and Fortress 5G is in Toxicity Category I for exposure by the oral and inhalation routes (females).

Fortress 5G is considered to be a soil fumigant and as such the active ingredient must volatilize. Concerns have been expressed by Toxicology Branch I to the Occupational Residential Exposure Branch (OREB) about potential worker exposure due to volatilized active ingredient in the headspace of the bags in which Fortress 5G is packaged. The registrant has reported that active ingredient could be expected to be in the bag headspace at the saturation value and has estimated that at 20-25 ppm. The registrant has mentioned the possibility of offering a closed-pour system so that workers would not have to open a container.

E. RfD Peer Review Evaluation

The HED RfD Peer Review Committee met on November 3, 1994 to evaluate the toxicology database for Fortress and set an RfD. The final report is not yet available but will be sent to Registration Division when it is. The Committee recommended an RfD of 0.0006 mg/kg/day based on a overall NOEL of 2 ppm (0.061 mg/kg/day) from the combined subchronic and chronic toxicity studies in dogs and an uncertainty factor of 100 to account for inter-species extrapolation and intra-species variability. The RfD will be made available to DRES.

F. Less than Lifetime Committee Evaluation

The Less than Lifetime Committee met on November 16, 1994 to determine what endpoints should be used for less than lifetime occupational/residential and acute dietary risk assessments for Fortress. A copy of the report is attached. It was determined that the same critical study and effect level (6-Month Ocular Toxicity Study in Dogs, NOEL for plasma cholinesterase inhibition of 2 ppm (about 0.06 mg/kg/day) should be used for acute dietary and short and intermediate term occupational exposure. 100% dermal absorption will be assumed.

These endpoints were made available to OREB and DRES.

G. Risk Assessments

Risk assessments will be performed by the HED/Chemical Coordination Branch/Registration Section.

TABLE 1
Toxicology Data Required for Full Section 3 Registration of Fortress Technical and Fortress 5G

FORTRESSS TECHNICAL

Gdln	Study Type	Submitted	Requirement Satisfied?	Supporting MRID(s)[1]
81-1	Oral LD50	Yes	Yes	408837-11
81-2	Dermal LD50	Yes	Yes	408837-15
81-3	Inhalation LC50	Yes	Yes	408837-16
81-4	Prim Eye Irrit.	Yes	Yes	408837-17
81-5	Prim Skin Irrit.	Yes	Yes	408837-18
81-6	Dermal Sens.	Yes	Yes	408837-19
81-7	Delayed Neurotox	Yes	Yes	408987-02
82-1a	Subchr Feeding (rat)	Yes	Yes (in combo)[2]	412906-27 425592-15 412906-32
82-1b	Subchr Feeding (dog)	Yes	Yes	408987-03 408987-04
83-1a	Chr Feeding (rat)	Yes	Yes[3]	417368-37 412906-27 425592-15
83-1b	Chr Feeding (dog)	Yes	Yes	417368-33
83-2b	Mouse Feeding Onco	Yes	Yes	417368-34 417368-35
83-2a	Rat Feeding Onco	Yes	No[4] (more info needed)	417368-37
83-5	Rat Chr Feeding/Onco	Yes	No[5] (more info needed)	417368-37 412906-27 425592-15
83-3a	Developmental (rat)	Yes	Yes	408987-05
83-3b	Developmental (rabbit)	Yes	Yes	412906-33 425592-19
83-4	Reproduction (rat)	Yes	Yes	417368-36
84-2	Mutagenicity (gene mutation)	Yes	Yes	408837-26[6] 408837-27 408837-28
84-2	Mutagenicity (chromosome aberr)	Yes	Yes	408837-29[6] 408837-31
84-2	Mutagenicity (DNA damage)	Yes	Yes	408837-30
85-1	Metabolism	Yes	Yes[2]	425592-20 412906-35

FORTRESSS TECHNICAL (cont.)

Gdln	Study Type	Submitted	Requirement Satisfied?	Supporting MRID(s)[1]
81-8ss	Acute Neurotox (rat)	Yes	No[7] (more data needed)	425592-10
82-7ss	Subchr Neurotox (rat)	Yes	Partial[8] (need for more data is Reserved)	425592-17
None	6 Month Visual System Toxicity (Dog)	Yes	Yes	425592-21
None	Enzyme Inhibition and Recovery[9]	Yes	Yes	425592-11 429661-01

1 There may have been more than one acceptable study submitted under a particular Guideline requirement for some acute studies with Fortress technical, but only one MRID is listed).
2 Satisfied by a combination of studies whose MRIDs are listed.
3 A chronic toxicity/carcinogenicity feeding study in the rat (MRID 417368-37) was submitted in support of this requirement (see Gdln 83-5). The chronic toxicity portion of MRID 417368-37 is Acceptable (Core Guideline) and is satisfied by a combination of studies whose MRIDs are listed.
4 A chronic toxicity/carcinogenicity feeding study in the rat (MRID 417368-37) was submitted in support of this requirement (see Gdln 83-5). A carcinogenicity issue remains unresolved and more information is needed from the registrant.
5 The chronic toxicity portion of MRID 417368-37 is acceptable but an issue is still outstanding for the oncogenicity portion of the study (finding of a slight increase in kidney tumors in high dose males). The registrant has been informed that more information is required for further evaluation by the Agency.
6 Each MRID represents a separate study.
7 Among other deficiencies, animals were not examined histopathologically (following perfusion) and there were questions about the accuracy of the dosing solution preparations and/or analytic method used. A new acute (gavage) neurotoxicity study in the rat (to include plasma, rbc and brain cholinesterase measurements following a single dose of the chemical, and body temperature evaluations) is required as is a neurotoxic esterase study in the hen (as per 1991 Neurotoxicity Guidelines), although these requirements need not hold up registration. The registrant should submit protocols for both studies in advance.
8 Results inconsistent with results of other studies (i.e. mortalities or at least toxic effects would have been anticipated at the HDT of 12.8 ppm in this study and cholinesterase activities were not available as a point of reference with other studies; The requirement for a new study (probably by gavage) is Reserved pending the receipt and evaluation of the new rat acute neurotoxicity study and neurotoxic esterase study in the hen.
9 A special study requested of the registrant.

FORTRESSS 5G

Gdln	Study Type	Submitted	Requirement Satisfied?	Supporting MRID(s)
81-1	Oral LD50	Yes	Yes	412906-22
81-2	Dermal LD50	Yes	Yes	425592-07
81-3	Inhalation LC50	Yes	Yes	417368-32
81-4	Prim. Eye Irrit.	Yes	Yes	412906-24
81-5	Prim. Skin Irrit.	Yes	Yes	425592-08
81-6	Dermal Sensitization	Yes	Yes	412906-26 425592-09

TABLE 2
1. Toxicology Assessment (technical material)

a. **Acute Toxicity**

SUMMARY OF FORTRESS TECHNICAL[1] GRADE ACUTE TOXICITY DATA

GIdn	Study Type	Results	Category	MRID/HED[2]	Status[3]
81-1	Oral LD_{50} (rat-Crl:CD BR; 8 wks old)	4.8 mg/kg (♂)[6] 1.8 mg/kg (♀)	I	408837-11 (007112)	A
81-1	Oral LD_{50} (rat-Fisher 344; 10 wks old)	2.0 - 4.0 mg/kg (♂)[6] 0.5 - 2.0 mg/kg (♀)	I	408837-12 (007112)	A
81-1	Oral LD_{50} (mouse-B6C3F1)	41 mg/kg (♂)[6] 26 mg/kg (♀)	I	408837-13 (007112)	A[8]
N/A	Oral Lethal Dose (rabbit-N.Zealand White)	6.7 mg/kg (♀)[7] (estimated; only 1 animal per dose group)	I	408837-14 (007112)	N/A
81-2	Dermal LD_{50} (rabbit)	18.5 mg/kg (♂) 12.5 mg/kg (♀)	I	408837-15 (007112)	A
81-3	Inhalation LC_{50} (rat)	0.58 ppm (♂ & ♀) (0.008 mg/l)[4]	I	408837-16 (007112)	A
81-4	Prim. Eye Irrit. (rabbit)	0.1 ml too toxic to test (♂ & ♀); 2/2 deaths with 0.05 ml within 4 hrs[5]	I	408837-17 (007112)	A
81-5	Prim. Skin Irrit. (rabbit)	0.5 ml (about 200 mg/kg) too toxic to test; no dermal irrit. with 0.02 ml (about 12 mg/kg) (♂)	I	408837-18 (007112)	A
81-6	Dermal Sensitization (Guinea pig)	Buehler Method not a sensitizer using 0.4 ml of a 1% solution of technical in 80% ethanol	N/A	408837-19 (007112)	A
81-7	Delayed Neuro-toxicity (Hen)	Negative (97% TGAI or 80% TGAI)[6]	N/A	408987-02 (007112)	A

1 Test material is Fortress Technical (TGAI) (a liquid) of 86% purity unless otherwise specified; Synonyms: IN 43898, SD 208304, Chlorethoxyfos, DPX 43898
2 MRID number and (HED document number)
3 Core Grade or Acceptability Status: A = Acceptable; U = Unacceptable; N/A = Not Applicable
4 Conversion of ppm to mg/l: ppm x M.W. Fortress/24450 = 0.58 x 335.8/24450 = 0.008 mg/l
5 pH of Fortress = 3.52 $\pm$ 0.03
6 vehicle = corn oil
7 vehicle = 0.5% methylcellulose
8 Study is not Core Classified in DER but is Acceptable as an oral LD_{50} study in the mouse

b. **Subchronic Toxicity**

SUMMARY OF FORTRESS TECHNICAL[1] GRADE SUBCHRONIC DATA

Gldn	Study Type	Results	MRID/HED[2]	Status[3]
82-1 (a)	90-day Feeding Study (Rat) (Crl:CD BR rat 4 weeks old at start) (performed 1987)	Dietary levels: 0, 0.1, 1.0, 5, & 10 ppm (0, 0.007, 0.071, 0.357, & 0.784 mkd[4] (♂) & 0, 0.010, 0.093, 0.472, & 1.10 mkd (♀)); Plasma & RBC ChE measure on days 45 & 90. No brain ChE measure; **NOEL (ChE inhibition) = 1.0 ppm** (0.071 mkd ♂ & 0.093 mkd ♀) **LOEL (ChE inhibition) = 5 ppm** (0.357 mkd ♂ & 0.472 mkd ♀) based on inhibition of plasma ChE (25-30%) on days 45 & 90 (♀), was considered to be part of a dose-related decreasing trend; At 10 ppm, plasma ChE was stat. sign. inhib. 37-42% (♂) & 69-77% (♀) days 45 & 90; No treatment-related inhibition of RBC ChE; **NOEL (tremor) = not established** **LOEL (tremor) = 0.1 ppm (LDT)** (0.007 mkd ♂ & 0.010 mkd ♀) based on single to multiple observations of tremor in 2/10 females (tremor was not observed at 1.0 ppm in (♀) but was observed in more females and/or with earlier onset at 5.0 & 10 ppm). Tremor was first observed in males at 10 ppm; **NOEL(systemic)$_{\text{other than tremor}}$ = 5 ppm** (0.357 mkd ♂ & 0.472 mkd ♀) **LOEL (systemic)$_{\text{other than tremor}}$ = 10 ppm** (0.784 mkd ♂ & 1.10 mkd ♀) based on mortality, tremors, and clinical signs (♂ & ♀); Females appear to be more sensitive than males to the toxic effects of Fortress. Keratitis was noted in a number of moribund or found dead females at 10 ppm. [Note: In the original review, an LOEL of 5 ppm for systemic effects other than tremor was assigned based on changes in clinical chemistry parameters and decreases in body weight gain/body weight and food efficiency (days 28-35) in females. Upon reevaluation, this LOEL is not well supported because the changes noted were slight or for the most part transient and no clear biological significance nor pattern was demonstrated. A LOEL in this case of 10 ppm would be clearly supported toxicologically].	412906-27 008330	Supplemental by itself (no brain ChE measure and unresolved issues including tremor at LDT but when taken together with another rat 90-day study (MRID 425592-15) & a rat 6-week feeding study (MRID 412906-32) the data are Minimum & satisfy the requirement for an 82-1 90-day feeding study.

82-1 (a)	90-day Special Feeding Study (Rat) (Crl: CD BR rat, females only, 42 days old at start) (performed 1992); This study was especially designed to address in particular issues of lack of NOEL for ChE inhibition in the rat & the need to find or confirm a NOEL for tremor.	Dietary levels: 0, 0.1, 1.0, 8.0, 12.8, or 16.0 ppm (0, 0.008, 0.080, 0.635, 1.23, & 1.63 mkd); Plasma & RBC ChE were measured on days 1, 7, 14, 21, 28, 45, & 90 (not fasted). Brain (homogenate) ChE was measured at termination (not fasted). **NOEL (ChE inhib)$_{acute}$ = 8 ppm** (0.635 mkd) **LOEL (ChE inhib)$_{acute}$ = 12.8 ppm** (1.23 mkd) based on stat. sign. plasma ChE inhib of 53% and RBC ChE inhib of 13% (♀) on day 1 of treatment; **NOEL (ChE inhib)$_{subchr}$ = 1 ppm** (0.080 mkd) **LOEL (ChE inhib)$_{subchr}$ = 8 ppm** (0.635 mkd) based on stat. sign. decreases in plasma (38-46%) and/or RBC (12-21%) ChE on days 7, 14, 21, 28, 45, & 90, & brain ChE (14%) on day 90; Further decreases in these activities were noted with increasing dose; **NOEL (systemic) = 8 ppm** (0.635 mkd) **LOEL (systemic) = 12.8 ppm** (1.23 mkd) based on mortality, clinical signs of toxicity, body weight & weight gain decreases, a reduced food efficiency. Tremor (additional observations for tremor were included in the study design) was observed in this study starting at 12.8 ppm. A dose-related increase in keratitis of the cornea was noted at the two highest dose levels (occurred mostly in moribund or animals found dead). No treatment-related retinal or optic nerve lesions were noted.	425592-15	The study is Acceptable for the purposes for which it was intended. When taken together with another rat 90-day feeding study (MRID 412906-27 & a rat 6-week feeding study (MRID 412906-32) the data are Minimum & satisfy the requirement for an 82-1a 90-day feeding study in the rat.

82-1 (b)	Subchronic (90-day) Feeding Study (Dog) (Beagle 4 to 5 months old)	Dietary levels: 0, 0.5, 5, & 50 ppm (0, 0.017, 0.185, 1.820 mkd (♂) & 0, 0.019, 0.186, 1.840 mkd (♀)); Plasma and RBC ChE measured on twice pretest & days 45 and 90 (fasted); Brain ChE (caudate n., cerebellum/medulla & cerebrum) were measured at termination; **NOEL (ChE inhibition) = 0.5 ppm** (0.017 mkd) **LOEL (ChE inhibition) = 5 ppm** (0.185 mkd) based on stat. sign. brain (33%) (caudate n.) (females only) at termination and plasma (38-43%) cholinesterase inhibition in both sexes at days 45 & 90; greater inhibition was seen at the high dose; RBC ChE may have been inhibited in high dose males and/or females but due to data variability even in pretest group mean values it was not clear; **NOEL (systemic) = 5 ppm** (0.185 mkd) **LOEL (systemic) = 50 ppm** (1.820 mkd ♂ & 1.840 ♀) based on, in females, tremors (one female), diarrhea, transient decreases in mean body weight, elevated ALT & lower serum calcium, albumin (males also), & total protein.	408987-03 408987-04 (dose-ranging) (007112)	Minimum

82-1	90-day Feeding Study (Mouse) (Crl:CD-1 (ICR) BR approx. 6 weeks old at start)	Dietary levels: 0, 7.5 (compromised), 15, 30, or 60 ppm (0, compromised, 2.19, 4.27, & 8.89 *mkd* (♂) & 0, compromised, 2.82, 5.78, & 10.7 mkd (♀); Analysis of 7.5 ppm conc. showed unacceptable variation of 7-100% (average about 75% of nominal) due to homogenization problems; Plasma and RBC ChE were measured at termination. Brain ChE was not assayed; **NOEL (ChE inhibition) = could not be determined** **LOEL (ChE inhibition) = 7.5 ppm** (nominal) (LDT) plasma ChE was stat. sign. inhibited about 21% (males) & 37% (females); Inhibition increased with increasing dose; also dosing compromised at 7.5 ppm; RBC ChE stat. sign. inhibited in males (20-30%) at 15 ppm & above; **NOEL (systemic) = 60 ppm (HDT)** **LOEL (systemic) = *>60 ppm*** At 60 ppm, increase, often stat. sign., in unilateral colored discharge, enophthalmus, & phthisis of eye relative to other groups & control, not obviously explainable by relationship to orbital sinus bleeding alone.	412906-29 (008330)	Supple-mental (low dose comprom ised)

N/A	Six-week Subchronic Feeding Study (Mice) (Crl: CD-1 (ICR)BR 6-8 weeks old at start)	Dietary levels: 0, 0.1, 1, 75, 100, 150, 225, or 300 ppm (0, 0.015, 0.15, 11.25, 15, 22.5, 33.75, & 45 mkd); 5 animals/sex/group except at two top doses (3/sex/group); Treatment up thru 150 ppm (including controls) was 7 weeks & 5-6 weeks for the top two dose groups.; Plasma & RBC ChE was measured at termination (prandial state not specified); Brain ChE was not assayed; **NOEL (ChE inhibition): = 0.1 ppm** (0.015 mkd) (♀) **LOEL (ChE inhibition): = 1.0 ppm** (0.15 mkd) based on stat. sign plasma ChE inhibition of 16% (♀) (taken as an indicator or flag that test material is "on board" the organism; At 75 ppm & above in both sexes plasma ChE inhibition was almost 95% & RBC ChE was also inhibited 20 to 57%. **NOEL (systemic): = 1 ppm (♂)** **100 ppm (♀)** **LOEL (systemic): = 75 ppm (♂)** **150 ppm (♀)** based on signs of toxicity & decreases in body weight or body weight gain;	412906-30 008330	Supple-mental (was dose ranging study for 18-month study in mouse)

N/A	Six-week Subchronic Feeding Study **Rat** (Crl:CD BR 36 days old at start) and **Mouse** (Crl:CD (ICR) BR) 43 days old at start)	Dietary levels **(Rat)**: 0, 0.1, 1, 5, or 10 ppm (0, 0.009, 0.091, 0.477 & 0.958 mkd (♂) & 0, 0.014, 0.132, 0.66 & 1.33 mkd (♀)); 10 animals/sex/group; Plasma, RBC, & brain (homogenate) ChE were assayed at termination (not fasted); **NOEL (ChE) = 1 ppm** (♀) (0.132 mkd); **LOEL (ChE) = 5 ppm** (0.66 mkd) based on stat. sign brain ChE inhibition of 6% (♀). In addition, brain (52% (♀), 25% (♂), plasma (72% (♀), 49% (♂)), & RBC (24% (♀), 30% (♂)) ChE activities were stat. sign. decreased at 10 ppm. **NOEL (systemic) = 5 ppm** (♂) (0.477 mkd) **LOEL (systemic) = 10 ppm** (0.958 mkd) based on stat. sign. decreases in body weight (7%), body weight gain (56%), & food efficiency (56% days 35-41) (♂). No clinical signs were observed (♂ & ♀). Dietary Levels **(Mice)**: 0, 0.1, 10, 15, or 100 ppm (0, 0.018, 1.98, 2.85 & 19 mkd (♂) & 0, 0.028, 2.94, 3.98, & 31.9 mkd (♀)); 10 animals/sex/group; Plasma & brain (homogenate) ChE were assayed at termination (prandial state unknown); There were no values for RBC ChE provided due to technical difficulties; **NOEL (ChE inhibition) = 0.1 ppm** (0.018 mkd (♂), 0.028 mkd (♀)) **LOEL (ChE inhibition) = 10 ppm** (1.98 mkd (♂), 2.94 mkd (♀) based on stat. sign plasma ChE inhibition in males (51%) and females (61%). In addition brain ChE was stat. sign. decreased in 15 ppm males (10%) and 100 ppm males (85%) & females (79%); **NOEL (systemic) = 15 ppm** (2.85 mkd (♂), 3.98 mkd (♀)) **LOEL (systemic) = 100 ppm** (19 mkd (♂), 31.9 mkd (♀)) based on stat. sign. decreases in food consumption (36%) & food efficiency (62%) in males; No clinical signs were observed (♂ & ♀).	412906-32 (008330)	Supplemental (used to aid in dose setting for a longer term study; No RBC ChE values (mice))

N/A	Ten-Dose Gavage (Rats- Females only) (CRl: CD BR) (8 weeks old at start)	6 females dosed 10 times over a two week period with dose of 0.68 mg/kg/day in corn oil; three deaths by day 13; overt signs of toxicity noted only in animals which died & commenced 5-8 days into the study, with majority appearing near the day of day; (Typical signs: tremors, fasciculations, dyspnea, nasa and periocular discharge, facial, ventral, and perianal staining, hunched posture, & lethargy); irreversible damage to intercostal muscles, body weight gain decrement during first half of study followed by a weight gain, lymphoid necrosis and liver inflammation observed in one animal.	412906-28 (08330)	Supple-mental (not re-quired by guide-lines)
N/A	Ten-Dose Gavage (Mice-Females only) (Crl:CD-1 (ICR) BR) (9 weeks old at start)	10 females dosed 10 times over a two week period with dose of 18 mg/kg/day in corn oil; four deaths by day 12; clinical signs, including tremor, noted only in animals which died & did not appear until the day before or day of death on day eleven or twelve; lymphoid necrosis of thymus, spleen, and lymph node; 10% loss of initial body weight versus 1% in controls; absolute and relative liver weight increases.	412906-31 (08330)	Supple-mental (not re-quired by Guide-lines)

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4 mkd = mg/kg body weight/day

c. **Chronic Toxicity and Carcinogenicity**

SUMMARY OF FORTRESS TECHNICAL[1] GRADE CHRONIC TOXICITY AND CARCINOGENICITY DATA

Gldn	Study Type	Results	MRID/HED[2]	Status[3]
83-1a	2-Yr Chronic Feeding (Rat)	A 2-Year combination Chronic/Carcinogenicity Feeding study in the rat was submitted to support this requirement (see Gdln 83-5 below)	417368-37	see below
83-1b	1-Yr Chronic Feeding (Beagle Dog)(about 6 months old at start)	Dietary levels: 0, 0.2, 2, 20, or 60 ppm (0, 0.007, 0.063, 0.616 & 2.24 mkd (♂) & 0, 0.006, 0.065, 0.591 & 1.86 mkd (♀); Plasma & RBC ChE determinations at 1, 3, 6, 9, & 12 months & brain ChE measured at 12 months (fasted) (caudate n., cerebellum/medulla, cerebrum); **NOEL (ChE inhibition) = 2 ppm** 0.063 mkd ♂ &0.065 mkd ♀) **LOEL (ChE inhibition) = 20 ppm** (0.616 mkd ♂ & 0.591 mkd ♀) based on stat. sign. inhibition of plasma ChE (53-63%) (♂ & ♀) at all time points, RBC ChE (30-71%) (♂ & ♀) at one or more time points, & cerebrum (26%) (♀); decreases in ChE activity in all three brain areas at 60 ppm in both sexes; **NOEL (systemic) = 20 ppm** (0.616 mkd ♂ & 0.591 mkd ♀) **LOEL (systemic) = 60 ppm** (2.24 mkd ♂ & 1.86 mkd ♀) increased relative liver weight, decreased body weight gains, decreased food efficiency, decreases in RBC count, HCT, & Hb (♂), & changes in serum biochemistry parameters indicative of alterations in hepatic function (♂ & ♀)	417368-33	Guide-line
83-2b	18-Month Feeding Oncogenicity (Mouse) (Crl:CD-1(ICR)BR) (49 days old at start)	Dietary levels: 0, 0.1, 2.5, 25, or 150/100 ppm (0, 0.013, 0.337, 3.25 & 14.9 mkd (♂) & 0, 0.018, 0.456, 4.63 & 25.9 mkd (♀); No ChE activity determinations; **NOEL (♂ & ♀) = 25 ppm** (3.25 mkd ♂ & 4.63 mkd ♀) **LOEL = 100 ppm (♂) & 150 ppm (♀)** (14.9 mkd ♂ & 25.9 mkd ♀) based on increased mortality & clinical signs & increased findings related to vomiting (♂ & ♀); decreased body weight gain, food consumption, and food efficiency (♂); **Carcinogenic potential:** No treatment-related increases in neoplasms	417368-34 417368-35	Minimum
83-2a	2-Yr Carcinogenicity (Rat)	A 2-Year combination Chronic/Carcinogenicity Feeding study in the rat was submitted to support this requirement (see Gdln 83-5 below)	417368-37	see below

83-5	2-Yr Chronic Feeding/Carcinogenicity (Rat) (Crl:CD BR rat about 35 days old at start) (in-life performed 1987 - 1989)	Dietary levels:0, 0.1, 0.8, 4,or 8 ppm (0, 0.004, 0.031, 0.154, & 0.311 mkd (♂) & 0, 0.005, 0.042, 0.208, & 0.416 mkd (♀)); Plasma & RBC ChE measured at 3, 6, 12, 18, & 24 months (fasted) & brain (homogenate) ChE (term); **NOEL (ChE inhibition) = 4 ppm** (0.154 mkd ♂ & 0.208 mkd ♀) **LOEL (ChE inhibition) = 8 ppm** (0.311 mkd ♂ & 0.416 mkd ♀) based on stat. sign. inhibition of plasma ChE (36%, mo.12 (♀)) & RBC ChE (9-15%, mo.6,12 (♂)) & (12-24%, mo.12,24 (♀)); No brain ChE inhibition; **NOEL (systemic) = 8 ppm** (0.311 mkd ♂ & 0.416 mkd ♀) **LOEL (systemic) > 8 ppm** no systemic effects; dose selection based on mortality & other signs at 10 ppm & above in two 90-day rat feeding studies (MRID 412906-27 & MRID 425592-15) **Carcinogenic Potential:** A slight increase in kidney tumors, not significant at $p \leq 0.05$ by the statistical methods used by the study authors, was observed in high dose group male rats. The issue has been referred to the HED Cancer Peer Review Committee. **Note: The chronic toxicity portion of the study is acceptable but conclusions in the DER regarding the carcinogenic potential of the chemical are Reserved pending the outcome of the committee's evaluation.**	417368-37 C1137	Guideline (for the Chronic Toxicity portion; Classification of the Carcinogenicity portion of the study is Reserved)

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4 mkd = mg/kg body weight/day

d. **Developmental and Reproduction Toxicity**

SUMMARY OF FORTRESS TECHNICAL[1] GRADE DEVELOPMENTAL AND REPRODUCTION TOXICITY DATA

GIdn	Study Type	Results	MRID/HED[2]	Status[3]
83-3a	Developmental Toxicity (Rat)(Crl:CD BR) (♀ 63 days old at start)	Gavage levels (suspended in 0.5% aq. methylcellulose):0 (vehicle), 0.05, 0.25, 0.50 or 0.60 mkd; **Maternal NOEL = 0.25 mkd** **Maternal LOEL = 0.50 mkd** based on increased mortality and decreased mean body weight gain during gestation days 13-17; **Devel. NOEL = 0.25 mkd** **Devel. NOEL = 0.50 mkd** based on decrease in the number of live fetuses per litter	408987-05 (007112)	Minimum
83-3b	Developmental Toxicity (Rabbit) (N. Zealand White)(♀ 26 wks old at start)	Gavage levels (suspended in 0.5% aq. methylcellulose): [Nominal doses of 0, 1, 2, 3 or 3.5 mkd had to be recalc. based on analysis data to 0 (vehicle), 0.76, 1.38, 2.1 & 3.1 mkd); **Maternal NOEL = 0.76 mkd** **Maternal LOEL = 1.38 mkd** based on treatment-related mortality assoc. with cholinesterase inhibition; **Devel. NOEL = 1.38 mkd** **Devel. LOEL = 2.1 mkd** based on stat. sign. increase in average number of early resorptions per litter relative to controls supported by an increase in the number of litters with at least one early resorption per total litters observed (relative to controls and lower dose groups); no evidence of teratology	412906-33 (008330) 425592-19	Originally Supplemental; response adequate to upgrade to Minimum but EPA dose recalculations remain with HDT corrected from 2.8 to 3.1 mkd

83-4	Reproductive Toxicity- 2-Gen (Rat)(Crl:CD BR) (F_0 43 days old at start); (performed 1988-1989)	Dietary levels: 0, 0.25, 1, 4, or 8 ppm (0, 0.018, 0.074, 0.296 & 0.607 mkd (♂) & 0, 0.022, 0.091, 0.357 & 0.776 mkd (♀)); **Parental NOEL = 4 ppm** (0.296 mkd ♂ & 0.357 mkd ♀) **Parental LOEL = 8 ppm** (0.607 mkd ♂ & 0.776 mkd ♀) based on increased incidence of tremors during lactation **Reproductive NOEL = 8 ppm** (0.607 mkd ♂ & 0.776 mkd ♀) **Reproductive LOEL = >8 ppm** (no findings in this study of possibly treatment-related staining/wetness of the perineum & inguinal areas in pups) **NOTE: The HED RfD Peer Review Committee (11/3/94) recommended that this two-generation study supersede a previous one-generation study in the rat (MRID 412906-27) which was considered to be inadequate. The Committee recommended that the two generation study (MRID 417368-36) be the reproduction toxicity study used for regulatory and risk assessment purposes.**	417368-36	Guide-line

83-4	Reproductive Toxicity - 1-Gen (Rat) (Crl CD BR (P1 4 weeks old at start); (performed 1987)	Dietary levels: 0, 0.1, 1, 5, 10 ppm (0, 0.007, 0.071, 0.357 mkd (♂) & 0, 0.010, 0.093, 0.472 mkd (♀)); Only 10 animals/sex/group; $Parental_{systemic}$ NOEL/LOEL = could not be established; unexplained death (path exam incomplete) at 1.0 ppm but some clinical signs which could be associated with ChE inhibition; $Parental_{repro\ effects}$ NOEL = 1.0 ppm $Parental_{repro\ effects}$ LOEL = 5 ppm decreased copulation or copulation success & decreased numbers of litters; $Offspring_{systemic}$ NOEL = 0.1 ppm $Offspring_{systemic}$ LOEL = 1.0 ppm *for suspected effects consistent with ChE inhibition based on clinical signs of stained perineum & inguine & wet perineum & inguine;* $Offspring_{repro\ effects}$ NOEL = 1.0 ppm $Offspring_{repro\ effects}$ LOEL = 5.0 ppm decreased pup size & group mean pup body weight (However, inadequate number of offspring to evaluate); **Note: This one-generation reproduction study in rats was a continuation of a 90-day feeding study. The HED RfD Peer Review Committee (11/3/94) commented that although the 90-day feeding portion of the study was adequate, the reproduction phase was inadequate due to many deficiencies. The reproduction phase was not considered to be a reliable assessment of the reproductive toxicity potential of this chemical in the rat. Therefore, the reproduction phase should not be used for regulatory or risk assessment purposes. Rather, it was recommended that the two-generation reproduction study in rats (MRID 417368-36) should supersede the one-generation study (MRID 412906-27) for risk assessment and regulatory purposes.**	412906-27 008330	Supplemental due to many deficiencies (only 1 generation, too few parents and litters and other design and reporting inadequacies); a new two-gen study was required

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4 mkd = mg/kg body weight/day

e. **Visual System Toxicity and Neurotoxicity**

SUMMARY of FORTRESS TECHNICAL GRADE[1] VISUAL SYSTEM TOXICITY AND NEUROTOXICITY DATA

Gldn	Study Type	Results	MRID/HED[2]	Status[3]
None	6-Month Ocular Toxicity (dog) (5-7 months old at start)	Dietary levels: 0, 2, 20, or 60 ppm (0, 0.061, 0.578, & 1.880 mkd (♂) & 0, 0.062, 0.619, & 1.852 mkd (♀)); Plasma & RBC ChE were measured pretest, days 2 & 3, weeks 1, 6, 13, & 26 (non-fasted). Brain (pons, cerebellum, hippocampus, caudate n.) and retinal and extraocular muscle ChE were measured at termination (fasted). **NOEL (ChE inhib.)$_{acute}$ = 2 ppm** (0.061 mkd ♂ & 0.062 mkd ♀) **LOEL (ChE inhib.)$_{acute}$ = 20 ppm** (0.578 mkd ♂ & 0.619 mkd ♀) considers only plasma and RBC ChE inhibition; plasma ChE inhib. of 38% (♂) & 30% (stat. sign.) (♀) on day 2 of treatment [on day 3, plasma ChE inhib. of 40% (♂) was stat. sign.; NOEL/LOEL (RBC inhib.)$_{acute}$ = 60 ppm/>60 ppm (1.880 mkd ♂ & 1.852 mkd ♀); **NOEL (ChE inhib.[1])$_{subchr.\ to\ chr.}$ < 2 ppm (LDT)** **LOEL (ChE inhib.[1])$_{subchr.\ to\ chr.}$ = 2 ppm (threshold response)** (0.061 mkd ♂ & 0.062 mkd ♀) plasma ChE inhibition of 12 to 21% in both sexes at wks 1, 6, 13 and 26 (stat. sign inhib. of 21% (♀) at wk. 6); further dose-related decreases in plasma ChE at higher doses at all timepoints, mostly stat. sign, both sexes; At 20 ppm: Cerebellum ChE inhib. 19-20% (both sexes) and retinal ChE inhib. 15% (males) & 31% (females) were not stat. sign. but considered to be of tox. concern since were part of dose-related trends; At 60 ppm: further decreases of 24 to 63% in ChE in all brain areas (mostly stat. sign. both sexes) & retinal ChE (52-56% stat. sign. both sexes). Possible effect on RBC ChE activity (both sexes) at 20 and 60 ppm but not clear cut because although decreases at some timepoints were statistically sign., dose-response curves were very shallow; No effect on Oc. Muscle ChE at any dose; [[1]- includes brain and ocular cholinesterase measurements] (continued next page)	425592-21	A

None	6-Month Ocular Toxicity (dog) (continued)	**NOEL (systemic) = 2 ppm** (0.061 mkd ♂ & 0.062 mkd ♀) **LOEL (systemic) = 20 ppm** (0.578 mkd ♂ & 0.619 mkd ♀) based on a stat. sign. increase in incidence of watery stool in each sex ($NOEL_{sys}$ set with regard given to deficiencies & discrepancies in stool data) **NOEL (ocular tox) = 60 ppm** (1.880 mkd ♂ & 1.852 mkd ♀) **LOEL (ocular tox) > 60 ppm (HDT)** based on absence of histopathology or clear evidence of ERG abnormalities with the techniques used.	425592-21	A
81-8 ss	Acute Neurotoxicity (Rat) (Crl:CD Br) (63-80 days old at start)	Gavage levels (suspended in 0.5% aq. methylcellulose): [Nominal doses of 0, 1.25, 1.6, 2.0, or 2.75 mk (♂) and 0, 0.5, 0.75, or 1.0 mk (♀) had to be recalc. based on analysis data to the following median concs.: 0 (vehicle, two groups), 1.14, 1.18, 1.95, & 2.78 mk (♂) & 0 (vehicle), 0.32, 0.76, & 0.746 mk (♀)]; All rats assessed daily for clinical signs & for FOB & motor activity pretest, day 0 (immed. post-dosing, and days 7 & 14); From Ammended DER: $NOEL_{neurotox}$ = 1.14 mk (♂) 0.32 mk (♀) $LOEL_{neurotox}$ = 1.18 mk (♂) 0.76 mk (♀) Based on decreases in horizontal (♂) and vertical (♂ & ♀) motor activity; At higher doses tremors, gait impairment, effects on locomotion and coordination, clinical signs, & death at the top dose (♂ & ♀). ChE activity <u>was not</u> measured; Deficiencies decrease confidence in NOELs/LOELs; **Note: A new rat acute (gavage) neurotoxicity study is required including histopath exam, ChE determinations in plasma, RBCs and brain and body temp. evaluations. An NTE study in the hen (as per 991 guidelines) is also required.**	425592-10	Supple-mental (cannot upgrade due to lack of histo-path exam (fol-lowing perfusi on) & prob-lem w/ dose soln. prep accur-acy or anal-ytical method

82-7 ss	Subchronic Neurotoxicity (Rat) (Crl:CD BR) (about 35 days old at start)	Dietary levels: 0, 0.05, 0.1, 0.8, 6.4, or 12.8 ppm (0, 0.003, 0.006, 0.049, 0.400, & 0.813 mkd (♂) & 0, 0.004, 0.007, 0.055, 0.452, & 0.908 mkd (♀) [Note: Diets were only assessed at one time during the study and variations were noted in analytical results (homogeneity and concentration), probably not severe enough to in and of itself compromise the study]; $NOEL_{neurotox}$ = 0.452 mkd (♀) 0.813 mkd (♂)(HDT) $LOEL_{neurotox}$ = 0.908 mkd (♀) > 0.813 mkd (♂) stained tail and decreased motor activity (horizontal); also slight decrease in body weight (♀); No effects in males; ChE activity <u>was not</u> measured; [Confidence in this study is reduced because of inconsistences with two other Fortress 90-day feeding studies (MRID 412906-27 & MRID 425592-15) in which frank signs of toxicity and mortality were noted at doses of 10 ppm and above. In this neurotox study, no frank signs of toxicity were apparent, even at 12.8 ppm. Doses for this study were approved at a meeting with the company 10/8/91 based on the results of the 1987 90-day rat feeding study (MRID 412906-27)]; **Note: A requirement for a new subchronic neurotoxicity study in the rat (probably by gavage) is Reserved pending the receipt and evaluation of the new rat acute neurotoxicity study and NTE study in the hen.**	425592-17	Supplemental (cannot upgrade due to inconsistencies of results with those at similar doses in other studies)

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4 mkd = mg/kg body weight/day
mk = mg/kg body weight

f. **Mutagenicity**

SUMMARY OF FORTRESS TECHNICAL[1] GRADE MUTAGENICITY DATA

GIdn	Study Type	Results	MRID/HED[2]	Status[3]
84-2	Salmonella Gene Mutation Study	The test material was not mutagenic even at cytotoxic doses of 5000 ug/plate in the presence or absence of metabolic activation.	408837-26 (007112)	A
84-2	Chinese Hamster Ovary (CHO) Cells Gene Mutation (HGPRT)	The test material was not mutagenic even at severely cytotoxic doses in the absence (30 ug/ml) or presence (65 ug/ml) of metabolic activation.	408837-27 (007112)	A
84-2	Mouse Lymphoma L5178Y Cells Gene Mutation (TK)	The test material was not mutagenic even at severely cytotoxic doses (320 ug/ml) under both activating and non-activating conditions.	408837-28 (007112)	A
84-2	In vivo micronucleus assay in male and female Crl: CD-1 (ICR) BR mice - (Chromosome Aberrations)	No statistically significant increases in micronuclei were found even in animals treated with toxic doses of the test material.	408837-29 (007112)	A
84-2	DNA Repair Assay in cultured Rat Hepatocytes (Other effects)	The test material did not cause DNA damage in two trials when tested up to the limit of solubility, even at cytotoxic concentrations of 200 ug/ml in the first trial and 100 ug/ml in the second trial.	408837-30 (007112)	A
84-2	In vitro Chromosome Aberration	The test material did not induce chromosomal aberrations in the presence or absence of metabolic activation even at cytotoxic concentrations (160 ug/ml).	408837-31 (007112)	A

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g. **Metabolism**

SUMMARY OF FORTRESS METABOLISM DATA

Gldn	Study Type	Results	MRID/HED	Status
85-1	Metabolism	After a single oral (high) dose of 1 to 1.5 mg/kg of purified radiolabeled Fortress to male and female rats, greater than 95% of the administered radioactivity was recovered by 7 days post-dosing. 60 to 66% of the radioactivity was eliminated in the urine, 13 to 26% in the feces, and about 11% was found in the expired air, & 5 to 6% in the tissues & carcass. Trichloroacetic acid, dichloroacetic acid, & trichloroethanol & its glucuronide conjugate (the major urinary metabolite) were detected in the urine & feces. Unchanged parent was the major fecal metabolite in females but was not detected in males. Fortress is activated by conversion to the oxon. Acceptable rationale for waiver of the single & multiple low dose and IV studies were provided.	425592-20 ( ) in combo with 412906-35 (008330)	Upgrade to Acceptable from Supplemental

h. **Special Studies**

SUMMARY OF FORTRESS TECHNICAL[1] GRADE SPECIAL STUDY DATA

Gldn	Study Type	Results	MRID/HED[2]	Status[3]
None	Enzyme Inhibition and Recovery Study	In a series of studies, the relationship between plasma, RBC, and brain cholinesterase inhibition and the appearance of clinical signs, and recovery from toxicity were examined.	425592-11 429661-01	Supplemental (this was a special study with no guideline number)

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2 MRID number and (HED document number)

3 Core Grade or Acceptability Status: A = Acceptable; U = Unacceptable; N/A = Not Applicable; Guideline; Minimum; Supplemental

2. Toxicology Assessment (product)

Acute Toxicity data for Fortress 5G

SUMMARY OF FORTRESS 5G[1] ACUTE TOXICITY DATA

GIdn	Study Type	Results	Category	MRID/HED[2]	Status[3]
81-1	Oral LD_{50} (rat-Crl: CD BR, 7 wks old)	124 mg/kg (♂) 44 mg/kg (♀)	II (♂) I (♀)	412906-22 (008330)	A
81-2	Dermal LD_{50} (rabbit-N.Zealand White)	> 2000 mg/kg (♂ & ♀) (limit test) test material was moistened with dimethyl phthalate to form a paste prior to application	III	412906-23 (008330)	Supplemental due primarily to questions about vehicle suitability
81-2	Dermal LD_{50} (rabbit-N.Zealand White); (repeat study)	> 2000 mg/kg (♂ & ♀) (limit test) test material was moistened with deionized water prior to application	III	425592-07	A
81-3	Inhalation LC_{50} (rat-Crl: CD BR)	0.064 mg/L (♀) 0.205 mg/L (♂) (a waiver request for this study was denied)	I (♀) II (♂)	417368-32	A
81-4	Prim. Eye Irrit. (rabbit - (♀) N.Zealand White)	conjunctival irritation & corneal opacity which subsided in < 72 hrs	III	412906-24 (08330)	A
81-5	Prim. Skin Irrit. (rabbit - N.Zealand White)	Not an irritant (test material was moistened with dimethyl phthalate prior to application)	IV	412906-25 (008330)	Supplemental due primarily to questions about vehicle suitability
81-5	Prim. Skin Irrit. (rabbit - N.Zealand White) (repeat study)	Not an irritant (PII = 0)	IV	425592-08	A
81-6	Dermal Sensitization (Guinea Pig)	Buehler Method Not a sensitizer (water or 80% ethanol vehicle)	N/A	412906-26 (008330) 425592-09	Upgrade to A from Supplemental

1 Test material is Fortress 5G (DPX-43898-26) (a brown solid granule) containing about 5.3% of the active ingredient, Fortress (chlorethoxyphos).
2 MRID number and (HED document number)
3 Core Grade or Acceptability Status: A = Acceptable; U = Unacceptable; N/A = Not Applicable

Meeting Minutes

Less than Lifetime Committee

Special Meeting for Fortress

November 16, 1994

Attendees:

K. Baetcke	K. Hamernick
W. Burnam	M. Ioannou
L. Dorsey	S. Irene
M. Dow	C. Lewis
E. Doyle	J. Rowe
R. Engler	C. Swentzel

The endpoints selected for use in less than lifetime occupational/residential and acute dietary risk assessments for Fortress considered at the November 16, 1994 Less than Lifetime Committee meeting are summarized below.

NOTE: Please include a listing of the appropriate acute toxicity studies and Tox Categories at the end of your writeups after the Cancer and RfD information.

Dermal Absorption: No data are available. Assume 100%. (Note that the validity of this assumption appears to be supported by the similarity of the Dermal and Oral LD50s in female rabbits (12.5 mg/kg/day and 6.7 mg/kg/day).

Acute Dietary: Required. In a 6-Month Ocular Toxicity Study in Dogs (MRID 425592-21), a NOEL = 2 ppm (≈ 0.06 mg/kg/day) was established based upon a decrease in plasma acetylcholinesterase activitiy of 38% at the next highest dose (LEL = 20 ppm in males). RBC cholinesterase was not affected in this study, however, this was not inconsistent with the results of other studies. Brain cholinesterase inhibition appears to parallel plasma cholinesterase inhibition closely for Fortress. Watery stool was reported in both sexes at 20 ppm. The appropriateness of the plasma cholinesterase inhibition as an endpoint for regulation was reinforced by the results of the 1-year dog study, in which clinical signs and RBC cholinesterase inhibition were reported at an LEL ≈ 60 ppm. In addition, the oral LD50 in Fisher rats ranged from 0.5 to 2.0 mg/kg/day, only an order of magnitude higher than the NOEL in the dog study.

Short and Intermediate Term Occupational: Required. Same critical study and effect level (NOEL = 0.06 mg/kg/day) as cited above. In addition to the corroborating data cited above, the appropriateness of the endpoint for longer term exposures is supported by day 7 RBC cholinesterase inhibition reported in a 90-day rat study with an NOEL = 1 ppm (≈ 0.05 mg/kg/day).