10-1-84

004026

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Pendimethalin Registration Standard, Toxicology Chapter.

TO: Amy Rispin
Science Integration Staff
Hazard Evaluation Division (TS-769C)

and

Robert J. Taylor, Product Manager #25
Herbicide/Fungicide Branch
Registration Division (TS-767C)

FROM: Albin B. Kocialski, Ph.D.
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C)

A.B.K. 9/28/84

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C)

and

William Burnam, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

10-1-84

The Toxicology Chapter for Pendimethalin is presented for incorporation into the Pendimethanlin Registration Standard.

OPP:HED:TOX:A.KOCIALSKI:sb 9/27/84 X73710 #4-013

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Use Summary: Pendimethalin (3,4-xylidine, N-(1-ethylpropyl)-2,6 dinitro) is a herbicide plant regulator formulated as a ninety-percent (90%) Technical. It is also recognized by the name PROWL®. End-use formulations are a 1% and 10% granular and 2.98 lbs./gal., 3.0 lbs/gal., and 4.0 lbs/gal. emulsifiable concentrates.

Pendimethalin controls germinating weeds. It is applied using both ground and aerial equipment and depends on mechanical and natural (rain) means for soil incorporation to be effective.

Pendimethalin has both terrestrial food crop and non-food uses. Tolerances exist for several food crops. Non-food crop uses include both ornamentals and tobacco. There are no aquatic, greenhouse, forestry, domestic, indoor/outdoor uses.

Tolerance Reassessment (40 CFR 180.361)

Permanent tolerances are established for the combined residues of the pesticide N-(1-ethylpropyl)-3,4-dimethyl-2,6 dinitrobenzenamine and its metabolite 4-[(1-ethylpropyl)amino]-2-methyl-3,5-dinitrobenzyl alcohol in/on the following raw agrcultural commodities:

CROP	TOLERANCE
Corn,grain	0.100
Cottonseen (oil)	0.100
Soybeans (oil)	0.100
Potatoes	0.100
Sorghum	0.100
Beans,dry edible	0.100
Beans, lima	0.100
Beans, snap	0.100
Peanuts	0.100
Sunflower	0.100
Corn, sweet	0.100
Rice	0.050

A tolerance is established for combined residues of the herbicide N-(1-ethypropyl)-3,4-dimethyl-2,6-dinitrobenzenamine and its metabolites 4-[(1-ethylpropyl)amino]-2-methyl-3,5-dinitrobenzyl alcohol and 3-[(1-ethypropyl)amino]-6-methyl-2,4-dinitrobenzyl alcohol in/on peanut hulls at 0.25 ppm.

The Acceptable Daily Intake (ADI) was originally based upon a two year rat study (Acc. No. 112849). However, this study was subsequently declared invalid and the ADI was then calculated using the 90 day portion of this same study (classified supplementary) rather than being calculated on the basis of the two year dog study (classified minimum, MRID No., 00058657). The reason the 90 day rat study was selected in lieu of the 2 year dog study lies in the fact that the (P)ADI value calculated for the rat is the more conservative value on a mg/kg basis than the dog (see Table 1).

Table 1

Species	NOEL (mg/kg)	SF	(P)ADI mg/kg/day	(P)MPI mg/day (60 kg)
Rat	25.0	2000	0.0125	0.750
Dog	12.0	100	0.125	7.500

Published permanent tolerances currently utilize 2.22% of the PADI, and the TMRC currently stands at 0.0166 mg/day (1.5 kg).

Unpublished Toxicology Branch approved tolerances currently exist for beans, peas, wheat, garlic, onion (dry bulb), safflower and tomatoes, all at 0.10 ppm.

The total TMRC for both published and unpublished Toxicology Branch approved tolerances stands at 0.0418 mg/day (1.5 kg) and the total percent of the PADI utilized is 5.57%.

Residue Chemistry Branch has raised the question of storage stability data for pendimethalin as parent [CL 92,553] and its metabolite 3,5-dinitrobenzyl alcohol [CL 202,347]. RCB stated that the storage stability of pendimethalin residues in/on plant and animal samples is not adequately understood for the parent compound and the metabolite [CL 202,347]. Depending upon the results of the storage stability data issued tolerances may either be increased or decreased and thereby directly affect the percentage of the ADI utilized.

Residue Chemistry Branch has also raised several issues with respect to the presence and/or concentration of residues in/on various commodities. Depending upon the findings presented in response to these issues raised by RCB the percentage of the ADI utilized will be adjusted accordingly.

It is noted here that Residue Chemistry Branch has received from the Food and Drug Administration (July 13, 1984) a report which indicated that during the years 1978 to the present, no residues of pendimethalin have been detected in either domestic or imported foods sampled or in Total Diet Studies. Pendimethalin is determined by multi-residue methodology which is used in analyzing a large number of non-fatty raw agricultural commodities. During the above mentioned time period, over 25,000 samples were analyzed.

It is also noted here that Toxicology Branch considers the CL 217,146 metabolite as well as the CL 113,072 metabolite, which are significant components of peanut hulls, not to be undue toxicological concern (memorandum from J. Doherty [Toxicology Branch/HED] to R. Taylor [Registration Division] in response to a RCB deferral of February 20, 1981, PP 6F1741). Based on this memorandum Residue Chemistry Branch in their Registration Standard Chapter, indicated that CL 217,146 should be deleted from the peanut hull tolerance.

Risk Assessment:

The technical preperation of this herbicide contains the N-nitroso contaminant, [redacted]. A risk assessment for the nitroso contaminant in the product and the calculations indicate that if the nitroso contaminant was not in excess of 135 ppm the associated upper level of risk would not exceed $1x10^{-6}$ [1/1,000,000]. Data submitted to the Agency showed that the level of the nitroso contaminant was below the level calculated [FR. Vol. 45 No. 145, Friday July 25, 1980].

It is also noted here that as of August 1980, the manufacturing process was modified to reduce the amount of nitrosamine formed. The analysis of 27 samples of the technical (EPA Reg. No. 241-245) was submitted by American Cyanamid Company in correspondence on EPA Reg. No. 241-243 and dated August 27, 1980 (Accession No. 243179). The analysis of these samples indicated that the quantity of [redacted]

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

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Toxicological Concerns:

Residue Chemistry Branch has indicated that the registrant only analyzed for the N-nitroso contaminant [redacted] RCB has therefore requested that the registrant indicate whether or not other nitrosoamines may be expected to be present and at what levels.

RCB has also stated that the manufacturing process indicates the use of [redacted]

Toxicology Branch is concerned whether or not additional nitrosamines and [redacted] are present in the technical formulation and to what extent. However, as noted elsewhere in this review, the registrant is also reconducting the rat study and will reconduct the mouse study. The results of these two rodent studies will be considered in conjunction with the chemical analytical findings. Furthermore, depending upon both the biological results and the chemical analytical findings the percentages of these kinds of impurities present in any formulated product will also be considered as to whether or not a risk assessment may be appropriate.

It is also noted here that Residue Chemistry Branch has received from the Food and Drug Administration (July 13, 1984) a report which indicated that during the years 1978 to the present, no residues of pendimethalin have been detected in either domestic or imported foods sampled or in Total Diet Studies. Pendimethalin is determined by multi-residue methodology which is used to analyze a large number of non-fatty agricultural commodities. During the above mentioned time period, over 25,000 samples were analyzed.

Metabolites: The following metabolites of pendimethalin [CL 92,553] have been identified in the tissues and urine of rats.

- the parent [CL 92, 553]
- 4[(1-ethylpropyl)-amino]-2-methyl-3,5-dinitrobenzyl alcohol [CL 202,347]
- 4[(1-ethylpropyl)-amino]-3,5-dinitro-o-toluic acid [CL 99,900]

- 3-(2,6-dinitro-3,4-xylidino-2-pentanol [CL 113,066]
- 4-[[(1-carboxymethyl)propyl]amino]-3,5-dinitro-o-toluic acid [CL 113,071]
- 4-[(1-ethyl-2-hydroxypropyl)amino]-3,5-dinitro-o-toluic acid [CL 113,072]

Two additional metabolites were found in rat urine but not in rat tissues.

- 4-amino-3,5-dinitro-o-toluic acid [CL 202,078]
- 4-[(1-ethyl-3-hydroxypropyl)amino]-3,5-dinitro-o-toluic acid [CL 202,345]

The attached table also shows the metabolites of pendimethalin found in plants. A copy of the technical formulation is also included.

Worker Protection Standards (Re-Entry)

No re-entry interval is required. The use summary indicates that the pesticide is soil incorporated using either mechanical means or rainfall.

The generic data requirements for pendimethalin are attached.

The Toxicology Branch "one-liners" are also attached.

The ADI printout for pendimethalin is also attached.

PENDIMETHALIN

Page_____ is not included in this copy.

Pages 7 through 8 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

X The product confidential statement of formula.

____ Information about a pending registration action.

____ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

CFR 180.361 pencimethalin(Prowl) 9/21/84

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File last updated 9/21/84

ACCEPTABLE DAILY INTAKE DATA

RAT,Older MOLE		S.F.	RfDI	PPI
mg/kg	ppm		mg/kg/day	mg/day(60kg)
25.000	500.00	2000	0.0125	0.7500

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Corn,grain(68)	0.100	1.00	0.00150
Cottonseed (oil)(41)	0.100	0.15	0.00022
Soybeans (oil)(148)	0.100	0.92	0.00138
Potatoes(127)	0.100	5.43	0.00814
Sorgnum(147)	0.100	0.03	0.00005
Beans,dry edible(10)	0.100	0.31	0.00047
Beans,lima(11)	0.100	0.19	0.00029
Beans,snap(12)	0.100	0.98	0.00147
Peanuts(115)	0.100	0.36	0.00054
Sunflower(156)	0.100	0.03	0.00005
Corn,sweet(40)	0.100	1.43	0.00215
Rice(137)	0.050	0.55	0.00041

PPI	TMRC	% ADI
0.7500 mg/day(60kg)	0.0166 mg/day(1.5kg)	2.22

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Unpublished,Tox Approved 6G1739,1923,2275,3G2857,3F2844,4F3042

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Beans(9)	0.100	2.04	0.00306
Peas(117)	0.100	0.69	0.00104
Wheat(170)	0.100	10.36	0.01554
Garlic(61)	0.100	0.03	0.00005
Onion(dry bulb)(106)	0.100	0.72	0.00107
Safflower(141)	0.100	0.03	0.00005
Tomatoes(163)	0.100	2.87	0.00431

PPI	TMRC	% ADI
0.7500 mg/day(60kg)	0.0418 mg/day(1.5kg)	5.57

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ADDENDUM

SUBJECT: Teratology. Second Species Data Requirement. Pendimethalin Registration Standard.

During the data review and compilation of the Pendimethalin Registration Standard the rabbit teratology study was inadvertantly omitted. This rabbit teratology study, classified as core-minimum, fulfills the data requirement for a teratology study in a second species. The data gaps for this study as noted in the table(s) for generic data requirements should therefore be ignored.

Reference: EPA Acc. No. 248659

Toxicology Branch Document Review #002406

TERRESTRIAL FOOD = A

TABLE A
GENERIC DATA REQUIREMENTS FOR PENDIMETHALIN

Data Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology					
ACUTE TESTING:					
81-1 - Oral LD_{50} - Rat	TGAI	A	Yes	MRID # 00072802 MRID # 00026657	No
81-2 - Dermal LD_{50}	TGAI	A	Yes	MRID # 00026657 MRID # 00072802	No
81-3 - Inhalation LC_{50} - Rat	TGAI	A	Yes	MRID # 00073342	No
81-4 - Primary Eye Irritation (rabbit)	TGAI	A	Yes	MRID # 00026657 MRID # 00072802	No
81-5 - Primary Dermal Irritation	TGAI	A	Yes	MRID # 00026663	No 4/
81-6 - Dermal Sensitization Study	TGAI	A	No		Yes (6 months)
81-7 - Acute Delayed Neurotoxicity - Hen	TGAI	A	*NR		
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding - Rodent, Non-rodent	TGAI	A	Partially	MRID # 00059468 (rat) MRID # 00058657 (dog)	yes (rodent) No 5/
82-2 - 21-Day Dermal	TGAI	A	Yes	MRID # 00026663	No
82-3 - 90-Day Dermal	TGAI		*NR		
82-4 - 90-Day Inhalation - Rat	TGAI		*NR		
82-5 - 90-Day Neurotoxicity- Hen/Mammal	TGAI		*NR		

* Not Required

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TABLE A
GENERIC DATA REQUIREMENTS FOR PENDIMETHALIN

Data Requirement	Composition 1/	Use Pattern 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B) 3/
§158.135 Toxicology (continued)					
CHRONIC TESTING:					
83-1 - Chronic Toxicity - 2 species: Rodent and Non-rodent	TGAI	A	Partially	Acc # 112849 MRID # 00058657	Yes (rodent 24 Mos.)
83-2 - Oncogenicity Study - 2 species: Rat and Mouse preferred	TGAI	A	No	Acc# 112849 MRID # 00040301	Yes (rat 24 Mos.) Yes (mouse 36 Mos.)
83-3 - Teratogenicity - 2 species	TGAI	A	Partially	MRID # 00025752	Yes (12 Mos.) other than rat
83-4 - Reproduction, 2-generation	TGAI	A	Yes	MRID # 00040304	No
MUTAGENICITY TESTING					
84-2 - Gene Mutation	TGAI	A	No	MRID # 00067519	Yes (12 Mos.) 6/
84-2 - Chromosomal Aberration	TGAI	A	No	MRID # 0026673	Yes (12 Mos.) 6/
84-2 - Other Mechanisms of Mutagenicity	TGAI	A	No		Yes (12 Mos.) 6/

TABLE A
GENERIC DATA REQUIREMENTS FOR PENDIMETHALIN

Data Requirement	Composition 1/	Use Pattern 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology (continued)					
SPECIAL TESTING					
85-1 - General Metabolism	PAI or PAIRA	A	Yes	MRID # 00046275	No
85-2 - Domestic Animal Safety	Choice		*NR		
85-3 - Dermal Absorbtion 7/ Studies		A			

* Not required

TABLE A
GENERIC DATA REQUIREMENTS FOR PENDIMETHALIN

§158.135 Toxicology
(continued)

1/ Composition: PAI = Pure active ingredient; PAIRA = Pure active ingredient, radiolabelled; Choice = Choice of several test substances determined on a case-by-case basis.

2/ The use patterns are coded as follows: A=Terrestrial, Food Crop; B=Terrestrial, Non-Food; C=Aqautic, Food Crop; D=Aquatic, Non-Food; E=Greenhouse, Food Crop; F=Greenhouse, Non-Food; G=Forestry; H=Domestic Outdoor; I=Indoor.

3/ Data must be submitted no later than _____.

4/ A 21 day subacute dermal study (MRID # 00026663) is being used to satisfy this acute data requirement.

5/ The chronic dog study satisfies the requirement for the subchronic dog study.

6/ The following mutagenicity studie are required (1) gene mutation in bacteria (2) gene mutation in mammalian cells in culture (3) chromosome aberration analysis in mammalian cells in culture (4) DNA damage in mammalian cells in culture.

7/ The Toxicology Branch reserves the option to request this kind of study.

TERRESTRIAL FOOD = A

TABLE B.
PRODUCT SPECIFIC DATA REQUIREMENTS FOR MANUFACTURING-USE PRODUCTS CONTAINING PENDIMETHALIN

Data Requirement	Composition 1/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 2/
§158.135 Toxicology				
ACUTE TESTING				
81-1 - Oral LD_{50} - Rat	MP	Yes	MRID # 00072802 MRID # 00026657	No
81-2 - Dermal LD_{50}	MP	Yes	MRID # 00026657 MRID # 00072802	No
81-3 - Inhalation LC_{50} - Rat	MP	Yes	MRID # 00073342	No
81-4 - Primary Eye Irritation - Rabbit	MP	Yes	MRID # 00026657 MRID # 00072802	No
81-5 - Primary Dermal Irritation	MP	Yes	MRID # 00026663	No 3/
81-6 - Dermal Sensitization	MP	No	-	Yes (6 Mos.)

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TABLE B

PRODUCT SPECIFIC DATA REQUIREMENTS FOR MANUFACTURING-USE PRODUCTS CONTAINING PENDIMETHALIN

§158.135 Toxicology
(continued)

1/ Composition: MP = Manufacturing-use product.

2/ Data must be submitted no later than _____.

3/ A 21 day subacute dermal study (MRID # 00026663) is being used to satisfy this acute data requirement.

TERRESTRIAL FOOD = B

TABLE B
GENERIC DATA REQUIREMENTS FOR PENDIMETHALIN

Data Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?3/
§158.135 Toxicology					
ACUTE TESTING:					
81-1 - Oral LD_{50} - Rat	TGAI	B	Yes	MRID # 00072802 MRID # 00026657	No
81-2 - Dermal LD_{50}	TGAI	B	Yes	MRID # 00026657 MRID # 00072802	No
81-3 - Inhalation LC_{50} - Rat	TGAI	B	Yes	MRID # 00073342	No
81-4 - Primary Eye Irritation (rabbit)	TGAI	B	Yes	MRID # 00026657 MRID # 00072802	No
81-5 - Primary Dermal Irritation	TGAI	B	Yes	MRID # 00026663	No4/
81-6 - Dermal Sensitization Study	TGAI	B	No		Yes (6 months)
81-7 - Acute Delayed Neurotoxicity - Hen	TGAI	B	*NR		
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding - Rodent, Non-rodent	TGAI	B	*NR		
82-2 - 21-Day Dermal	TGAI	B	Yes	MRID # 00026663	No
82-3 - 90-Day Dermal	TGAI		*NR		
82-4 - 90-Day Inhalation - Rat	TGAI		*NR5/		

TABLE B

GENERIC DATA REQUIREMENTS FOR PENDIMETHALIN

Data Requirement	Composition 1/	Use Pattern 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology (continued)					
CHRONIC TESTING:					
83-1 - Chronic Toxicity - 2 species: Rodent and Non-rodent	TGAI	B	Partially	Acc # 112849 MRID # 00058657	Yes (rodent 24 Mos.) 6/
83-2 - Oncogenicity Study - 2 species: Rat and Mouse preferred	TGAI	B	No	Acc# 112849 MRID # 00040301	Yes (rat/mouse 24/36 Mos.)
83-3 - Teratogenicity - 2 species	TGAI	B	Partially	MRID # 00025752	Yes (12 Mos.) other than rat
83-4 - Reproduction, 2-generation	TGAI	B	Yes	MRID # 00040304	No
MUTAGENICITY TESTING					
84-2 - Gene Mutation	TGAI	B	No	MRID # 00067519	Yes (12 Mos.) 7/
84-2 - Chromosomal Aberration	TGAI	B	No	MRID # 0026673	Yes (12 Mos.) 7/
84-2 - Other Mechanisms of Mutagenicity	TGAI	B	No		Yes (12 Mos.) 7/

TABLE B

GENERIC DATA REQUIREMENTS FOR PENDIMETHALIN

Data Requirement	Composition 1/	Use Pattern 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology (continued)					
SPECIAL TESTING					
85-1 - General Metabolism	PAI or PAIRA	B	Yes	MRID # 00046275	No
85-2 - Domestic Animal Safety	Choice	*NR			
85-3 - Dermal Absorbtion 8/ Studies		B			

* Not required

TABLE B

GENERIC DATA REQUIREMENTS FOR PENDIMETHALIN

§158.135 Toxicology
(continued)

1/ Composition: PAI = Pure active ingredient; PAIRA = Pure active ingredient, radiolabelled; Choice = Choice of several test substances determined on a case-by-case basis.

2/ The use patterns are coded as follows: A=Terrestrial, Food Crop; B=Terrestrial, Non-Food; C=Aqautic, Food Crop; D=Aquatic, Non-Food; E=Greenhouse, Food Crop; F=Greenhouse, Non-Food; G=Forestry; H=Domestic Outdoor; I=Indoor.

3/ Data must be submitted no later than _____.

4/ A 21 day subacute dermal study (MRID # 00026663) is being used to satisfy this acute data requirement.

5/ A 90-day inhalation study is not required. However, a 21 day inhalation study was submitted since the pesticide is used on tabacco. The study (MRID # 00031974) is provisionally invalid. Additional information or data is required.

6/ A rodent study of at least 12 months duration is required.

7/ The following mutagenicity studie are required (1) gene mutation in bacteria (2) gene mutation in mammalian cells in culture (3) chromosome aberration analysis in mammalian cells in culture (4) DNA damage in mammalian cells in culture.

8/ The Toxicology Branch reserves the option to request this kind of study.

TERRESTRIAL NON-FOOD = B

TABLE B

PRODUCT SPECIFIC DATA REQUIREMENTS FOR MANUFACTURING-USE PRODUCTS CONTAINING PENDIMETHALIN

Data Requirement	Composition 1/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 2/
§158.135 Toxicology				
ACUTE TESTING				
81-1 - Oral LD_{50} - Rat	MP	Yes	MRID # 00072802 MRID # 00026657	No
81-2 - Dermal LD_{50}	MP	Yes	MRID # 00026657 MRID # 00072802	No
81-3 - Inhalation LC_5^0 - Rat	MP	Yes	MRID # 00073342	No
81-4 - Primary Eye Irritation - Rabbit	MP	Yes	MRID # 00026657 MRID # 00072802	No
81-5 - Primary Dermal Irritation	MP	Yes	MRID # 00026663	No 3/
81-6 - Dermal Sensitization	MP	No	-	Yes (6 Mos.)

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TABLE B
PRODUCT SPECIFIC DATA REQUIREMENTS FOR MANUFACTURING-USE PRODUCTS CONTAINING PENDIMETHALIN

§158.135 Toxicology
(continued)

1/ Composition: MP = Manufacturing-use product.

2/ Data must be submitted no later than _____.

3/ A 21 day subacute dermal study (MRID # 00026663) is being used to satisfy this acute data requirement.

Tox Chem No. Prowl 454BB | File Last Updated _____ | Current Date 9-19-83

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute Oral LD50 (mice) American Cyanamid Co. Report# A-72-4, 6/1/72 MRID #00026657	Technical	Not Known	AOLD50: Males greater than 1620.0 mg/kg Females greater than 1340.0 mg/kg	3	Minimum
Acute Oral LD50 (dogs) American Cyanamid Co. Report #A-72-4, 6/1/72 MRID #00026657	Technical	Not Known	AOLD50: Greater than 5000 mg/kg	4	Minimum
Acute Oral LD50 (rat) American Cyanamid Co. Report #A-72-4, 6/1/72 MRID #Not Assigned	Technical AC 92,553 93%	Not given	AOLD50: 2140.0 mg/kg (NOTE: This study may be the same as MRID# 00072802. The report number and date my be in 3 error.)	3	Minimum/000543
Acute Oral LD50 (rat) American Cyanamid Co. Report #A-73-133, 11/28/73 MRID #00072802	Technical	Not Known	AOLD50: 2140.0 mg/kg 95% C.L. (1330.0-4430.0) mg/kg	3	Minimum
Acute Oral LD50 (rat) American Cyanamid Co. Report #A-72-4, 6/1/72 MRID #0026657	Technical	Not Known	AOLD50: Males - 1250.0 mg/kg Females - 1050.0 mg/kg	3	Minimum/000543
Acute Dermal LD50 (rats) American Cyanamid Co. Report #A-72-4, 6/1/72 MRID #00026657	Technical	Not Known	ADLD50: Greater than 5000 mg/kg (HDT)	3	Minimum/000543
AILC50 (rat) Affiliated Med. Res. Inc Contract #122-1968-43 10/24/73 MRID #00073342	Technical AC 92,533 (15% aq. sol. fog)	Not given	AILC50: Greater than 320 mg/l (nominal concentration) at the end of a 4.0 hour exposure. No deaths or adverse effects other than irritability and sluggishness were observed.		Minimum/000543

Tox. Chem No. Prowl 454BB | File Last Updated _____ | Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Primary Eye Irritation (rabbit) American Cyanamid Co. Report #A-72-4, 6/1/72 MRID #00025657	Technical	Not Known	Transient conjuctivitis in one rabbit at 24 hours (unwashed eyes).	3	Minimum/000543
Acute Dermal LD50 (rabbit) American Cyanamid Co. 11/28/73 Report #A-73-133 MRID #00072802	Technical	Not Known	ADLD50: > 5000 mg/kg	3	Minimum
Primary Dermal Irritation American Cyanamid Co. 11/28/73 Report #A-73-133 MRID #00072802	Technical	Not Known	(NON-IRRITATING). Study need not be repeated. See 21-day subacute dermal MRID#00026663 which satisfies this requirements.	3	Supplementary
Primary Eye Irritation American Cyanamid Co. 11/28/73 Report #A-73-133 MRID #00072802	Technical	Not Known	Technical pendimethalin produces slight irritation in unwashed eyes of rabbits.	3	Minimum
Primary Dermal Irritation, (rabbit) American Cyanamid Co. Report #A-72-4, 6/1/72 MRID #00026657	Technical	Not Known	Erythema scores were not available. Edema was not observed. May be non-irritating. Study need not be repeated. See 21-day subacute dermal MRID#00026663 which satisfies this requirement.	3	000543 Changed to Supplementary from Minimum

Tox. Chem No. Prowl 454BB | File Last Updated _____ | Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute Oral LD50 (mice) American Cyanamid Co. Report #A-73-70, 9/5/73 MRID # Not Assigned	Metabolites of Prowl (CL 99,900) o-Toluic Acid, 4[(1-ethylpropyl)amino]-3, 5-dinitro	Not given	Acute Oral LD50: 1440 mg/kg (95% 1160-1770)		UNCLASSIFIED. Study not available.
	(CL 113,072) o-Toluic Acid, 4[(1-ethyl-2-hydroxypropyl) amino]-3,5-dinitro		Acute Oral LD50: 1650 mg/kg (95% C.L. 1310-2080)		UNCLASSIFIED. Study not available.
	(CL 202,345) o-Toluic Acid, 4[(ethyl-3-hydroxypropyl) amino)3,5-dintro		Acute Oral LD50: 2330 mg/kg (95% C.L. 1860-2920)		UNCLASSIFIED. Study not available.
Acute Oral LD50 (mice) American Cyanamid Co. Study #A-73-72 Sept. 1973 MRID #00059475	o-Toluic Acid, 4[(1-caboxy-methyl)propyl] amino)-3,5-dinitro [(CL 113, 071) Assumes purity of > 90%]	Not Known	Two doses tested: 2500 and 5000 mg/kg. No signs or deaths at low dose. One death at high dose. Diuresis at high doses. AOLD50 greater than 5000 mg/kg.	4	Minimum
	(CL 202,347) Benzyl Alcohol 4[(1-ethylpropyl)amino)-2-methyl-3,5-dintro		Acute Oral LD50: 2140 mg/kg (1690-2720) mg/kg		UNCLASSIFIED. Study not available.

Tox Chem No. Prowl 454BB File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
21-Day Subacute Dermal Toxicity (rabbits) Food Drug Res. Labs Lab #1613, 8/24/73 MRID #00026663	Technical AC 92,553	Not given	Doses administered were 250, 500 and 1000 mg/kg for 6 hours/day, 5 days/week for 3 weeks. No systemic toxicity was noted in the treated animals. Histopathology was however limited. Animals exposed to the compound showed only slight to Mild signs of edema and erythema at 500 and 1000 mg/kg. No erythema or edema was noted at the low dose.		Minimum/000544
21-Day Inhalation (rat) Food Drug Res. Labs. Report #2935, 1/6/75 MRID #00031974 [Smoke inhalation with tobacco treated herbicide]	AC 92,553		Comprehensive examination of rats revealed no treatment related effects on weight gain, hematologic, or biochemical parameters or organ weights. No reported pathological lesions that were test chemical related (see also review of John Doherty, dated Oct. 12, 1979).		Provisionally Invalid (see review)
30-Day Feeding - Dietary (rat) American Cyanamid Co. Report #A-72-4, 6/1/72 MRID #000106754	AC 92,553 Technical	Not Known	Doses tested were 800, 1600 and 3200 ppm. No firm conclusions can be drawn from the study. Increased liver weight at 3200 ppm. Study gives some suggestive evidence that the compound may have a low toxicity. Data suggests a NOEL of 1600 ppm.		Supplementary
30-Day Feeding - Dietary (mice) American Cyanamid Co. Report #A-72-4, 6/1/72 MRID #00106754	AC 92,553 Technical	Not Known	Doses tested were 500, 1000 and 2000 ppm. No firm conclusions can be drawn from the study. Study gives some suggestive evidence that the compound may have a low toxicity. Data suggests a NOEL of 2000 ppm.		Supplementary

Tox Chem No. Prowl 454BB | File Last Updated _____ | Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
30-Day Feeding - Dietary and Gavage (dogs) American Cyanamid Co. Report #A-72-4, 6/1/72 MRID #00106754	AC 92,553 Technical	Not Known	Doses of 250 and 125 mg/kg given for 16 days in diet followed by administration for 14 days by cap-capsule. Single dose of 1000 mg/kg given by capsule for 30 days. Compound was unpalatable in the diet. Results of low doses uncertain. High dose showed decreased body weight. Data do not suggest a NOEL.		Supplementary
14-Day Feeding - Dietary Rats and Mice. American Cyanamid Co. Report #A-72-4 6/1/72 MRID #00106754	AC 92,553 Technical	Not Known	MICE: Doses tested were 4000, 8000 and 16,000 ppm (equivalent to 2x the AOLD50/day). No deaths. Decreased food consumption, decrease weight gain. Study suggests compound may have low toxicity.		Supplementary
			RATS: Doses tested were 6400 and 12,800 ppm (equivalent to AOLD50/ day). No deaths, decreased food consumption, decreased weight gain. Study suggests compound may have low toxicity.		Supplementary

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
90-Day Feeding (Long-Evans rat) Bio/Dynamics Inc. Project #72R-746 8/21/74 MRID #00059468	Technical AC 92,553	112849	Interim sacrifice in 2 year rat chronic feeding/oncogenicity study. NOEL (provisional) 500 ppm. Mean body weights were lower for each sex (N = 60 per sex) in the high dose group (2500 ppm raised to 5000 ppm after six weeks) starting with the 5th week. AP enzyme levels for high and medium (500 ppm) dosed males (N = 6 sex/dose) and all treated females (N = 6 sex/dose) were statistically significantly lower (this effect was not however noted at 24 months). Pathology (N = 10 sex/dose) did not support his finding. Liver weights for both sexes were significantly higher at the high dose for both sexes as well as the mid dose at 90 days. Pathology did not support these findings. Females had a terminal weight which was noticeably below control values. Male weights were comparable to controls. Changes is liver organ to body weight ratio were not consistent between sexes at the low dose of 100 ppm. Blood clotting time decreased with increased dose in both sexes and appeared dose related. Hyperplasia of the male mammary gland was observed. A separate 90 day study to further examine this effect was conducted and was found to be negative.		Originally Not Classified/ 000544, (see also two year chronic rat study) but was classified as supplementary during the course of Registration Standard Development.

Tox Chem No. Prowl 454BB

File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
90-Day Beagle Dog study (feeding & gavage) Food Drug Res. Labs Lab. #1421, 9/12/73 MRID #00026672 or MRID #00040305. (Identical study in both)	Technical AC 92,553	Not given	NOEL: 62.5 mg/kg (equal to 2500.0 ppm). LDT Note: The LDT was given as an additive in the diet. The middle and high dose groups of 250 and 1000 mg/kg/day were administered by oral gavage.		NOTE*/000544 *The Toxicology Branch has taken the position that in the development of a Registration Standard existing reviews and/or one-liners for SUBCHRONIC studies are NOT to be re-evaluated when existing chronic studies were completed using the same species and route of exposure. These reviews and/or one-liners are to be accepted "as is" and Registration Standard references (MRID numbers) assigned without further comment.

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Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
					This condition has been fulfilled by the submission of a 2-year dog study (oral route capsule) which has been classified as Core-Minimum (see MRID #00058657). Reference: Standard Operating Procedures for Registration Standards. Dated November 6, 1982. And signed off by William L. Burnam. Actual date on document is November 19, 1982. Invalid as of April 13, 1983/ 000544, 001223
18-Month Mouse Oncogenic Study Bio/dynamics, Inc/ Project #72R 747, 4/2/74 MRID #00040301	High Purity AC 92,553 utilized for 0-6 months, followed by technical (commercial grade) material.	Not given	NOEL: 500 ppm No oncogenic effects noted. Doses tested were 100, 500 and 2500 ppm. After 8 weeks the high dose group received double the dose (5000 ppm) in the feed.		

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
			LEL: 2500-5000 ppm Significantly decreased female body weight. Adrenal absolute wts. (males) and adrenal/body wts. ratios (males/females) were higher as were thyroid absolute wts. and thyroid/ body wt. ratios.		
2-Year Chronic Feeding/ Oncogenic (rat, Long-Evans) Bio/dynamics Inc. Project #72R-746, 8/21/74, MRID # Not Assigned	High Purity AC 92,553 utilized for 0-6 months followed by technical material.	112849	NOEL: 500 ppm No oncogenic effects noted at HDT. Doses tested were 100, 500 & 2500 ppm (5000 ppm after 6 wks). LEL: 2500-5000 ppm. Mean body wts. lower for both sexes in the high-dose group starting with the 5th wk Liver wts. for males and females were significantly higher ($p < 0.01$) at the high dose level at 90 days. The effect on liver wts. persisted at the high dose level. No effects noted at lower dose levels on the liver. Hepatocyte hypertrophy & hyperplasia noted in the high dose level after 2 yrs. No increase in tumor or cancer incidence was noted at any feeding level. Mammary gland hyperplasia in male rats occurred to a greater degree of change & incidence in treated rats occassion-ally accompanied by dysplastic changes. The changes were not dose dependent & not considered treat-ment related. A few mammary glands exhibited cystic and degenerative changes with and without associated inflammation.		Invalid as of April 13, 1983/ 000544, 001223

Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
2-Year Chronic Feeding/ Oncogenic (rat, Long-Evans) Bio/dynamics Inc. Project #72R-746, 8/21/74, MRID#Not Assigned	Technical AC 92,553	112849	Revised NOEL: The original NOEL for this study (500 ppm) is being revised downward to 100 ppm. The reviewer and the pathologist for the Toxicology Branch both concur with the reassignment. The rationale for this reassignment is as follows: An increase in secretory globules was observed in the follicular epithelial cells of the thyroid in both the high dose (5000 ppm) and intermediate dose (500 ppm) males & females when compared to controls. This increase appears to be dose dependent and to have resulted from administration of the test material. This reassignment of the NOEL for this study to 100 ppm supersedes an earlier interpretaton of the same additional pathologic data given in a memo by R. Gessert, 1/16/79. Although the observed thyroid effect is not considered to be a degenerative morphologic lesion, it nevertheless is considered to be a significant effect due to administration of the test material. (See review of 3/25/80.)		

Study/Lab/Study #/Date	Material	No.	LD50, LC50, PIS, NOEL, LEL	Category	Doc. No.
2-Year Chronic Feeding/ Oncogenic (rat, Long-Evans) Bio/dynamics Inc. Project #72R-746 8/21/74 MRID#Not Assigned	Technical AC 92,553	112849	Re-revised NOEL: (Ref: Review by J. Doherty, dated 11/3/82. Review of pathology report submitted as an addendum to the 2-yr. chronic toxicity/oncogenesis study with pendimethalin). The chronic feeding aspects of the study do not show a NOEL for lesions which develop in the liver. This conclusion is based upon the addendum pathology report prepared by R. F. McConnell, D.V.M and dated 6/15/81 (see EPA Acc. Nos. 246347-49). The addendum pathology report was prepared in response to questions/suggestions presented in the review by J. Doherty dated 11/27/81. The low dose group had many more incidences of liver lesions, when compared to controls, as manifested by periportal hepatocyte hypertrophy, ground glass cytoplasmic changes and fatty changes. Additionally the mid-dose group (females) and high dose group (males and females) also had cytoplasmic laminated bodies. No effects were observed on the thyroid at 100 ppm. Evidence of oncogenicity may be present. The bladder of males were found to have 3 incidences of transitional cell carcinoma in the high dose group vs. 2 in all other groups combined. Since bladder carcinomas are rare in rats, the urinary bladder is a suspect target organ. However, a final TB position has not been taken and this result is under active discussion. (cont. on next page)		

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
			Statistical analysis of uterine data suggested that the high dose (5000 ppm) endometrial adenocarcinomas may be compound related. This lesion is considered relatively rare in rats and is considered a suspect target organ. A final TB position has not been taken and this result is also under active discussion. NOTE: Bladder and uterine tumors are known to be associated with nitroso compounds. NOTE: In the initital 5-6 months of the studies (both rat and mouse), a "high purity" grade of test substance was utilized. The later months of these studies utilized a technical or commercial grade of substance. Nitrosamines were present in the commerical grade but not in the "high purity" grade. Thus, the animals were not exposed to the potential carcinogens during the critical periods of growth and development. (See H. L. Avallone memo dated 5/12/80 regarding the laboratory audit.)		

Tox Chem No. Prowl 454BB File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
90-Day Male Feeding Study (Effects on Mammary Glands) (rats) Pharmacopathics Res. Lab Inc. Report #Not Known 6/1/73, MRID #00059469	Technical AC 92,553	Not Known	Twenty weanling rats of the Sprague-Dawley strain were fed 2500 ppm for 6 wks. and 5000 ppm thereafter. Mammary glands were examined histologically. The appearance of the glands were unremarkable without any signs of hyperplasia. NOTE: After 60 days, 5 rats from each group were examined for microscopic mammary changes with the remainder examined at 90 days.		Supplementary
Three-Month Oral Dose Range Study of the Effects of AC 92,553 Upon Mammary Tissues of Male Rats Bio/dynamics Inc. Report No. 73R-869 September 14, 1973 MRID #00059468	Technical AC 92,553	Not Known	Male Long-Evans strain rats, 25 per dose level, received 0, 25, 50, 100, 500 and 2500 (2500 increased to 5000 after 8 weeks) mg/kg/day of test compound in the diet. Mammary gland tissues were considered not unlike that detected in untreated rats of similar age. (See also review. See also study referenced by MRID #00059469).		Supplementary

Tox Chem No. Prowl 454BB | File Last Updated _____ | Current Date 3/ /83

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
2-Year Feeding (dog) (Gelatin capsule) Litton Bionetics Inc. Study #20755, 12/79 MRID #00058657	Technical AC 92,553 91.4% Batch #77-02	Acc 244444 244445	NOEL: 12.5 mg/kg/day LEL: 50 mg/kg/day - increase in alkaline phosphatase level in blood, increased liver weight, presence of microscopic lesions in the liver including , inflammation and hemosiderosis. NOTE: Chronic inflammation of the 3rd and 4th ventricles was observed in the mid (50 mg/kg/day) and high (200 mg/kg/day) dose group. The testing lab concluded that this lesion was incidental. Toxicology Branch notes the presence of the findings but does not consider the findings to be conclusively linked to the presence of the chemical.		Minimum/ 001035
Teratology (rat) Industrial BioTest IBT #B1374(A), 7/20/72 MRID #Not Assigned	Technical AC 92,553		This study was validated by American Cyanamid and found to be Invalid. The reader should also refer to the review in TB files dated 2/4/80. NOTE: This study is not the IBT study referenced in pesticide petitions requesting tolerances. The referenced IBT study is IBT #B2324 dated 12/12/72. The company should clarify this situation.		Invalid
Teratology (rat) Industrial BioTest IBT #B2324 December 12, 1972 MRID #00027237	Technical AC 92,553	Not Known	The results are not reported here. The results are not meaningful. The study was validated and found to be invalid. "Summary of IBT Review, Program Office of Pesticide Programs, July 1983.		Invalid

TOX Chem No: 41001 45455 File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Teratology (rat) Hazleton Labs Project #362-155 8/17/79, MRID #00025752	AC 92,553 (Technical)	241595	The compound was not teratogenic or fetotoxic up to 500.0 mg/kg (HDT)		Guideline/ 000544
Reproduction (3-Generation rat) Bio/dynamics Inc. Project #72R-748 ca. 3/6/74 MRID #00040304	AC 92,553 (Technical)	Not Known	NOEL: 500 ppm in diet (LDT). The HDT was 5000 ppm. Slightly reduced number of offspring, with no corresponding increase in deaths. Decreased litter survival and/or reduced mean offspring weights. Decreased survival primarily during the lactation period (ie. when nursed by mothers during days 0-21). (NOTE: High dose diet removed from lactating females for most litters to increase survivability of offspring. However it is not clear to the TB reviewer if the decrease in post-natal survival should be confined for cause to the lactation period alone or the administration of the compound in general). Decreased weight gain from weaning to maturity.		Minimum/ 000544

Teratology (rabbit) Hazleton Labs # 362-164 5/11/82	Technical 92.2%	248659	NOEL > 60.0 mg/kg/day (HDT)		MINIMUM 002406

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004026

Tox Chem No. Prowl 454BB File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenicity (Ames) American Cyanamid Co. Study # - Not given ca. 6/10/77 MRID #00067519	Technical 94% (lot # AC 1984-79-3) 91.4% (lot # AC 2318-141-3) 91.0% (lot # AC 2771-101-D)	230618	Test compounds were evaluated with and without activation provided by a rat liver enzyme preparation in histidine-dependent Solmonella strain TA-1535, TA-1537, TA-98 and TA-100 both by disc (spot) and plate incorporation methods. A tryptophan dependent strain of E. coli, WP-2, was also included. Doses tested were 1000 micrograms for disc and 10, 100 and 1000 micrograms per ml by plate. Provisional Conclusion: The reviewer tends to agree that the data support the conlcusion that technical Prowl was not mutagenic under test conditions.		Supplementary (may be upgraded pending resolution of questions raised in 2/11/80 review by I. Mauer).
Mutagenicity (rat) (Dominant Lethal) Food & Drug Res. Labs Lab #2006 ca. 10/5/73 MRID #00026673	AC 92,553 (Technical)		The mutagenic index indicated no statistically significant differences between controls and treated groups (500 and 2500 ppm, HDT). However, the index appeared to indicate some effect at 2500 ppm (HDT).		Supplementary/ 000544

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Host-Mediated Assay American Cyanamid Co. Study # - Not given ca. 7/73 MRID #00067519	Prowl Intermediate 76.2% (Lot #AC 2174-114)	230618	NOTE: The test chemical is a process intermediate in Prowl production claimed to typify the product prior to denitrosation (containing 76.2% technical Prowl and a minimum [redacted] MANUFACTURING PROCESS INFORMATION IS NOT INCLU MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED Host-mediated assays (2 replicates) using mice as host and a histidine-dependent strain of S. typhimurium (his G-46) as indicator were conducted according to the methods of Legator and Malling. Mice were dosed at 20.0 and 26.8 milligrams per mouse (mice weigh about 20-25 grams). The reviewer did not agree with the stated conclusion that the test compound was non-mutagenic in the assay as performed. The reviewer raised several questions which apparently have yet to be addressed by the registrant.		Unclassified pending resolution of question raised by I. Mäuer in his review of 2/11/80.

Tox Chem No. Prowl 454BB File Last Updated _____ Current Date _____

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenicity (Ames) American Cyanamid Co. Study # - Not given ca. 6/10/77 MRID #00067519	CL 94,269 97% pure (lot # AC 2911-2) [nitrosoamine]	230618	The compound, [redacted] was evaluated with and without activation provided by a rat liver enzyme preparation in histidine-dependent Solmonella strains TA-1535, TA-1537, TA-98 and TA-100 both by disc (spot) and plate incorporation methods. A tryptophan dependent strain of E. coli, WP-2, was also included. Doses tested were 1000 micrograms for disc and 10, 100 and 1000 micrograms per ml by plate. Provisional Conclusion: The reviewer tends to agree that the data support the conlcusion that CL 94,-269 Prowl was not mutagenic under test conditions.		Supplementary (may be upgraded pending resolution of questions raised in 2/11/80 review by I. Mauer).

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

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Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Host-Mediated Assay American Cyanamid Co Study # - Not given ca. 1/72 MRID #00067519	CL 94,269 99% pure (lot #AC 2096-44) (Nitrosamine)	230618	Host-mediated assays (2 replicates) using mice as host and a histidine-dependent strain of S. typhimurium (his G-46) as indicator were conducted according to the methods of Legator and Malling. Mice were dosed at 6.4 10.0 & 16.6 milligrams per mouse (equivalent to about 640 mg per kg for HDT). The reviewer did not agree with the stated conclusion that the test compound was non-mutagenic in the assay as performed. The reviewer raised several questions which apparently have yet to be addressed by the registrant.		Unclassified pending resolution of questions raised by I. Mauer in this review of 2/11/80.
17-Day Cataractogenic Study (white Leghorn chickens) Industrial Bio Test IBT #8580-09771 1/5/77 MRID #00054244	Technical	Not given	No birds receiving the test chemical died. The HDT was 3000.0 ppm in the feed. Gross necropsy revealed no pathology in the lens of the chicks receiving test chemical. Positive control groups developed bilateral cataracts. NOTE: IBT DATA AUDIT GROUP concluded that the study is valid.		Supplementary/ 000545,002133
Metabolism Study (rat) American Cyanamid Co. Project No. 2-463 November 7, 1983 MRID #00046275	Radiolabeled CL 92,553 (parent)	Not given	The following metabolites were present in either urine, muscle, blood, fat, kidney or liver. The metabolites identified by code here (see review for structures) were as follows: CL 92,553; CL 99,900; CL 113,066; CL 113,071; CL 113,072; CL 202, 078; CL 202,345; CL 202, 347.		Supplementary

Subject: Acute Oral LD_{50}-Rat

Test Compound: AC 92553 Technical

Synonyms: 3,4-xylidine, N-(1-ethylpropyl)-2,6-dinitro

Accession No.: Not known

MRID No.: 00037471

Testing Facility: Industrial Bio-Test Laboratories, Inc.

Report No.: IBT No. A1373

Testing Period: March-April 1972

Report Submitted to Sponsor: April 17, 1972

Materials and Methods: Young female rats of the Charles River strain (COBS) were used as test animals. All animals were observed for 5 days prior to the initiation of the study for general health and suitability. Animals were housed in stock cages and were permitted a standard laboratory diet plus water ad libitum, except during the 16-hour fast immediately prior to oral intubation when food was withheld. Selected groups of 5 female albino rats were administered the test material as a 50% (w/v) suspension in corn oil at the following dose levels 4.5, 6.8, 10.2 and 15.3 grams per kilograms. All rats were housed individually and observed for 14 days. Necropsies were performed on all animals dying intercurrently and those sacrificed at termination.

Results: Mortality: No animals died at the low dose. Two animals died in each of the two middle dose levels. All animals died at the high dose level. All animals dying generally expired between 6 hours and 2 days after compound administration.

Observations: Signs observed were hypoactivity, ruffed fur, diuresis, diarrhea, muscular weakness, yellow pelts, tremors, emaciation, spasms, pale eyes and alopecia.

Necropsy: Animals that died revealed hemorrhages in the gastrointestinal tract. No gross pathological alterations were noted among animals sacrificed at the end of the 14-day observation period.

Conclusion: The AOLD50 in females was calculated to be 9.1 grams/kilogram with a standard deviation of 1.28 grams/kilogram.

Category of Toxicity: Category 4

Classification: Invalid

[redacted]

Justification for Classification: Previously reviewed acute oral LD_{50} studies (MRID# 00026657) conducted on male and female rats of the RH Wistar strain and male and female mice have indicated AOLD50 levels for rats of about 1250 mg/kg for males and 1050 mg/kg for females. AOLD50 values for male and female mice were 1620 mg/kg and 1340 mg/kg, respectively. Even considering strain differences it is our opinion that the disparity between the results of the previously reported study (MRID# 00026657) and the value reported in this study are too diverse to be taken at face value. It was therefore concluded that the results for this study (MRID# 00037471) are invalid unless the study is audited and found acceptable by the Agency.

004026

Subject: Acute Oral LD_{50} - Rat

Test Compound: Prowl Herbicide Technical

Synonyms: 3,4-Xylidine, N-(1-ethylpropyl)-2,6-dinitro-
CL 92,553
Pendimethalin

Accession No.: Not known

MRID No.: #00026657

Test Facility: American Cyanamid

Report No.: A-72-4

Testing Period: June 1, 1972.

Report Submitted to Sponsor: June 1, 1972.

Materials and Methods: Forty (40) male and 20 female RH Wistar strain albino rats were divided into 4 separate groups of 10 and 5 animals per sex per group. All animals were fasted for 24 hours and were dosed with a 20% w/v corn oil dispersion of the technical product.

Animals were observed for 14 days. All animals received 3 common dose levels of 625, 1250 and 2500 mg/kg. Females received an additional low dose of 313 mg/kg and males recieved an additional high dose of 5000 mg/kg.

Results: MALES: Six males in the high-dose group died within 24 hours accompanied by signs of prostration and lethargy. The remaining 4 animals died prior to day 14. Five males died at each of the other dose levels. At least one recorded death was noted at each of the 2 low dose levels on day 2. Signs were as previously noted.

Gross necropsy showed survivors to be normal.

Conclusion: The AOLD50 for males was determined to be 1250 mg/kg with 95% CL of 560 to 2780 mg/kg.

Category of Toxicity for Males: Category 3

Classification: Core-Minimum

Results: FEMALES: At least one death was recorded in each of the 2 high dosed groups and the low dose group by the end of the day 2. Signs observed in the two high dosed groups of animals were prostration and

dyspnea. At least one death each was recorded in the 2 low dose groups.

Gross necropsy showed survivors to be normal.

Conclusion: The AOLD 50 for females was determined to be 1050 mg/kg with 95% CL of 310 to 3610 mg/kg.

Category of Toxicity for Females: Category 3

Classification: Core-Minimum

Subject: Acute Oral LD_{50} - Rat

Test Compound: Prowl Herbicide Technical

Synonyms: 3,4-xylidine,N-(1-ethylpropyl)-
2,6-dinitro

AC1984-79-3
CL 92,553
Pendimethalin

Accession No: Not known

MRID: No. # 00072802

Testing Facility: American Cyanamid

Report No: A-73-133

Testing Period: November 28, 1973

Report Submitted to Sponsor: November 28, 1973

Materials and Methods:

Fifty male albino rats of the RH Wistar strain were divided into 5 groups of 10 animals per group. Animals were fasted for 24 hours and were dosed with a 20% w/v corn oil dispersion of the technical product. Animals were observed for 14 days. The five doses administered were 313, 625, 1250, 2500 and 5000 mg/kg.

Results:

Signs were observed on day of dosing at the 3 high dose levels. They were, prostration, diarrhea and diuresis. The first recorded deaths were between 6-24 hours in the 3 high dose groups. Nine of 10 animals in the high dose group were dead by the end of day 2. One animal died in each of the 2 low dose groups.

Gross autopsy was not performed.

Conclusion

The $AOLD_{50}$ was determined to be 2140 mg/kg with 95% CL of 1330 to 4430 mg/kg.

Category of Toxicity: Category 3

Classification: Core-Minimum

004026

Subject: Acute Oral LD_{50} - Mouse

Test Compound: Prowl Herbicide Technical

Synonyms: 3,4-Xylidine, N-(1-ethylpropyl)-2,6-dinitro-
CL 92,553
Pendimethalin

Accession No.: Not known

MRID No.: #00026657

Test Facility: American Cyanamid

Report No.: A-72-4

Testing Period: June 1, 1972.

Report Submitted to Sponsor: June 1, 1972.

Materials and Methods: Twenty male and 20 female albino mice (CF-1 strain) were divided into 4 groups of 5 mice per sex per group. Animals were dosed (apparently in an unfasted state) with a corn oil dispersion of the product at a constant volume of 0.5 ml/mouse. Doses administered were 625, 1250, 2500 and 5000 mg/kg. Animals were observed for 14 days.

Results: Males: Signs (lethargy) and death were recorded for all dose groups within 2 days. All animals (males) died at the high dose and 3/5 died at 2500 mg/kg. A gross necropsy was not performed.

Females: Signs (lethargy) and death were recorded for the 3 high dose levels within 3 days. All females died at the 2 high dose levels. No females died at the low dose. A gross necropsy was not performed.

Conclusion: Males: Acute oral LD_{50} with 95% CL is 1620 (860-3070) mg/kg.

Females: Acute oral LD_{50} with 95% CL is 1340 (950-1880) mg/kg.

Cateogory of Toxicity: Category 3

Classification: Core-Minimum

47

Subject: Acute Oral LD_{50} - Dog

Test Compound: Prowl Herbicide Technical

Synonyms: 3,4-Xylidine, N-(1-ethylpropyl)-2,6-dinitro-
CL 92,553
Pendimethalin

Accession No.: Not known

MRID No.: #00026657

Test Facility: American Cyanamid

Report No.: A-72-4

Testing Period: June 1, 1972.

Report Submitted to Sponsor: June 1, 1972.

Materials and Methods: Four male and 4 female Beagle dogs were divided into 4 groups of 1 male and 1 female per dose group. Animals were fasted for 24 hours and dosed by oral gavage (gelatin capsule) with the technical product. Doses administered were 625, 1250, 2500 and 5000 mg/kg. Animals were observed for 14 days.

Results: No signs were observed and no animals died. A necropsy on surviving animals was not performed.

Conclusion: The AOLD50 for either male or female dogs was greater than 5000 mg/kg.

Category of Toxicity: Category 4

Classification: Core-Minimum

004026

Subject: Acute Dermal LD_{50} - Rabbit

Test Compound: Prowl Herbicide Technical

Synonyms: 3,4-xylidine,N-(1-ethylpropyl)-
2,6-dinitro

AC1984-79-3
CL 92,553
Pendimethalin

Accession No: Not known

MRID: No. # 00072802

Testing Facility: American Cyanamid

Report No: A-73-133

Testing Period: November 28, 1973

Report Submitted to Sponsor: November 28, 1973

Materials and Methods:

Ten male albino rabbits were divided into 2 groups of 5 animals per group. An aqueous paste of the product was held under an impervious cuff in continuous 24-hour contact with the shaved skin. Two doses were applied 2500 and 5000 mg/kg and animals were observed for 14 days.

Results: No signs of intoxication were observed. No animals died while on the study. No edema was observed; however, the product colored the skin orange and therefore an accurate assessment of the erythema response was not possible.

A gross autopsy was not performed.

Conclusion: The $ADLD_{50}$ is greater than 5000 mg/kg.

Category of Toxicity: Category 3

Classification: Core-Minimum.

Subject: Acute Dermal LD_{50} - Rabbit

Test Compound: Prowl Herbicide Technical

Synonyms: 3,4-Xylidine, N-(1-ethylpropyl)-2,6-dinitro-
CL 92,553
Pendimethalin

Accession No.: Not known

MRID No.: #00026657

Test Facility: American Cyanamid

Report No.: A-72-4

Testing Period: June 1, 1972.

Report Submitted to Sponsor: June 1, 1972.

Materials and Methods: Ten male albino rabbits were divided into 2 groups of 5 animals each. An aqueous paste of the product was held under an impervious cuff in continuous 24-hour contact with the shaved skin of the rabbit. Animals were observed for 14 days. The two doses administered were 2500 and 5000 mg/kg.

Results: No signs of intoxication were observed and no animals died. No edema was observed. Gross autopsy revealed no readily apparent adverse effects.

The erythema response could not be evaluated accurately since the product colored the skin yellow.

Conclusion: The ADLD50 is greater than 5000 mg/kg.

Category of Toxicity: Category 3

Classification: Core-Minimum

Subject: Rabbit Skin Irritation

Test Compound: Prowl Herbicide Technical

Synonyms: 3,4-xylidine,N-(1-ethylpropyl)-
2,6-dinitro

AC1984-79-3
CL 92,553
Pendimethalin

Accession No: Not known

MRID: No. # 00072802

Testing Facility: American Cyanamid

Report No: A-73-133

Testing Period: November 28, 1973

Report Submitted to Sponsor: November 28, 1973

Materials and Methods:

Six rabbits were administered 500 mg of the product prepared as an aqueous paste. The paste was held under an impervious patch in continuous contact with shaved skin for 24 hours. Animals were observed for 72 hours and scored according to the method of Draize.

Results:

Scores for erythema and edema for intact and abraded skin were zero for all observation periods (See note).

The primary irritation score was zero.

Category of Toxicity: Non-irritating.

Classification: Core-Supplementary

Company Note: It was reported that the erythema response in the skin irritation test could not be evaluated in every instance at either the 24- or the 72-hour reading since the product colored the skin orange. Therefore, the PIS shown for the product is the sum of the mean values for erythema at 72 hours and edema at both 24 and 72 hours divided by 3.

Toxicology Branch Comment: Toxicology Branch believes that sufficient evidence is available to determine the skin irritancy potential of the compound (see also $ADLD_{50}$ study, MRID #00072802). Although this study is classified supplementary the study need not be repeated.

Subject: Skin Irrigation - Rabbit

004026

Test Compound: Prowl Herbicide Technical

Synonyms: 3,4-Xylidine, N-(1-ethylpropyl)-2,6-dinitro-
CL 92,553
Pendimethalin

Accession No.: Not known

MRID No.: #00026657

Test Facility: American Cyanamid

Report No.: A-72-4

Testing Period: June 1, 1972.

Report Submitted to Sponsor: June 1, 1972.

Materials and Methods: Six rabbits were administered 500 mg of the product prepared as an aqueous paste. The paste was held under an impervious patch in continuous contact with shaved skin for 24 hours. Skin was both abraded and intact. Animals were observed for 72 hours and scored according to the method of Draize.

Results: Since the product colored the rabbit skin yellow, the erythema response in the skin irritation test could not be evaluated. No erythema scores were reported. All recorded scores for edema were zero. The primary irritation score for edema was zero.

Conclusion: The skin irritation potential can only be partially determined since erythema scores were not available. Edema was not observed.

Category of Toxicity: May be non-irritating. The product did not produce edema.

Classification: Core-Supplementary

Comment: See also MRID #00072802 Report No. A-73-133. See the results of the ADLD50 study and the primary skin irritation study.

004026

Subject: Rabbit Eye Irritation Study

Test Compound: Prowl Herbicide Technical

Synonyms: 3,4-xylidine,N-(1-ethylpropyl)-
2,6-dinitro

AC1984-79-3
CL 92,553
Pendimethalin

Accession No: Not known

MRID: No. # 00072802

Testing Facility: American Cyanamid

Report No: A-73-133

Testing Period: November 28, 1973

Report Submitted to Sponsor: November 28, 1973

Materials and Methods:

Six rabbits were administered with 100 mg of technical product into the conjunctival sac of the eye (Draize method and scoring criteria). Eye irritation scores were recorded for cornea, iris and conjunctiva at 24, 48 and 72 hours.

Results: Cornea and iris showed no adverse responses. Mean conjunctival scores at 24 and 48 hours were 2 and 0.3 respectively. One animal showed a conjunctival score of 10 (maximum mean score is 20) at 24 hours, which was reduced to 2 at 48 hours. All eyes were clear of irritation at 72 hours.

Conclusion: Technical pendimethalin produces slight irritation in the unwashed eyes of rabbits.

Category of Toxicity: Category 3

Classification: Core-Minimum

004026

Subject: Rabbit Eye Irritation Study

Test Compound: Prowl Herbicide Technical

Synonyms: 3,4-Xylidine, N-(1-ethylpropyl)-2,6-dinitro-
CL 92,553
Pendimethalin

Accession No.: Not known

MRID No.: #00026657

Test Facility: American Cyanamid

Report No.: A-72-4

Testing Period: June 1, 1972.

Report Submitted to Sponsor: June 1, 1972.

Materials and Methods: Six rabbits were administered with 100 mg of technical product into the conjunctival sac of the eye (Draize method and scoring criteria). Eye irritation scores were recorded for cornea, iris and conjunctiva at 24, 48 and 72 hours.

Results: Cornea and iris showed no adverse reaction. The mean conjunctival score at 24 hours was 1 and reflected a single score of 6 for 1 rabbit. All other scores for this parameter were zero at all other time periods.

Conclusion: The technical material under these test conditions is minimally irritating in the unwashed eyes of rabbits.

Category of Toxicity: Category 3

Classification: Core-Minimum.

Subject: Acute Inhalation Study of AC 92,553 in Rats

Test Compound: AC 92,553 Technical (brown crystals).
Note: The technical material is an orange solid.

Synonyms: 3,4-xylidine, N-(1-ethylpropyl)-2,6-dinitro

Accession No.: Not known

MRID No.: 00073342

Testing Facility: Affiliated Medical Research, Inc.

Contract No.: 122-1968-43

Testing Period: September/October, 1973 (best estimate).

Report Submitted to Sponsor: October 24, 1973

Materials and Methods: A 100 liter dynamic chamber was used in this study. Room air was monitored by means of a differential pressure flow meter and a critical orifice previously calibrated.

The Wright Dust Feed mechanism was charged with the compound as received, however, because of the crystalline nature of the compound, little of the chemical was delivered to the chamber. AC 92,553 was melted and held at a temperature of 45°C in a water bath and the molten liquid was then passed through the DeVilbis atomizer. As the liquid was dispersed into fine droplets, crystals tended to form at the orifice, even with local heating, giving uneven and intermittent delivery into the chamber air stream.

A concentration of AC 92,553 was established by dispersing a 15% suspension of the crystals in water containing 2% Tween 80. The suspension was readily and evenly dispersed by the DeVilibis apparatus to produce a dense fog. Concentrations greater than 15% did not readily pass through the apparatus and were unsatisfactory.

For animal exposures, the chamber airflow was 7.5 liters/minute and the AC 92,553 suspension was delivered at a rate of approximately 14.7 ml./min. using compressed air flowing at a rate of 4 liters/min. at a pressure of 40 psia. Under these conditions the maximum nominal concentration in the chamber was calculated to be 320 mg/l over the 4-hour exposure period. The corresponding concentration of Tween 80 was calculated to be 39.2 mg/l.

Five male and 5 female albino rats (167-350 grams) were acclimated to laboratory conditions. Animals were individually housed and provided with food and water ad libitum. Rats were exposed to the 15% aqueous suspension of the aerosol for

4.0 hours. This was the only concentration tested. Animals were observed during exposure and following exposure for 14 days. Animals at termination were weighed, anesthetized with chloroform and exsanguinated. Animals were then necropsied and any gross pathology noted.

Results: All animals showed signs during the exposure period. Signs observed were irritation, sluggishness, lethargy, hyperexcitability and fur stained yellow. Five males and 4 females recovered by the end of day 2. No animals died during the 14-day observation period. Gross autopsy revealed two animals of each sex to have enlarged spleens.

Conclusion: The AILC50 was greater than 320 mg/liter (nominal concentration) for a 15% aqueous suspension of the technical product for a 4-hour exposure in male and female rats.

Category of Toxicity: Category 4

Classification: Core-Minimum

Registration Standard: Pendimethalin.

Subject: Smoke Inhalation Study in Rats with Cigarette Tobacco Treated with AC 92,553.

Test Compound: Prowl 3E. (34.4% ai). Sprayed on crops at rates of 0, 75 and 375 mg/ai/plant.

Fiche/Master ID: 00031974

Accession No.: Not known.

Testing Facility: Food and Drug Research Laboratories, Inc.

Laboratory Report No.: 2935

Testing Period: December 2-23, 1974

Report Submitted to Sponsor: January 6, 1975

EPA Registration No. 241-EUT

DCR-32838:Kocialski:Tox-37:Rm816E:CM#2:557-3710:9/12/83:efs
REVISED-9/14/83:DCR-32990:TOX-37:efs

Protocol:

Three groups of 10 rats (5 male and 5 female) were placed into a 72 liter exposure chamber and the air flow rate was adjusted to 6 liters per minute. A cigarette smoking device was attached to the inlet port and smoke was injected at the rate of 30 ml of smoke each 30 second interval. Exposure was set for 1 hour. This corresponds to 9 mg/liter interims of tobacco burned (not including condensable tars).

The rats were exposed 5 days a week for 3 weeks for a total of 15 exposures. The test material consisted of three lots of cigarettes impregnated with AC92553 (pendimethalin) at 0, 1X or 5X concentrations. The X refers to cigarettes prepared from lots grown at 0, the recommended use level (X) and 5 times this level (5X).

Results:

Comprehensive examination of the rats revealed no treatment related effects on weight gain, hematologic or biochemical patameters, or organ weights. There were no reported pathological lesions that were test chemical related. In both controls and treated rats, there was an unexpectedly high incidence of respiratory problems. These included peribronchial lymphoid tissue and necrotic delres and acute imflammatory cells.

Conclusion:

Provisionally INVALID. The protocol states that 6 mg per liter smoke from cigarette tobacco is the LD50 for a one hour exposure. However, the test results state that the chamber consistantly reached 9 mg/liter and there were no deaths. This discrepancy must be resolved (for example, by actual determinations made in the atmosphere). This test might otherwise be upgraded.

NOTE: Analytical data indicate that the residue of pendemethelin in smoke was <0.10 and 1.347 ppm when 79 mg or 375 mg/tobacco plant were used.

EPA:OTS:HED:TOX:RD BUDD:sb: 10/3/79 X77395

Registration Standard: Pendimethalin

Subject: 21-Day Subacute Dermal Toxicity in Rabbits of AC92,553

Test Compound: AC 92,553 Technical (Commercial Grade)

Lot No.: AC-1984-79-3

MRID No.: 00026663

Accession No.: Not known

Testing Facility: Food Drug Research Laboratories, Inc. East Orange, New Jersey

Laboratory Report No.: 1613

Testing Period: May-June 1973

Report Submitted to Sponsor: August 24, 1973

Materials and Methods: Fifteen male and 15 female New Zealand white rabbits, weighing between 2.5-3.5 kg. were individually housed in temperature and humidity controlled quarters. A standard laboratory rabbit chow and tap water were provided ad libitum.

Approximately 1 day prior to the first application of test material animals were shaved over approximately 10% of the body surface. The area of exposure was then abraded in one-half the number of animals per sex per group. The test material was applied by gentle inunction to the intact and abraded skin of the test animals 5 days per week for 3 weeks. Exposure was limited to 6 hours each day.

The trunk of each animal was wrapped with a suitable occlusive dressing to preclude ingestion. Removal of the dressing at the end of the daily exposure was followed by removal of the test material with water.

Application sites were examined daily for erythema and edema and scored using the method of Draize.

The control group consisted of 3 males and 3 females and each received 2.0 ml/kg of corn oil. The three treated groups consisted of 4 males and 4 females and each received respectively 250, 500 and 1000 mg/kg of test material.

Animals were observed daily for food and water intake, elimination and behavior. Hematological examinations included, white blood cell count, white blood cell differential count, erythrocyte count, hemoglobin and hematocrit. Urine was tested for acidity, specific gravity, albumin, glucose, potassium and the presence of blood. Gross and microscopic pathology was conducted on all surviving animals as well as any sacrificed in a moribund condition prior to termination. Treated skin sites were described and the entire area removed and saved in neutral buffered formalin. All organs or representative samples of organs were likewise preserved in formalin. Histopathology was conducted only on liver, both kidneys, treated skin (two sections), untreated skin and all sites of gross pathology. Processed tissues were cut at 5 microns and stained with H and E stain.

Results and Discussion: Food and water intake was monitored but not reported. However, body weight gain was generally comparable between treated groups and the control group indicating comparable food and water intake for all experimental groups. Values reported for hematology and urinalysis were comparable between all groups. Limited histopathology revealed no compound-related systemic effects. Microscopic examination of skin did, however, reveal slight focal acanthosis and/or slight hyperkeratosis which were attributed to compound. Gross observations revealed areas of reddening at the application site that increased in intensity and/or area with increased dose. The test compound manifested a very slight to a slight edema and a very slight to a well defined erythema. The irritation was dose responsive. One animal in the high dose group died an accidental death.

Conclusion: The techical grade (commercial grade) of active ingredient produced a slight-to-mild skin irritation under the conditions of the study for the mid and high dose groups. No erythema or edema was observed at the low dose of 250 mg/kg.

Classification: Core-Minimum. This study is classified as core minimum in spite of the following deficiencies - the absence of clinical chemistry data and the lack of extensive histopathology, for the following reasons:

o The exposure was extensive and the doses administered were high at 250, 500 and 1000 mg/kg. There was no compound-related histopathology for the liver and kidney and no observable gross systemic pathology. Since the limited histopathology data were not adverse, a lack of adverse effect on the usual clinical chemistry parameters monitored, regulated and influenced by these two organs is suggested.

o The comparability of body weight gain between groups (an indicator of unspecified systemic toxicity) would seem to suggest a lack of general systemic toxicity at such high doses, and therefore a general lack of adverse histopathological findings.

o Urinalysis and hematological analysis indicate that the results were comparable to control values suggesting no adverse effects on general metabolism and/or hematology.

TOX:KOCIALSKI:DCR-10632:TOX-30:8/2/83
REVISED-8/5/83:DCR-32863:efs

004026

Subject: Combination Dietary Feeding/Oral (Capsule) Gavage Study in Dogs.

Test Compound: 3,4-xylidine, N-(1-ethylpropyl)-2,6 dinitro

Synonyms: CL 92,553
pendimethalin.

Accession No.: Not known.

MRID #: 00106754.

Testing Facility: American Cyanamid Company.

Report No: A-72-4.

Testing Period: April - May, 1972

Report Submitted to Sponsor: June 1, 1972.

Purity of Test Material: 98.7% Technical.

Sample Source Number: AC-2002-43-3.

Materials and Methods: The test article was incorporated into the diet to give concentrations of 1.25% [0.25 g/kg (250 mg/kg) body weight/day] and 0.625% [0.125 g/kg (125 mg/kg) body weight/day] and fed at these levels to groups of young (8-12 months old) beagle dogs, 2 males and 2 females per group for 16 days. It was noted however, that during these 16 days the animals were not consuming the diet mixture at these dose levels. The protocol was therefore modified and the animals were given the compound orally by gelatin capsule from day 17 to 30 inclusive. A third dose group of 2 males and 2 females was added and received 1.0 g/kg of b.wt. per day (equivalent to 5% of the diet) by gelatin capsule for 30 days. For animals receiving the compound by capsule, dosages were adjusted weekly according to changes in body weight. All animals were observed for appearance, behavior and mortality. Visual estimates were made of the amount of food consumed. Body weight change was monitored before and at periodic intervals during the study. All animals were killed and subjected to a thorough gross autopsy at the end of the test period. Liver and kidney weights were recorded and reported as a percent of body weight. Clinical chemistry and hematology were monitored prior to feeding of the test compound, after 2 weeks on study and at termination. Hematological values determined were for hematocrit, hemoglobin, total WBC, prothrombin time, and WBC differential count. Clinical chemistry parameters monitored were blood glucose, plasma urea nitrogen, plasma GOT, and plasma GPT.

Results: It was reported that the overall appearance and behavior of both control and treated dogs were good. No dogs died during the study period. Analysis of the visual estimates of food consumption data showed no significant interaction between dosage and sex. The data for males and females was therefore pooled for statistical evaluation. Administration of the test article by capsule at a dosage of 1.0 gm/kg for 30 days depressed food consumption significantly ($p<0.05$) when compared to controls. Administration of the low dose by food/gavage depressed the food consumption values significantly ($p<0.01$) when compared to controls. Depression of food consumption was also reported for the mid-dose level but the decreased food intake was not statistically significant when compared to control values. It was also noted that data were examined by period (i.e., dietary administration vs. capsule). This analysis revealed that the greatest effects on food intake occurred when the test article was incorporated into the diet. This observation coupled with the fact that the dose of 1.0 g/kg/bw. given by oral gavage had less of an effect on food intake when given by capsule indicated a palatability factor with the test article in the diet. Preliminary analysis of body weight change data indicated no significant interaction between dosage and sex. Data for males and females was therefore pooled for statistical evaluation. During the experimental period the control dogs gained weight normally. Animals receiving 1.0 g/kg per day for 30 days showed statistically significant body weight decreases ($p<0.05$) at termination. As noted earlier in this report when the compound was offered in the diet for 16 days it was not readily accepted. However, when the compound was encapsulated and administered to these same dogs an overall improvement in food intake of 49% (low dose group) and 47% (high dose group) was noted at these levels. A lower but non-significant body weight change was recorded for the low dose group at termination. The middle dose group produced a weight depression at termination that was reported to be significantly different from controls ($p<0.01$) as well as the low dose ($p<0.05$). It was reported that mean values for liver and kidney were greater than the control mean. However the differences were not significant. Additionally organ to body weight ratios for liver and kidney showed no log-dose response increases. Hematocrit, hemoglobin and total WBC count showed no meaningful changes when pretreatment values were compared to post-treatment values or when treated groups were compared to control groups for either males or females. Values for WBC differential count and prothrombin time showed no meaningful changes at any time period for any dose for either sex. Examination of clinical chemistry parameters revealed no biologically meaningful changes. Necropsy revealed no relevant gross pathology.

Conclusion: The only apparent effect as defined by the limits of the experimental design was decreased body weight gain at all three treatment levels with decreased weight gain noted with an increased dose. It is noted that the decreased weight gain at the lower dose levels was due in part or totally to the unpalatability of the diet. The later administration of compound by gelatin capsule may also have affected weight gain. The reason for the loss of weight for this portion of the experiment therefore remains uncertain. Additionally those animals receiving the compound by capsule (ie., 1.0 g/kg) did show a statistically significant weight decrease which was attributed to the compound.

NOEL: The data do not suggest a NOEL.

Classification: Core-Supplementary.

Subject: Fourteen (14) Day Feeding Study in Rats and Mice.

Test Compound: 3,4-xylidine, N-(1-ethylpropyl)-2,6 dinitro

Synonyms: CL 92,553
pendimethalin.

Accession No.: Not known.

MRID #: 00106754.

Testing Facility: American Cyanamid Company.

Report No: A-72-4.

Testing Period: April - May, 1972

Report Submitted to Sponsor: June 1, 1972.

Purity of Test Material: 98.7% Technical.

Sample Source Number: AC-2002-43-3.

Purpose: This study was designed to see what effects, if any, dosages calculated to give as much as an LD50/day to rats and two LD50s/day to mice had on weight gain and food intake when administered in the diet.

Materials and Methods: Rats: The product was incorporated into the diet of rats to give concentrations in the feed of 6400 and 12,800 ppm. This diet was fed to male and female albino rats for 14 days. Each dose group (including controls) consisted of 5 males and 5 females per dose group. Food consumption was measured and body weights were determined. Mortality was recorded. Gross pathology was conducted but no histopathology.

Results Rats: No animals in the treated groups died and only one animal in the male control group died. Food consumption for males decreased 10% and 16% for the low and high dose groups respectively. Mean weight gain decreased 8% for both dose groups in males. Females showed decreased food consumption values of 16% and 24% for the low and high dose respectively. Mean weight gain decreased 41% and 64% for the low and high dose group respectively.

Gross necropsy revealed that the lungs of rats at both treatment levels were hemorrhagic and the peritoneal fatty tissue of all treated rats were stained yellow. It was also reported that it appeared as though the seminal vesicles and

uteri of several animals at both these levels were greatly enlarged when compared to control animals.

Materials and Methods: Mice: The product was incorporated into the diet of mice to give concentrations in the feed of 4000, 8,000 and 16,000 ppm. This diet was fed to female mice for 14 days. Each dose group (including controls) consisted of 10 mice per group. Food consumption, body weight gain and mortality were recorded. Gross pathology but not histopathology was conducted at terminal sacrifice.

Results: Mice: No animals died. Mean food intake decreased 23% for the low dose and 18% and 30% for the mid and high dose respectively. Mean body weight gain in the low dose group was only 60% of controls whereas the mid and high dose showed actual weight loss of 1.29 and 3.28 grams (note: mean weight gain for controls was 2.58 grams).

Gross necropsy of female mice fed 16,000 ppm had pale kidneys and smaller uteri than controls.

Conclusion: Male and female rats and female mice showed decreased food consumption, decreased weight gain, and no deaths in the treated groups. The compound appears have a very low toxicity as defined by the experimental design.

Classification: Rats: Core-Supplementary
Mice: Core-Supplementary

DCR-17985:TOX-23:Kocialski:Rm820D:557-7395:5/31/83:efs
REVISED-6/3/83:DCR-11391:efs
REVISED-6/8/83:DCR-11332:efs

Subject: Thirty (30) Day Feeding Study in Rats.

Test Compound: 3,4-xylidine, N-(1-ethylpropyl)-2,6 dinitro

Synonyms: CL 92,553
pendimethalin.

Accession No.: Not known.

MRID #: 00106754.

Testing Facility: American Cyanamid Company.

Report No: A-72-4.

Testing Period: April - May, 1972

Report Submitted to Sponsor: June 1, 1972.

Purity of Test Material: 98.7% Technical.

Sample Source Number: AC-2002-43-3.

Materials and Methods: The test material was incorporated into the diet to give concentrations in feed of 800, 1600 and 3200 ppm. This diet was fed to male and female RH Wistar strain albino rats for 30 days. Each dose group (including controls) consisted of 10 males and 10 females per dose group. All animals were observed for general appearance, and survival. Food consumption was measured weekly and body weights determined bi-weekly. Blood samples were taken for clinical chemistry from 5 males and 5 females per group at the time of necropsy. The remaining rats were bled the following day for hematology studies. Clinical chemistry parameters monitored were plasma urea nitrogen, glucose and plasma glutamic-pyruvic transaminase. Hematology parameters monitored were hematocrit, hemoglobin, total white blood cell count, prothrombin time and white cell differential count (except basophils). Kidney and liver organ weights (absolute weights) were determined for 5 animals of each sex from each group. No histopathology was conducted.

Results and Discussion: The general appearance and behavior of all animals was reported as good. Urine from rats receiving 3200 and 1600 ppm of compound in the diet was reported to be much darker in color than their respective controls. However, it was reported that gross autopsy revealed no readily apparent lesions which were attributable to the ingestion of the compound. Food intake for treated males and females was comparable on a statistical and numerical basis when compared to the control group. It is interesting to note however,

that whereas males showed large percentage (and absolute) weight gains in all groups, females in all groups (including controls) showed absolute weight decreases at the end of 30 days when animals were compared to their initial weights. Mean liver and kidney weight values in males (5 animals per group) were comparable to controls for all doses. Mean liver and kidney weight for females were comparable between treated (800 ppm and 1600 ppm) and controls. Liver weight in the high dose female group was however, statistically significantly increased at the $p<0.05$ level. However, due to the small sample size the value is difficult to interpret. Kidney values in the high dose female group were comparable to controls. It is noted however, that liver weights for females and males were somewhat raised over control values in treated groups. A dose response did not appear evident. Relative percent increases noted for males with increasing dose for liver were 7.5, 22 and 12.7%; for females 24, 18 and 29% with the last value being statistically significantly increased. Hematocrit, hemoglobin and total WBC count for males and females were comparable to control values. Prothrombin time and white blood cell differential counts for both sexes appeared comparable to controls (and within normal limits as stated by the company). Clinical chemistry values for plasma urea nitrogen and plasma GPT in males and females were comparable to controls for all dose levels. Glucose values for females were comparable between treated and controls. Glucose values in the high dose male group were statistically significantly increased ($p<0.05$). This statistically significant increase may not have been biologically meaningful due to the sample size and/or stress of handling.

Conclusion: No firm conclusions can be drawn from the study. However, based upon the parameters monitored and the experimental design the study gives some suggestive evidence that the compound may have a low toxicity.

NOEL: The data suggests a NOEL of 1600 ppm.

Classification: Core-Supplementary.

Subject: Thirty (30) Day Feeding Study in Mice.

Test Compound: 3,4-xylidine, N-(1-ethylpropyl)-2,6 dinitro

Synonyms: CL 92,553
pendimethalin.

Accession No.: Not known.

MRID #: 00106754.

Testing Facility: American Cyanamid Company.

Report No: A-72-4.

Testing Period: April - May, 1972

Report Submitted to Sponsor: June 1, 1972.

Purity of Test Material: 98.7% Technical.

Sample Source Number: AC-2002-43-3.

Materials and Methods: The test material was incorporated into the diet to give concentrations in the feed of 500, 1000 and 2000 ppm. This diet was fed to male and female CF-1 strain albino mice for 30 days. Each dose group (including controls) consisted of 10 males and 10 females per dose group. All animals were observed for general appearance and survival. Food consumption was measured weekly and body weights determined bi-weekly. Clinical chemistry and hematology were not monitered. Kidney and liver organ weights (absolute weights) were determined for 5 animals of each sex from each group. No histopathology was conducted. Gross pathology was conducted on each of 5 animals per sex per dose.

Results and Discussion: The general appearance and behavior of all animals was reported as good. Urine from mice fed 1000 and 2000 ppm was much darker in color than respective control animals. However, it was reported that gross autopsy revealed no readily apparent lesions which were attributable to the ingestion of the compound. Food consumption for both sexes in all dose groups was comparable on a statistical and numerical basis to controls. Mean weight gain for both sexes for all dose groups was numerically similar and not statistically significant from controls. Mean kidney weight for males and females was not statistically significant from controls. However, values reported for 1000 and 2000 ppm were lower. Liver weights for both sexes were only statistically significantly decreased at the 1000 ppm dose. However, even

though values for all treated groups were lower than control group for both sexes at all doses the reported values between dose groups were similar. A dose response was not observed. One mortality was recorded, and that was in the mid-dose female group.

Conclusion: No firm conclusions can be drawn from the study. However, based upon the parameters monitored and the experimental design the study gives some suggestive evidence that the compound may have a low toxicity.

NOEL: The data suggests a NOEL of 2000 ppm.

Classification: Core-Supplementary.

10

[redacted]

004026

Registration Standard: Pendimethalin

Subject: The Effect on Mammary Glands of a Ninety-Day Male Rat Feeding Study with Acc. 92,553.

Test Compound: AC 92,553 (Technical)

Fiche/Master ID: 00059469

Accession No.: Not known

Testing Facility: Pharmacopathics Research Laboratories, Inc., Laurel, Maryland.

Laboratory Report No.: Not known

Testing Period: January - April, 1973

Report Submitted to Sponsor: June 1, 1973

Batch or Lot No.: Lot No. 1984-79-3

Materials and Methods: A total of 40 weanling male Sprague-Dawley rats were quarantined at the test facility for 2 weeks, then randomly distributed into 2 groups of 20 animals each. All animals were housed in individual suspended wire cages and kept in a room controlled for temperature, humidity and air change. Water was available ad libitum. One group of 20 animals (control group) was fed a standard laboratory diet. The second group of 20 animals were fed the same diet mixed with AC 92,553 at a concentration of 2500 ppm for the first 6 weeks and 5000 ppm for the last 7 weeks. The diets were prepared fresh weekly and available ad libitum. Mixing of AC 92,553 into the diet was achieved with a twin-shell blender. All animals were weighed weekly for the first six weeks and bi-weekly thereafter. After 60 days, 5 male rats from each group were sacrificed and given a very thorough gross and histologic examination of mammary tissue. At the conclusion of this study the survivors received a similar examination.

Results: All animals survived the experiment. Body weights between the treated group and the control group were comparable. Gross necropsy revealed no remarkable differences between the two groups. Histopathology of the mammary glands showed no remarkable differences between the 2 groups.

The following table reveals the various degrees of hyperplastic activity recorded in mammary gland tissue for the two groups.

	Control	Treated
Normal Histology	27	33
Minimal Hyperplasia	16	8
Moderate Hyperplasia	20	25
Marked Hyperplasia (exhibiting secretory activity)	6	1
Total No. of Glands Examined	69	67

Conclusion: No adverse findings were revealed in male mammary glands under the test conditions.

Classification: Core-Supplementary.

DCR-32849:Kocialski:TOX-37:CM#2:Rm816E:557-3710:9/12/83:efs
REVISED-9/14/83:DCR-32990:TOX-37:efs

Registration Standard: Pendimethalin

Subject: A Three Month Oral Dose Range Study of The Effects of AC 92,553 Upon Mammary Tissue of Male Rats.

Test Compound: AC 92,553 (Technical)

Fiche/Master ID: 00059468

Accession No.: Not known

Testing Facility: Bio/dynamics, Inc.
East Millstone, N.J.

Laboratory Report No.: 73R-869

Testing Period: March-June 1973

Report Submitted to Sponsor: September 14, 1973

Lot Nos. Tested: AC2031-106
AC2031-120
AC2233-5
AC2233-28

Materials and Methods: A total of 150 weanling male Long-Evans rats were obtained from the Blue Spruce Farms of Altamount, New York. Twenty-five litters, each containing a minimum of six males, were divided among 6 experimental groups with one male of each litter assigned to each group utilizing a table of random numbers. Each group consisted of 25 males with each male in a group having a brother assigned to each of the other groups. Animals were housed individually and had free access to water and the standard laboratory diet. The experimental diet with the appropriate amounts of compound were mixed and presented weekly. The standard laboratory feed without the test compound added served as the control diet. Dose levels administered in the treated diet were as follows:

Group	Dose Level (mg/kg/diet)
1	0
2	25
3	50
4	100
5	500
6	2500 (5000)*

* dose level was increased from week 3-13.

Animals were observed daily for physical appearance signs of local or systemic toxicity, pharmacologic effects or mortality. Body weights and food consumption were examined once pretest, weekly and terminally (after fasting). Immediately prior to study initiation the animals ranged between 153-160 grams in weight.

All animals were subject to a gross necropsy and all animals were sacrificed using chloroform.

The following tissues were fixed:

Adrenals (2)
Aorta
Bone marrow, sternal
  (differential count)
Brain
Eye
Gonad
Heart (with coronary
  vessels)
Intestine
  colon
  duodenum
  ileum
Kidney
Liver
Lung
Lymph node (mesenteric)
Mammary glands (four sections, two from each side of the abdominal region)
Nerve (peripheral)
Pancreas
Pituitary
Salivary gland
Skeletal muscle
Skin
Spinal cord
Spleen
Stomach
Thyroid
Urinary bladder (including neck)
  gross lesions
  tissue masses

Only mammary glands were examined histologically from 10 rats per group. Two sections from each side of the abdominal region were examined.

Mammary glands were stained with hematoxylin and eosin. Eyes and testes were preserved in Bouin's solution and all other tissues fixed in 10% buffered neutral formalin.

Compound treated groups were compared to controls by the F-test and Student's t-test.

Results: No effects on mortality or symptomatology were observed. Reduced body weights from controls were observed in the high dose group at 4, 8 and 13 weeks. The decreases were statistically significant ($P < 0.05$). Decreased body weights were observed as a trend in nearly all groups. Food consumption was comparable to controls for all dose groups at all time intervals with two exceptions. Food consumption was statistically signficantly decreased at 500 and 2500 (5000) ppm at week 13 ($P < 0.05$).

The summary of incidence of mammary gland tissue and related histologic changes was as follows:

Histologic Findings	Group I	II	III	IV	V	VI
No identificable mammary gland tissue	38	29	31	36	33	39
Mammary gland tissue within normal histological limits	1	9	7	4	5	0
Cystic and degenerating changes of mammary gland tissue	0	2	0	0	1	0
Cystic, degenerating and inflammatory changes of mammary gland tissue	0	0	1	0	1	1
Total number of sections examined	39	40	39	40	40	40

Histopathologic examination of mammary gland tissue failed to reveal identifiable mammary gland in the majority of the sections from each group. "The mammary gland tissue detected in some animals was considered within normal histological limits with considerable variation in the quantity of gland and secretory activity. A few glands exhibited cystic and degenerative changes with or without associated inflammation.

The incidence of mammary gland tissue with normal histology within the defined sections was greater in 4 of the 5 dose groups than in the control group. The highest incidence occurred in the lowest dose group, with a suggestion of decreased incidence with increased dose levels.

Mammary gland tissue was not detected in the highest dose group animals, with the exception of one section of one animal that exhibited cystic degenerative changes. In addition, the incidence of the cystic degenerative changes was restricted to the dose groups and not detected in the control group.

The incidence and morphology of the mammary gland tissue, as well as that of the cystic degenerative changes of the gland, were considered not unlike that detected in untreated laboratory gland and the morphological variations together with the occasional cystic glands in the tested animals were considered

fortuitous findings unrelated to the administration of AC 92,553 under conditions of this study."

Classification: Supplementary

Registration Standard: Pendimethalin.

Subject: Three-month Interim Report. A 3 and 24 Month Oral Toxicity and Carcinogenicity Study of Compound AC 92,553 in Rats.

Test Compound: AC 92,553 Technical [3,4-xylidine,N-(1-ethylpropyl)-2,6 dinitro]

Fiche/Master ID: 00059468

Accession No: Not given.

Testing Facility: Bio/dynamics Inc.

Laboratory Report No.: 72R-746

Report Submitted to Sponsor: August 21, 1974

Batch or Lot Nos. AC 2031-10
AC 1913-82
AC 1913-90
AC 1913-95

Materials and Methods: Three hundred (300) male and 300 female weanling Long-Evans rats having a mean weight of 140 grams for males and 123 grams for females were obtained from the Blue Spruce Farms of Altamount, New York. Animals were housed individually in raised wire mesh cages and had free access to food and water.

The test material was supplied as a pre-mix containing 50,000 ppm (5.0%) of active ingredient. The test material was mixed with standard laboratory chow which served as the vehicle and the control feed. The diet was prepared fresh weekly.

Animals were divided into 5 groups of 60 males and 60 females per group as follows:

Group	Dose (ppm)
I (control	0
II (control)	0
III (low dose)	100
IV (mid-dose)	500
(V) (high dose)	2500 raised to 5000 on day 35).

Animals were observed daily for physical appearance signs of local or systemic toxicity pharmacological effects or mortality. Body weights and food consumption were measured weekly beginning one week prior to study initiation.

Five rats/sex from each control group and 10 rats/sex from each dose group were sacrificed at 90 days. The animals to be used for hematology and clinical chemistry were sacrificed using ether. Chloroform was used to sacrifice the remaining animals.

Clinical studies were conducted on 3 rats of each sex in each control group and 6 rats of each sex in each dose group. The parameters monitored at 90 days were:

Hematology: Clotting time, hemoglobin, hematocrit, RBC, total and differential leucocytes, and erythrocyte morphology.

Clinical Chemistry: SGPT, AP, fasting blood sugar, and BUN.

Urinalysis: Gross appearance, protein, glucose, pH, refractive index, ketones, bilirubin and occult blood.

The following organs in all groups were weighed, heart, kidneys, liver (fresh weight), thyroid (after fixation) as well as any gross lesion observed during necropsy.

Microscopic examination was made on all tissues taken from all the control and high dose animals and selected tissues (kidneys, liver, lung, heart and mammary gland) from all low and mid-dose animals.

The following tissues were fixed for histopathologic examination.

- Adrenals
- Aorta
- Bone marrow (sternum)
- Brain (2 sections)
- Gonad
- Heart (with coronary vessels)
- Eye (with optic nerve)
- Intestine
  - colon
  - duodenum
  - ileum
- Kidneys
- Liver
- Lung
- Lymph node (mesenteric)
- Mammary gland
- Pancreas
- Pituitary
- Salivary gland
- Prostate
- Spinal cord (thoracic)
- Skin
- Spleen
- Stomach (fundic, pyloric)
- Thyroids
- Urinary bladder (with neck)
- Uterus
- Skeletal muscle with nerve
- Any unusual tissue or lesion

The eyes were fixed in Bouin's solution and the rest of the tissues in 10% buffered neutral formalin. Tissues were stained with hematoxylin and eosin.

Statistical analysis was carried out on body weights, food consumption, hematology and clinical chemistry parameters, organ weights and organ/body weight ratios were analyzed. All dose groups were compared to the combined control group.

Results: Mean body weights for all males in the high dose group were statistically significantly lower ($p < 0.01$) than controls at weeks 5, 11 and 13. Mean body weights for all male animals receiving 100 and 500 ppm of test compound in the diet were comparable to controls. Mean food consumption was comparable between the treated groups and controls. Mean body weights for all females in the dose group were statistically significantly lower ($p < 0.01$) in the high dose group at weeks 5 and 13. Food consumption during these two time periods and dose level was comparable to the control group. Body weights and food consumption was generally comparable to controls at all other dose levels and time periods.

There were no spontaneous deaths reported for any group, at 90 days.

Signs observed in treated animals were not considered to be treatment related, and were also observed in control animals.

Values reported for hematology in males showed no statistically significant differences from controls. However a decreased clotting was observed with an increased dose. Values reported for females revealed no biologically meaningful changes with the exception of deoreased clotting time with increased dose. Comparison of male and female clotting times with doses administered were as follows:

Clotting Time (Seconds)
Mean Values and (S.D.)

Dose (ppm)	Males	Females
Control	240 (155)	190 (15)
100	165 (41)	155 (44)
500	150 (42)	155 (44)
2500** (5000)	120 (37)	130 (40)*

*$p < 0.05$
**raised to 5000 on day 35.

Clinical chemistry values for alkaline phosphatase in treated males and females were statistically significantly lower than control values. However, in neither case was a log-dose response evident. Blood sugar values were not statistically significantly increased over control values for males or females. However, values were notably higher with increased dose for both sexes.

Values for pH and refractive index were comparable to controls for both males and females.

Terminal body weights for males were comparable or higher in treated groups when compared to controls.

Statistically significant increases in absolute organ weights or organ to body weight ratios were as follows:

MALES

Absolute Organ Weights

Dose (ppm)	100	500	2500 (5000)
Organ			
liver	*	*	**
kidney		*	
heart			
thyroid			*

Organ/Body Wt. Ratio

liver		*	**
kidney			*
heart			
thyroid			*

*p <0.05
**p <0.01

NOTE: Terminal body weights for these sacrificed animals were comparable between treated and control groups.

It is noted here that the mean organ/body weight ratio for thyroid and liver in males was (1) substantially above the control values and (2) showed an apparent dose related increase in weight for all doses administered.

Statistically significant increases in abslute organ weights annd organ/body weight ratios were as noted below for females.

FEMALES
Absolute Organ Weights

Dose (ppm)	100	500	2500 (5000)
Organ			
liver			**
kidney			
heart			
thyroid			

Organ/Body Wt. Ratio

liver	*	*	**
kidney			*
heart	*	**	**
thyroid			

* p <0.05
** p <0.01

It is noted here that the terminal body weights for these sacrificed females at 100 and 2500 (5000) ppm were 8-10 grams lower than the combined values for controls but were not statistically significantly lower. However the terminal body weight at 500 ppm was 20 grams lower than the combined value for controls and was statistically significant.

Thyroid organ/body weight ratio though not statistically significant showed numerical increases at 100 and 2500 (5000) ppm with both increases being greater than controls and the high dose level being greater than the group receiving the low dose.

Necropsy examinations as noted previously, were conducted and specified tissues were preserved in fixative for histological

processing. All the specified tissues from the control and high dose groups and kidney, liver, lung, heart and mammary gland tissues from the low and mid dose groups were examined.

Gross and microscopic examination of selected organs and tissues revealed no remarkable differences between groups with one exception. Hyperplasia of mammary gland tissue occurred in varying degrees in male animals in all groups with the incidence and degree of hyperplasia considered to be remarkable. (NOTE: A separate 90-day feeding study was conducted to determine the effects of the test compound on male mammary glands. The study produced results which were not remarkable. See MRID #00059469. Pharmacopathics Research Lab, report submitted June 1, 1973 to sponsor.)

Discussion: Food consumption in all treated groups was comparable to control groups for all animals. Body weight gain was decreased only in the high dose group for both sexes at 5, 11 and 13 weeks. Decreased body weight in the high dose group without a concurrent decrease in food consumption indicated that the decreased body weight was the likely result of compound ingestion and not decreased food intake. The high dose is therefore considered a maximum tolerated dose.

Separately however, it is noted that the body weights of the 10 animals per sex per dose in the female group were noticeably lower in the low dose (100 ppm) and high dose group but were statistically lower only in the mid-dose (500 ppm) group. These decreased body weights may explain the statistically significant increases observed in the female organ to body weight ratios particularly since neither gross or microscopic pathology supported the organ to body weight changes.

Terminal body weights for males showed values which were higher or equal to control values. Organ to body weight ratios were higher for liver at 500 and 2500 (5000) ppm, kidney and thyroid in the high dose. However, microscopic examination of these tissues produced no changes which could support the organ to body weight ratios. The significance of these changes in males therefore remains uncertain.

Blood glucose levels were raised in treated groups but values were not significant. These elevated levels may reflect a combination of the stress of handling, of compound ingestion and ether administration.

It was also interesting to note that clotting time decreased in males and females with increased dose. A readily available speculation for this observation is not proffered.

Alkaline phosphatase levels were decreased significantly in both sexes for all treated groups. However, a log-dose response was not observed and numerical values were within

very narrow limits regardless of dose. The decreased AP values do not appear to be biologically meaningful.

Hyperplasia of mammary gland tissue was observed in male animals receiving compound when values were compared to controls. However differences between dose levels were not considered remarkable. Nonetheless a separate 90 day feeding study was conducted to determine the effects of the test compound on male mammary glands. The 90-day study produced results which were not remarkable. (Reference MRID #00059469. Pharmacopathics Research Lab, report submitted June 1, 1973 to sponsor.)

NOEL: (Provisional) 500 ppm

LEL: 2500(5000) ppm HDT. Decreased body weight based on mean of 60 animals per sex per dose.

Classification: Supplementary.

This study was classified as supplementary because in the initial 5-6 months of the study a high purity grade of test substance was utilized. The later months of this study utilized a technical or commercial grade of substance. Nitrosamines were present in the commercial grade but not in the high purity grade. Thus the animals were not exposed to the potential carcinogens during critical periods of growth and development, and were not exposed to the manufacturing impurities ofthe technical material.

Fiche/Master ID Number Not Available: The 2-Year Chronic Feeding/ Oncogenic Rat Study was not included in the bibliography. The MRID number was therefore not available. The study has been previously reviewed and judged to be INVALID.

Registration Standard: Pendimethalin

Subject: Two year Chronic Feeding and Oncogenic Study

Test Compound: Technical AC92553 and High Purity AC 92,553

Fiche/Master ID: Not Available

Accession No: 112849

Testing Facility: Bio/dynamics Inc.

Project No.: 72R-746

Testing Period: Not Available

Report Submitted to Sponsor: August 21, 1974

This 2 year rat chronic feeding/oncogenicity study has not been found to be supportive of the registration of pendimethalin. The study has been judged to be INVALID. The documentation which supports this conclusion is attached. The documents are referenced by subject/title as follows:

1. Prowl, N-(1-ethylpropyl)-3,4,-dimethyl-2,6-dinitro benzenamine, also CL 92553 and AC 92553. American Cyanamid, Herbicide. Review by Reto Engler dated February 22, 1975.

2. Toxicology Branch Response to Prowl (Pendimethalin) Audit of Rat and Mouse Oncogenicity Studies and Assignment of Core Classification to these Studies. Review by John Doherty dated November 27, 1981.

3. EPA Reg. No. 241-243. Rat Chronic Feeding/Oncogenesis Study and Mouse Oncogenesis Study with Pendimethalin Review by John Doherty dated April 13, 1983.

4. Prowl Herbicide, 24-month Oral Toxicity and Carcinogenicity Study in Rats, Statistical Evaluation. Review by Bertram Litt dated April 13, 1983.

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SUBJECT: Prowl, N-(1-ethylpropyl)-3, 4-dimethyl-2,6-dinitro benzenamine, also CL 92553 and 92554. American Cyanamid, Herbicide.

DATE: 2/22/75

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FROM: TB

TO: Product Manager

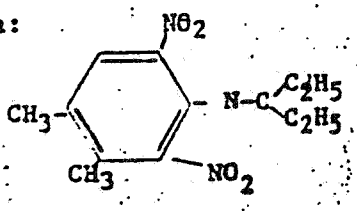
Pesticide Petition and requested tolerances:

5F1556	5G1567	5G1580
0.1 ppm in corn grain forage, and fodder, and cotton seed	0.1 ppm in cotton seed	0.1 ppm in soy beans forage and hay

Registration: Prowl 4E 241-EXP-X

Previous Petitions: 4G 1451 0.1 ppm in corn grain, forage and fodder

Chemical Formula:



Formulation:

PROWL 4E Herbicide

Active Ingredient:	%W/W
PROWL Technical	49.2
Inerts:	(44.3 real)
[redacted]	

* are cleared under 180.1001(d). We have no records of clearance of the [redacted] as permitted for use on growing crops.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

EPA Form 1320-6 (Rev. 6-72)

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Comments and Conclusions:

Registration: The parent comp and has a very low toxicity, but the formulation contains a high percentage of [redacted] and also is irritating to the skin. TB therefore requests that the signal word be changed to "Danger" and that the side panel warnings be extended to include "causes eye and skin irritation". The first aid statment also must be changed because with benzene containing formulations vomiting should NOT be induced.

Tolerances: Prowl, N-(1-ethylpropyl)-2,3,-dimethyl-2,6,-dinitro-benzenamine has a very low toxicity. In long-term studies, reproduction studies and 90-day studies the Nel for rats, mice, and dogs was at least 500 ppm. At the next higher dose (5000 ppm) toxic effects were marginal, showing slight depressions of weight gains, increased liver weight, etc, but no severe toxic signs, Other considerations permitting, the requested tolerances of 0.1 ppm on corn, cotton seed, and soy beans can be toxicologically supported.

Toxicological Evaluation:

Some of these tests were previously reviewed, Dr. R. Schmidt, PP# 1451, but expecially long term studies had only interim reports at that time.

Acute tests:	Oral LD_{50} male rat	1250(560-2780) mg/kg	prostration and lethargy
	Oral LD_{50} female rats	1050(310-3610) mg/kg	
	Oral LD_{50} dog (f.and m)	>500 mg/kg	
	Oral LD_{50} male mouse	1620(860-3070) mg/kg	lethargy
	Oral LD_{50} female mouse	1340(950-1880) mg/kg	
	Dermal LD_{50} male rabbit	>5000 mg/kg	

Skin irritation: (rabbit) no irtttation (score 0), 0.5 g/application.

Eye irritation: (rabbit) no irritation (transient conjunctivitis in one rabbit at 24 h,, 0.1 g/eye)

30-day feeding studies with rats and mice: rats were fed 800, 1600 and 3200ppm and mice 500, 1000 and 2000 ppm (10 m and 10 f per level). Plasma glucose for male rats at 3200 ppm was slightly higher than controls. organ weights (livers and kidneys) were sometimes statistically different ($p<0.05$) but the effects were neither dose related nor consistent (liver-weights increased for rats, decreased for mice).

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90-day feeding with dogs: Beagles were exposed to 0.125, 0,25 and 1.0 g/kg/day. At the lower dose in the diet for two weeks then by gelatin capsule at the high doses by gelatin capsules only. Food consumtion was slightly affected by the treatment, and thus weight gains, but the changes were very minor. Other parameters such as organ weights, hematology, and clinical blood chemistry showed no deviations from the norm.

Acute studies with 4E formulation:

LD_{50} male rats 3380(2810-4070) mg/kg. The formulation was irritating to the skin (score 5 on a scale of 8; Draize score). The formulation was less irritating to eyes (Draize score of 17 at 24 h.; 6 at 72 h.)

Inhalation study: Rats were exposed to the technical compound at a nominal concentration of 320 mg/l for 4 hours. No death or adverse effects other than irritability and sluggishness were observed.

21-day dermal study: (technical and 4E formulation) Rabbits were treated daily for 6 hours, 5 days per week for 3 weeks. The technical product was applied at levels of 250, 500 and 1000 mg/kg and the formulation was applied at 0.5, 1.0, and 2.0 ml/kg. Controls received sham formulation (vehicle) without technical compound. No systemic toxicity was noted in the treated animals. The animals exposed to the technical product showed only slight or no signs of edema and erythema. The animals treated with formulation showed slight to moderate erythema and edema but less so than the vehicle treated controls which showed moderate to severe reactions.

18-month carcinogenicity studies in mice: (Bio-dynamics, East Milestone, N.J.) Mice (Charles River CD-1) were exposed to 100, 500, and 2500 ppm tech, product. After 8 weeks the 2500 ppm group was exposed to 5000 ppm. There were 150 mice per group. The mean body weights of high-dose females were significantly lower througout the experiment; this effect was not related to lessened food intake. Adrenal weights (males) and adrenal/body weights (males and females) were higher at the high-dose level, so were thyroids and thyroid/body weights. No histopathology in these tissues was apparent. Hematology was normal in all groups. Clinical chemistry, including ChE was normal with the exception of an elevated blood glucose level in one female exposed to 100 ppm (no dose response). Histopathological examination showed no remarkable pathology and carcinomas.

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90-day and 2-year studies in rats: Rats (Long-Evans) were exposed to 100, 500, and 2500 (5000 after 6 weeks) ppm via diet. 120 rats were used per group, 20 were sacrificed for the 90-day study. The mean body weights were lower for both sexes in the high-dose group starting with the 5th week. Hematology was unremarkable. At 90 days the alk. phosphatase levels for high and medium males and all females were slightly depressed. This effect was not noted at 24 months. Fluctuations in ChE levels were noted but were not dose related nor were the differences extreme. The liver weights for males and females were significantly higher ($p<0.01$) at the high-dose level at 90 days. At the lower level the significance of any effect was less ($p<0.05$) and not consistent. After 24 months the effect on liver weights persisted at the high level but at the lower levels no effects were noted. There was also a hepatocyte hypertrophy and hyperplasia noted at the high level after 2 years. No increase in tumor or cancer incidence was note at any feeding level.

Effects on male mammary glands after 90-feeding; 20 weanling rats (Sprague-Dawley) were fed 2500 ppm for 6 weeks and 5000 ppm thereafter. The mammary glands were examined histologically. The appearance of the glands was unremarkable, without any signs of hyperplasia (Pharmacopathics. Res.)

3-generation reproduction study in rats (Long-Evans): 10 males and 20 females per generation. The animals were exposed via diet to 500 and 5000 ppm of techn. material. The parents F_0 were mated three times. The second generation was selected from the F_{1c} group; they were mated twice to produce the F_{2a} and F_{2b} litters. Each of these litter groups were mated once to produce the F_{3a} and $F_{3a'}$ litters. The most flagrant evidence of toxicity at the high-dose was the decreased mean weight of pups at 21 days and a slight possibility of lessened survival rate of pups to 21 days. The investigator, therefore, removed the high-dose diet from lactating females until pups were weaned to avoid these minor effects. Considering the minimally toxic effects, this would really not have been necessary. The two F_3 generations were investigated for abnormalities. No significant abnormalities were found in treated groups (small or missing testicles were observed in 4 of 243 offsprings; about 120 males).

90-day feeding tests with dogs: The feeding levels were 62.5 mg/kg/day (2500 ppm) 250, and 1000 mg/kg/day. The two higher doses were administered with gelatin capsules. 8 dogs were used per level. The effects noted were weight losses in two of the middle-dose group and in 6 of the dogs in the high-dose group. Hematology was normal. Clinical chemistry values were also normal with one elevated BUN value at the high-dose level. Tissues examined grossly and microscopically did not show any pathological changes.

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Dominant lethal test (rat): Each group consisted of 15 weanling male rats. They were exposed for 10 days to 500 and 5000 ppm via diet and then mated once a week for 8 weeks to virgin females. The females were sacrificed on the 13th day of pregnancy. The number of pregnancies, corpora lutea, implantation sites, live fetuses and resoprtion sites were determined. There were no remarkable differences between controls and treated animals.

Teratology Study (rats, Charles River): 20 animals per group were dosed with 500 and 1000 mg/kg/day orally (intubation) on day 6 to 15 of gestation. No teratogenic effect was noted. At the high dose 2 females died and fetal body weights were slightly reduced.

Reto Engler, Rh.D.
Toxicology Branch
Registration Division

cc: Branch Reading File
REngler:ir: 2/22/75
Initial G.E. Whitmore

G. E. Whitmore initialed
draft 2/21/75 G. E. W.

004026

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

MEMORANDUM

DATE: NOV 27 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Toxicology Branch Response to PROWL (Pendimethalin) Audit of Rat and Mouse Oncogenicity Studies and Assignment of Core Classification to these Studies.

TOX Chem No 454BB

FROM: John Doherty 11/12/81
Toxicology Branch/HED (TS-769)

TO: Robert J. Taylor, PM #25
Registration Division (TS-767)

Background:

The registrant previously submitted rat and mouse oncogenic studies and these were reviewed by Dr. R. Engler (see Engler memo dated 2/22/75 concerning pesticide petitions 5G1556, 5G1567, and 5G1580). No Core assignment was made at the time this review was conducted. Dr. Adrian Gross requested that these studies be audited and Mr. Larry Chitlik visited the Bio/dynamics Laboratory for that purpose.

The rat chronic feeding and oncogenic study and the mouse oncogenic study have been rereviewed in terms of the results of the audit and for assignment of Core classification, and for their suitability in meeting EPA's requirement for oncogenic testing.

The identification of the chronic feeding/oncogenesis studies under consideration for this chemical are as follows:

1. An 18-month carcinogenicity study of AC 92,553 in mice.

   Bio/dynamics, Project No. 72R-747, April 2, 1974.

2. A three and twenty-four month oral toxicity and carcinogenicity study of AC 92,553 in rats.

   Bio/dynamics, Inc., Project No. 72R-746, August 21, 1974.

Conclusions:

The studies are Invalid and additional oncogenic testing is required to support registrations and petitions for the use of pendimethalin. Any future oncogenic study must use the commerical grade of pendimethalin.

The assignment of an Invalid classification is based on the following:

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1. In the initial 5-6 months of the studies (both rat and mouse), a "high purity" grade of test substance was utilized. The later months of these studies utilized a technical or commercial grade of substance. Nitrosamines were present in the commercial grade but not in the "high purity" grade. Thus, the animals were not exposed to the potential carcinogens during the critical periods of growth and development. (See H. L. Avallone memo dated 5/12/80 regarding the laboratory audit.)

2. There was no data submitted for either of these studies which presented the gross necropsy findings for all of the animals inspected. Thus it could not be determined if gross lesions were followed up histologically in an acceptable manner.

3. For both the rat and mouse studies, only a very limited number of rats or mice were scheduled to be given a "complete" histopathological examination. For example, only 10 rats/sex/dose and only 15 mice/sex /dose were examined. Moreover, all of these animals were survivors and no rats or mice dying while on the study were examined histologically. In the rat study, the audit revealed that only 5 of 10 randomly selected animals had complete sets of slides--even though these animals were reported to have complete sets of slides. In the mouse study, although examination of 15 animals was called for, inspection of Appendix D of the final report indicates that only as few as 3-4 adrenals were actually examined. For other tissues, only 10-11 were actually examined. Numerous masses and lesions grossly observed in other animals were not followed up by histological examination.

   The failure to examine animals which died while on study prevents an evaluation as to whether or not the test chemical caused an earlier development of neoplasms.

   NOTE: Items 2 and 3 might possibly be corrected by submission of the raw data and appropriate tables made for the gross necropsy observations and by extensive preparation and examination of additional slides. However, item 1 is a deficiency that cannot be corrected in this manner.

   New oncogenic studies will be required to support future registrations and tolerances for this chemical in which the increased incremental exposure and/or risk is judged to be significant.

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

MEMORANDUM APR 13 1983

TO: Robert J. Taylor, Product Manager #25
Registration Division (TS-767)

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

THRU: William L. Burnam, Acting Branch Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

WLB

SUBJECT: EPA Reg. No. 241-243. Rat Chronic Feeding/Oncogenesis Study and Mouse Oncogenesis Study with Pendimethalin.

TOX Chem. No. 454BB

Background:

The rat chronic feeding/oncogenesis study and the mouse oncogenesis study with the herbicide Pendimethalin were rereviewed by Toxicology Branch (TB) and determined to be Invalid (see J. Doherty review dated 11/27/81). In an effort to upgrade the rat study, the registrant (American Cyanamid Company) did an extensive repreparation of slides for most remaining tissues and submitted the results of the microscopic analysis. The reanalysis of the rat study data were reviewed by TB and several problems were indicated (see J. Doherty review dated 11/3/82). These problems included: 1. assignment of a NOEL for lesions which occur in the liver; 2. possible oncogenic response in the bladder of males; and 3. possible oncogenic response in the uterus.

Before the memo (dated 11/3/82) listing the problems associated with the rat study was sent to Registration Division, the American Cyanamid Company Toxicologist met with EPA (date of meeting: June 16, 1982) and several of the problems related to the rat study were discussed. The registrant prepared this response to these problems and included a defense for acceptability of the mouse oncogenesis study.

NOTE: Refer to EPA Acc. No. 248792.

Recommendations and Comments:

1. TB has considered the registrants comments regarding the acceptability of the mouse study and maintains its previous conclusion that insufficient histological examination of the tissue precludes accepting this study for registration purposes.

TB recommends that a second oncogenicity study in mice be conducted and submitted.

An acceptable oncogenic study im mice is critical for the registration purposes of Pendimethalin because of the oncogenic questions raised in the rat study.

2. TB does not consider the 3 problems indicated above with the rat chronic feeding/oncogenesis study to be resolved. For example, the study does not show a NOEL for adverse effects in the liver. The registrant provided some explanation for the occurrence of fatty liver, but the low dose group showed higher incidences of fatty liver plus periportal, hepatocyte hypertrophy and ground glass cytoplasmic change relative to the controls. In addition the registrant has not provided an acceptable defense that the uterine and bladder tumors are not related to the presence of the test material in the diet.

TB recommends that a second rat study be initiated, conducted and submitted for review.

3. The test material for the second set of rat and mouse oncogenesis studies must be the technical material which will be used for making the various formulations of PROWL.

4. TB statistician has reviewed the statistical report submitted by the registrant (see B. Litt memo dated March 31, 1983) and does not concur with the appropriateness of the methods used. TB statistician has concluded that the experiment demonstrates a statistically significant oncogenic effect in the high dose test group. Because of problems associated with the execution of the experiment (changes in dose and test material), the biological significance of the apparent positive oncogenic response is undefinable. Additional testing is recommended to resolve this possible oncogenic effect of pendimethalin.

4/11/83

John D. Doherty, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)

4/11/83

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

MEMORANDUM APR 13 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

March 31, 1983

TO: John Doherty and Ed Budd
Toxicology Branch, HED (TS-769)

SUBJECT: PROWL Herbicide, 24-month Oral Toxicity and Carcinogenicity Study in Rats, Statistical Evaluation

The basic design of this study has been compromised first by the alteration of dose levels tested and secondly by the change in the test substance from the pure form fed for the first six months to a nitrosamine mixture used in the manufactured product. While the latter compound is probably a more suitable substance for test, the most significant exposure may (or may not be) during the first six months of the study. If an important result were observed it is not clear how one would draw inferences about either the pure or the impure compound.

The only tumor data which suggests a statistically significant increase over the control rate is the incidence of Endometrial Adenocarcinoma of the uterus. As this is a late forming tumor there is no scientific basis for the use of life-table analysis. In fact the most striking alternative for testing seems to be the high dose effect:

$Control_1$	3/55	= 10/209
$Control_2$	2/55	
100 ppm	4/50	
500 ppm	1/49	
5000 ppm	9/49	

Fisher's Exact Test

(C+100+500) vs 5000; p~.003
C vs 5000; p~.007
100 vs 5000; p~.11
500 vs 5000; p~.007

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The one-sided significance test for determining that there may be an increased rate in the 5000 ppm group compared to all other groups (combined) according to the continuity corrected X^2 statistic yields a P <.002; Fisher's Exact Test indicates P~.003. Pair-wise comparison of high dose with either control or mid-dose by Fisher's Exact Test P~.007. Other types of tests of these data may be misleading because almost all of the tumors were detected at terminal kill and because of the spacing of the study doses.

Any effect attributed to this compound at other tumor-sites must rely on dose-weighted trends which will overestimate the significance levels because of the low incidence of the observed data and the 5 and 10 fold differences between dosage at 100, 500 and 5000 ppm diets.

As a result of the foregoing it seems that there may be an observed increase in the terminal incidence of uterine adenocarcinoma at the high dose of 5000 ppm. It is not clear how this of observation should be interpreted due to the changes in the study chemical added to the diet.

Bertram Litt, Statistician
Toxicology Branch
Hazard Evaluation Division