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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM JUL 20 1982

TO: Robert Taylor (25)
Registration Division (TS-767)

THRU: Orville E. Paynter, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Alachlor (Lasso), a Herbicide. EPA Reg.#524-316, -285, -296, and -314. Proposed tolerances in or on Potatoes (1.0 ppm instead of 0.1 ppm), PP#1F2551; Sunflower Seeds (0.5 ppm), PP#1F2441; Sugarcane (0.2 ppm), PP#9F2144; Peanuts (0.1 ppm instead of 0.05 ppm), PP#0F2313; Corn Fodder and Forage (0.5 ppm instead of 0.2 ppm), PP#0F2348; and Sorghum Seeds (0.1 ppm) and Forage and Fodder (0.5 ppm), PP#0F2338. An Addendum to Alachlor Memo of 6/16/82 (A review of the Rat Chronic Feeding/Oncogenic Study, BD-77-421, 11/13/81; submitted on 1/5/82).

Registrant: Monsanto Company
1101 17th Street, N.W.
Washington, D.C. 20036

Action Requested:

I. Review of the following pending petitions for Alachlor (a herbicide; 2-chloro-2',6'-diethyl-N-(methoxymethyl) acetanilide) to establish the following proposed tolerances:

Petition	Proposed Tolerances (ppm)	Petition Number	Date Submitted
Lasso (sugarcane; and forage and fodder)	0.2	9F2144	11/3/78
Lasso (cabbage)	0.3	9F2156	11/30/78
Lasso EC (Peanuts - Postemergence)	0.1 (instead of present tolerance of 0.05 ppm	0F2313	12/12/79

Petition	Proposed Tolerances (ppm)	Petition Number	Date Submitted
Lasso (sorghum seeds, and forage and fodder)	0.1 0.5	0F2338	3/17/80
Lasso (Postemergence [lay by] on corn)	0.5 (instead of present tolerance of 0.2 ppm)	0F2348	3/31/80
Lasso (sunflower seeds)	0.5	1F2447	11/4/80
Lasso (Postemergence [lay by] on potatoes)	1.0 (instead of present tolerance of 0.1 ppm)	1F2551	8/3/81

II. Risk assessment of Alachlor uses based on the rat chronic feeding/oncogenic study, BD-77-421, submitted on 1/5/82 and reviewed on 6/16/82.

Recommendations:

I. Toxicology Branch is unable, at this time, to make a recommendation on the requested tolerances because of the following data gaps:

Data Gaps

- A NOEL for Alachlor chronic toxicity was not demonstrated in rats at 14 mg/kg/day (LDT) in the submitted (1/5/82) two-year chronic feeding/oncogenic study in rats (BD-77-421, a replacement study of IBT#621-01180), see review of 6/16/82 by Amal Mahfouz and memo of 1/8/80 by E. Budd.

- A NOEL for Alachlor subchronic toxicity was not demonstrated in dogs at 5 mg/kg/day (LDT) in the submitted (12/1/81) six-month subchronic feeding study in dogs (PR-80-015, a replacement study of IBT#C-1181), see review of 6/25/82 by Amal Mahfouz.

- A rabbit teratology study (IR-79-022 submitted on 2/3/81 to replace IBT#J-1183) was determined to be invalid, see Amal Mahfouz's review of 6/23/81 (a memo is in preparation in response to Monsanto's letter of 8/26/82).

Consequently, Toxicology Branch is unable at present to make a hazard assessment for the pesticide until the following studies are submitted and reviewed:

1) A 2-year chronic feeding study in rats with a demonstrated NOEL for ocular effects (uveal degeneration syndrome) and for all other chronic toxicity findings.

2) A one-year feeding study in dogs with a demonstrated NOEL.

In addition to the above 2 studies the following studies are also considered data gaps and should be submitted for review within a reasonable time.

3) A teratology study in rabbits.

4) Mutagenicity studies:

a) Dominant Lethal in Mice: (IBT#E1184, 7/26/72)	Valid* but classified as Core Supplementary.
b) Host-Mediated Assay: in mice and rats (IBT#8533-8849, 8/16/76)	Valid* but classified as Core Supplementary.
c) Reverse Mutation Assay: IBT#8536-8852, 6/10/76	Invalid*
d) Recombination Assay: IBT#8536-8850, 4/20/76	Invalid*

5) Skin sensitization study in guinea pig for the technical material.

6) A metabolism study in rats.

*See HPB Canadanian validation (memos of H.M. Cunningham to David Clegg on 1/9/79).

We also note that study #IR-81-015, a 21-day dermal toxicity study in rabbits with Alachlor, has not yet been submitted for review. Although the registrant stated in the 1/5/82 submission package that this study would be filed in the first quarter of 1982, this study is still considered a data gap.

Also, the submitted 2 dermal penetration studies (The in vitro penetration of human skin, study # UW-81-262, 11/20/81; and the monkey study #MA-81-26, 11/28/81) were reviewed in this action and were found to be inadequate as submitted for the estimation of Alachlor dermal penetration (see reviews on p. 16 to 19). Thus, adequate skin penetration studies are requested in order to appropriately estimate the applicator exposure.

II. The oncogenic risk from the existing and proposed tolerances resulting in dietary exposure is estimated to be lower than 10^{-6} by the Mantel-Bryan Model. This model was used with the most sensitive site (nasal turbinate tumors in males) determined from the chronic feeding/ oncogenic study (BD-77-421) which we reviewed on 6/16/82. Additional risk

estimates of the applicator exposure (worst case) indicated that the flagman for aerial application of the EC formulation is exposed at a relatively high risk of 6.5×10^{-4} followed by the ground applicator (for combined mixing/loading and application operations) exposed at an estimated risk of 2×10^{-6} to 6×10^{-5} assumming a 10% to 50% dermal absorption respectively. Other applicator categories are at a risk level of 10^{-5} to 10^{-6} when a 50% dermal absorption is assumed, see discussion section on p. 5 to 7.

We note that a 50% dermal absorption was used in our calculations because the 2 submitted dermal penetration studies (#UW-81-262 and MA-81-261) were not useful in determining the rate of Alachlor penetration, especially the diluted EC formulation (i.e., in study # UW-81-262, 50% of the applied C^{14} Alachlor EC formulation was not accounted for). A new estimate of the applicator exposure (worst case) will be calculated when adequate dermal penetration studies are submitted.

We also note that the ground applicator group (all categories) for the EC formulation is the most exposed group to the inert, [redacted] presently under testing by NCI (see attached EFB's exposure tables).

III. RPAR criteria have been exceeded due to an oncogenic trigger. Alachlor is oncogenic in rats (nasal turbinate tumors and stomach tumors in both sexes, and thyroid tumors in males) and mice (lung tumors in females).

IV. Epichlorohydrin, an ingredient in several Lasso formulations, is an RPAR Candidate (11/2/77) based on neurotoxicity in chickens and eye effects in humans. The registrant stated recently that due to the oncogenic effect of epichlorohydrin, it will be eliminated from all products [redacted] see Accession No. 070582, part 2, p. 19; submitted on 1/5/82.

At present, it is not clear to what extent the presence of epichlorolydrin in the Alachlor technical material affected the outcome of the chronic feeding study in rats (BD-77-421) as far as the oncogenic data are concerned. However the registrant indicated that a repeat of this study is underway using an Alachlor product with [redacted] instead of epichlorohydrin.

Discussion of the Oncogenic Risk Assessment:

Alachlor was found to be oncogenic in both rats (BD-77-421, 11/3/81; see review of 6/16/82) and mice (BD-77-423, 10/9/81; see review of 6/16/82). A quantitative risk assessment for Alachlor oncogenicity was performed based on the rat study (see attached review of 7/16/82 by Dynamac Corporation).

In this rat study, tumors were found at many different sites, however only 5 incidences of tumor site/sex were significantly above background levels . These were malignant stomach tumors in males and females, tumors of the nasal turbinate in males and females and follicular adenoma/carcinoma of the thyroid in males. On the basis of this information, it appears that the most informative and sensitive tumor/sex incidence is nasal turbinate tumors in males. Nine computer models were used in this risk analysis. The female stomach tumor incidence reflected the best fit for all models (except the one-hit model). The independent probit (IP) offered the best estimation of risk associated with this tumor.

Because the data from the most sensitive site (male nasal turbinate tumors) showed such a poor fit to the 9 models, analysis of this data set was carried using the Mantel-Bryan Method. The aim of this model is to provide conservative estimates of the "safe" dose for humans. The test data are regarded only as establishing some upper bound on the risk (e.g. here we used the 95% level).

Using the Mantel-Bryan Model with the most sensitive oncogenic site (male nasal turbinate tumors), the lowest safe dose for oncogenic effects would be 0.42×10^{-2} mg/kg/day with a risk level of 10^{-6}; this risk is greater than the risk resulting from dietary exposure to existing and proposed tolerances, i.e. 0.57×10^{-3} mg/kg bw/day (existing TMRC) and 0.204×10^{-2} mg/kg bw/day (proposed TMRC) respectively, see TMRC Evaluation Section, on p. 25.

Additional risk estimates of the applicator exposure indicated that the worst risk is for the flagman (aerial application of EC formulation). This risk is estimated at 5×10^{-4} for a calculated exposure of 0.9×10^{-1} mg/kg bw/day (assuming a 10% to 50% dermal absorption, 100% inhalation absorption and a 35 working years of 70 years lifetime. The estimate did not take into account the number of days worked per year because these data were not available according to the EFB reviewer). The next highest group at risk is the farmer (combined mixer/loader and applicator for ground

application of EC formulation) this group is at an estimated risk of 2×10^{-6} to 6×10^{-5} (assuming 10% to 50% dermal absorption). Other applicator categories are at a risk level of 10^{-5} to 10^{-6} when a 50% dermal absorption is assumed, the table below reflects these data.

Additional Risk Estimates of the Applicator Exposure
(Worst case estimates)

Aerial Application (EC)	Exposure assuming 10% dermal absorption mg/kg/day	Level of Risk	Exposure assuming 50% dermal absorption mg/kg/day	Level of Risk
Mixer/Loader	0.94×10^{-3}	$<10^{-6}$	0.224×10^{-2}	$<10^{-6}$
Pilot	0.33×10^{-3}	$<10^{-6}$	0.625×10^{-3}	$<10^{-6}$
Flagman	0.91×10^{-1}	5×10^{-4}	0.912×10^{-1}	5×10^{-4}
Ground Application (EC)				
Mixer/Loader	0.488×10^{-2}	1×10^{-6}	0.241×10^{-1}	4×10^{-5}
Applicator/Inc	0.985×10^{-3}	$< 10^{-6}$	0.461×10^{-2}	2×10^{-6}
Combined	0.587×10^{-2}	2×10^{-6}	0.287×10^{-1}	6×10^{-5}
Ground Application (Granular)				
Mixer/Loader	0.182×10^{-3}	$< 10^{-6}$	0.55×10^{-2}	2×10^{-6}
Applicator/Inc	0.85×10^{-4}	$< 10^{-6}$	0.85×10^{-4}	$< 10^{-6}$
Combined	0.192×10^{-2}	$< 10^{-6}$	0.46×10^{-2}	2×10^{-6}
Ground Applicator (Probe Transfer System)				
Mixer/Loader	0.129×10^{-2}	$< 10^{-6}$	0.627×10^{-2}	4×10^{-6}
Applicator/Inc	0.985×10^{-3}	$< 10^{-6}$	0.461×10^{-2}	2×10^{-6}
Combined	0.228×10^{-2}	$< 10^{-6}$	0.109×10^{-1}	8×10^{-6}

55 gal probe	Exposure assuming 10% dermal absorption mg/kg/day	Level of Risk	Exposure assuming 50% dermal absorption mg/kg/day	Level of Risk
Mixer/Loader	0.249×10^{-2}	$< 10^{-6}$	0.121×10^{-1}	9×10^{-6}
Applicator/Inc	0.985×10^{-3}	$< 10^{-6}$	0.461×10^{-2}	2×10^{-6}
Combined	0.348×10^{-2}	$< 10^{-6}$	0.167×10^{-1}	2×10^{-5}

Note:

1. The number of days which the applicator is working per year was not available for the EFB reviewer to use in the estimation of exposure.

2. EFB used for calculation a 70 kg. bw man instead of a 60 kg. bw man.

3. The above table assumes a 35 working years of a 70 year lifetime and a 100% respiratory absorption.

Toxicology Branch used 50% dermal absorption in the calculations of the applicator exposure (worst case) because the submitted in vitro dermal penetration study with human skin (UW-81-262) did not account for at least 50% of the applied Alachlor in the case of Alachlor technical and Lasso EC dilution experiments (Lasso EC is considered to cause the most skin irritation of all Alachlor products, with a primary skin irritation index of 3.2 to 4.8). Also a 10% dermal absorption was used in our calculations (see table above) because Monsanto selected this absorption rate in their calculations.

A new estimate of the applicator exposure will be calculated when adequate dermal penetration studies are submitted.

Referenced Petitions

Tolerances are established for the combined residues of the herbicide Alachlor and its metabolites (calculated as alachlor) in or on raw agricultural commodities as follows:

Permanent Tolerances:

3F1334 - 2.5 ppm in or on peanut forage; 1.0 ppm in or on peanut hulls.

3F1372 - 0.2 ppm - potatoes

3F1406 - 0.2 ppm - field beans, lima beans, and peas
0.1 ppm - field beans, green lima beans, peas w/pods

7F0622 - 0.2 ppm - corn forage, corn grain, and soybeans

9F0740 - 0.75 ppm in or on soybean forage
0.2 ppm in or on corn grain, corn grain fodder and forage and soybeans
0.02 (negligible residues) in milk; in eggs; and in meat, fat, and meat by products of cattle, goats, hogs, horses, sheep, and poultry.

9F0776 - 0.2 ppm in or on cotton and peanut forage
.05 ppm in or on cotton and peanuts

1F1009 - 0.2 ppm blackeyed peas, cabbage, dry beans, lima beans, peas with pods and pea forage, snap beans, sweet corn, and sweet corn fodder and forage.

Temporary Tolerances:

2G1176 - 0.2 ppm processing peas, blackeyed peas, dry beans, lima beans, snap beans, lima beans, popcorn & popcorn forage.

7G2002 - 0.5 ppm in or on peanuts; 1.5 ppm in or on peanut hulls.

0G2335 - sorghum forage and fodder 0.5 ppm; sorghum grain 0.1 ppm.

Refer also to the existing tolerances in CFR 40, 180.249 and the attached printout.

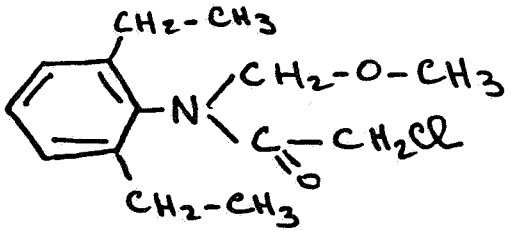
REVIEW

Substance Identification:

Chemical Name: 2-chloro-2',6'-diethyl-N-(methoxymethyl) acetanilide.

Synonyms: Alachlor, Lasso, CP50144

Chemical Structure:



M.W. 269.5

Technical Product (EPA Reg.#524-316)

Components	Percent
2-chloro-2',6'-diethyl-N-(methoxymethyl) acetanilide	90-94%
[redacted]	
Epichlorohydrin*	
[redacted]	

*Monsanto indicated that due to the carcinogenicity of epichlorohydrin, the company will replace it [redacted] see Accession#070582, part 2, page 19.

Physical/Chemical Data:

a) Appearance: White crystalline solid
b) Melting Point: 40-41°C
c) Specific Gravity: 1.133 (25/15.6°C)
d) Solubility: Soluble in ether, acetone, benzene, alcohol, ethyl acetate; slightly soluble in hexane; insoluble in water.

Formulations:

A. Granular

Lasso II (formally Granular Lasso 15) (EPA Reg.#524-296, 1/14/78).

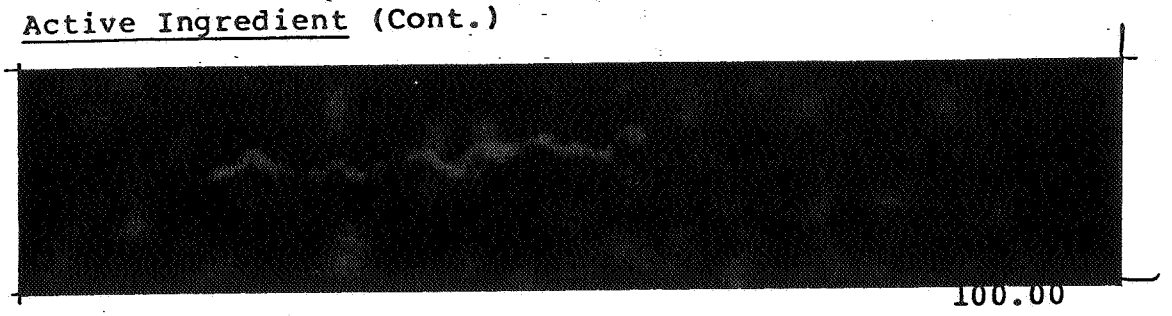
Active Ingredient	Percent by Weight
2-chloro-2',6'-diethyl-N-(methoxymethyl) acetanilide	15.00

Inert Ingredients*

[redacted]

Percent by Weight

Active Ingredient (Cont.)

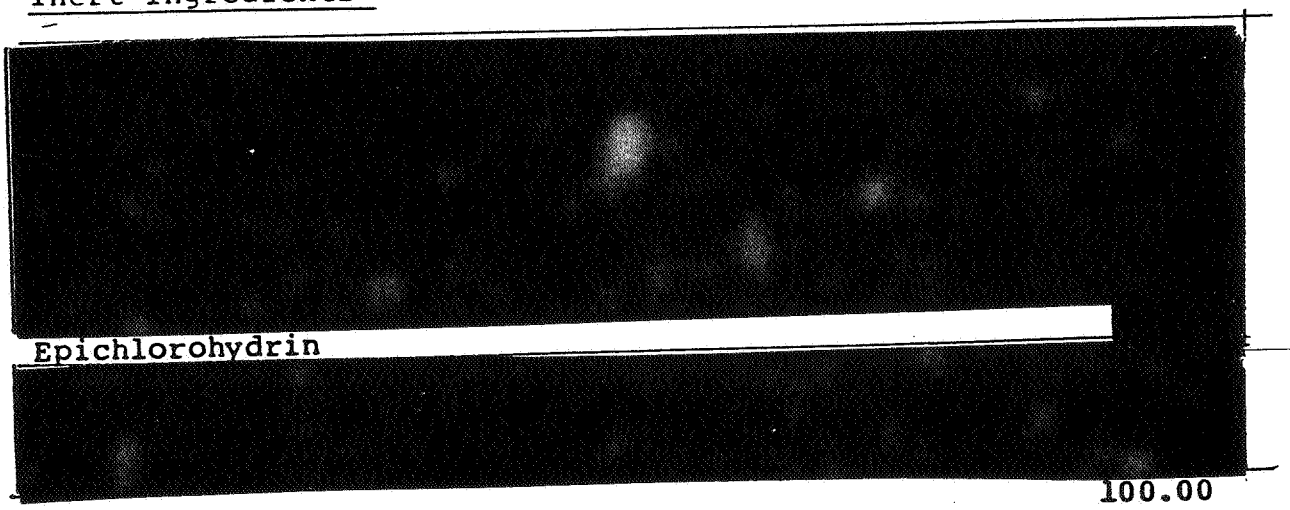


B. Emulsifiable Concentrates

1. Lasso (EPA Reg. No. 524-285)

Active Ingredient	Percent
2-chloro-2',6'-diethyl-N-(methoxymethyl) acetanilide	43.00
Isomers and related intermediates	3.87

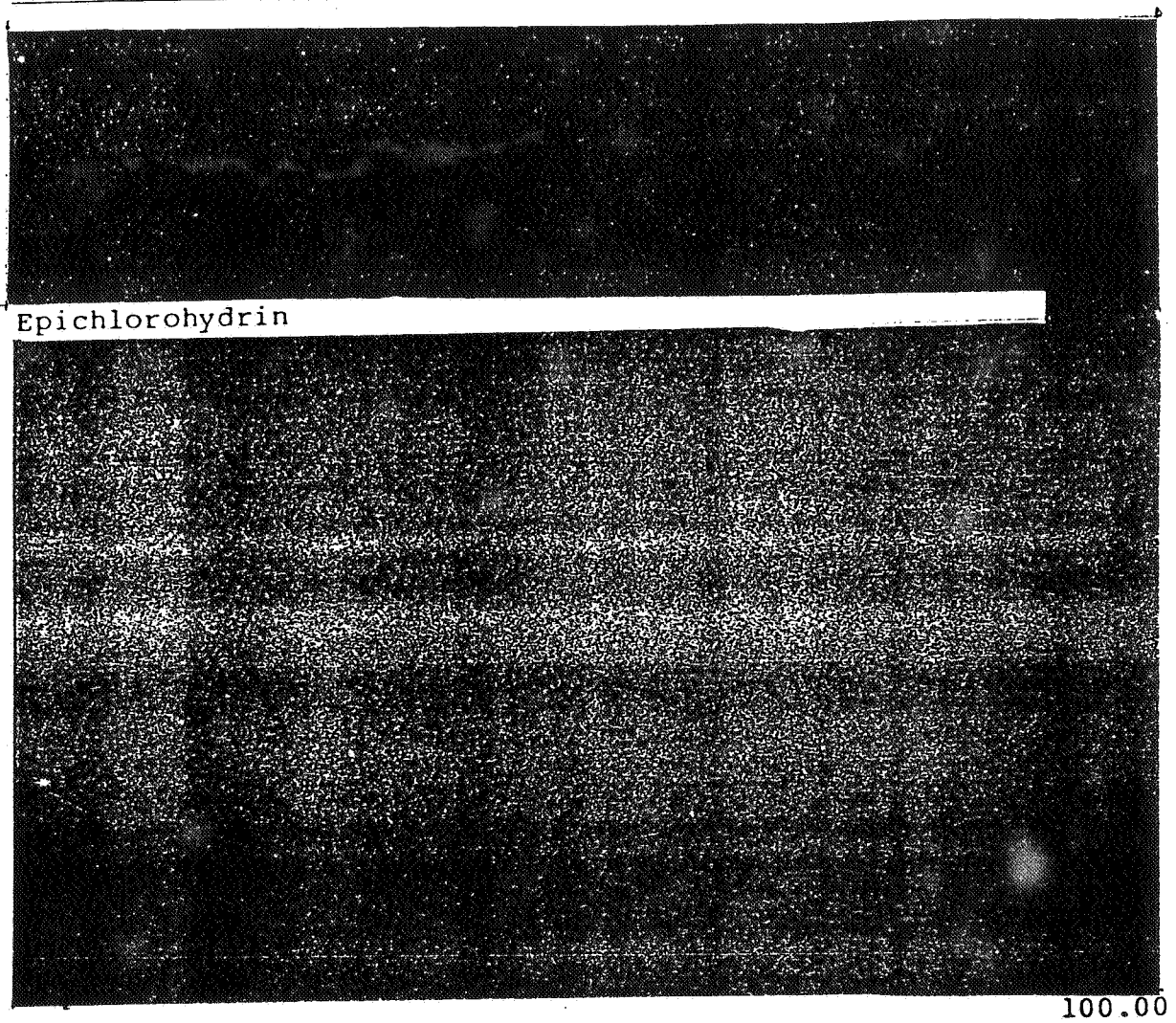
Inert Ingredients*



2. Lasso EC (EPA Reg. No. 524-314)

Active Ingredient	Percent
2-chloro-2',6'-diethyl-N-(methoxymethyl) acetanilide	45.09
Isomers and related intermediates	4.6

Inert Ingredients*



Epichlorohydrin	100.00

*Inerts are cleared under 180.1001 (c) and (d).

Review of the Proposed Tolerances

A. Five of the 7 proposed tolerances have already been reviewed:

1) PP#9F2144 is proposing a tolerance of 0.2 ppm on sugarcane and forage and fodder. It was reviewed by L. Anderson (TOX) on 3/9/79. The tolerance was not recommended pending validation review of raw data of Industrial Bio-Test Laboratories. RCB's M.K. Leovey recommended against the tolerance in a 1/31/79 review, however an amendment submitted on 10/16/79 to RBC was favorably accepted in a 1/15/80 RCB's review.

2) PP#9F2156 is proposing a tolerance in or on cabbage of 0.3 ppm. It was reviewed by R. Gessert (TOX) on 6/22/79. The tolerance was not recommended pending validation of IBT studies. RCB's John Olney also recommended against this tolerance.

3) PP#0F2313 is proposing to increase the tolerance in or on peanuts from 0.05 ppm to 0.1 ppm (tolerances on hulls of 1.5 and on forage and fodder of 3.0 ppm were to remain unchanged as previously accepted). It was reviewed by W. Dykstra (TOX) on 3/20/80. The tolerance was not recommended pending the outcome of the ophthalmoscopic examination in the rat chronic feeding study (BD-77-421), and pending the replacement of the IBT invalid studies. RCB's P.V.Errico also recommended against the requested tolerance in a 6/5/80 memo.

4) PP#0F2338 is proposing a tolerance of 0.1 ppm on sorghum seed and 0.5 ppm on forage and fodder. It was reviewed by W. Dykstra (TOX) on 8/19/80. The tolerance was not recommended for the same reasons mentioned under #3 above. RCB's L.S. Propst reviewed a temporary tolerance 0G2335 for this use and recommended in favor of the tolerance in a memo dated 8/1/80.

5) PP#0F2348 is proposing to increase the tolerance in or on corn forage and fodder from 0.2 ppm to 0.5 ppm. It was reviewed by W. Dykstra (TOX) on 9/30/80. The tolerance was not recommended for the same reasons stated above under #3. RCB's P.V. Errico recommended against the tolerance in a 10/23/80 memo. However an amendment dated 2/5/81 was favorably recommended in a 3/24/81 RCB review.

B. The two remaining proposed tolerances PP#1F2551 (in or on sunflower seeds); and PP#19F2447 (in or on potatoes, a proposed increase of the already existing tolerance) have both been reviewed by RCB's P.V. Errico on 4/16/81 and 1/27/82 respectively. In both cases RCB recommended against the proposed tolerances. A summary of these 2 petitions is presented below:

1) PP#1F2551 is proposing a tolerance in or on sunflower seeds of 0.500 ppm. Emulsifiable concentrates, Lasso and Lasso EC are the selected formulations for this use.

Directions for Use:

Lasso is proposed for use alone and as a tank mix with Amiben. The proposed uses will be discussed separately.

Lasso:

As a broadcast treatment apply 3 to 4 lbs a.i. of Lasso in 15 or more gallons of water per acre after planting and before crop or weeds emerge. In areas of heavy grass or broadleaf weed infestation, or on soils with 3% or more organic matter, use the higher rate.

For preplant incorporation, apply 3 to 4 lbs a.i. per acre of Lasso and incorporate into the top 2 inches of soil within 7 days prior to planting. Use 4 quarts per acre of Lasso when soil organic matter is 3% or more, or where heavy weed infestations exist.

Lasso plus Amiben*:

Broadcast 2.5 to 3 lbs a.i. of Lasso plus 2 lbs a.i. of Amiben in 15 or more gallons of water per acre after planting and before crop or weeds emerge. Use the higher rate of Lasso in this tank mixture when there is heavy weed infestation or when soil organic matter is 3% or more. When yellow nutsedge is present, use 3 lbs a.i. per acre of Lasso in this tank mixture and shallowly incorporate within 7 days prior to planting.

There is no sunflower forage feeding restriction.

*This reviewer notes that Amiben is an oncogen (see Chloramben Registration Standard, July 1981).

2) PP#9F2447 is proposing to increase the existing tolerance in or on potatoes from 0.1 ppm to 1.0 ppm. Emulsifiable concentrates, Lasso and Lasso EC, are the selected formulations for this use. However one inert ingredient in these 2 formulations, [redacted] to use before edible parts of plants begin to form. RCB indicates that "tuber initiation on the stolen occurs approximately 60 days after planting. Depending on weather conditions and soil temperature, emergence occurs in 25 to 42 days after planting. Tuber initiation can occur within approximately 60 days after planting. Therefore, the petitioner will have to have [redacted] cleared for use when edible parts are present or add to the label the restriction 'do not apply beyond 20 days of crop emergence. Do not use on early maturing varieties of potatoes'. This restriction applies to proposed applications of Lasso alone and Lasso plus metribuzin tank mixes", (see RCB's memo of 1/27/82).

Direction for Proposed Use:

Lasso and Lasso tank mixed with metribuzin presently have a preemergence use on potatoes against certain weed species. The petitioner now proposes to include a directed postemergence (lay-by) application of Lasso and Lasso tank mixed with metribuzin on potatoes. Metribuzin is marketed as Lexone 4L, Lexone DF, Sencor 4 Flowable and Sencor 50 WP formulations. Inerts for each formulation are cleared for this use. For control of weeds using a directed postemergence treatment of Lasso at lay-by, apply 1.5 to 3 lbs a.i./acre in 15 or more gallons of water following final hilling or cultivation. Use the higher rate on hard to control weeds and medium and fine textured soils. The total amount of Lasso applied should not exceed 6 lbs a.i./acre/year.

For Lasso plus Lexone or Lasso plus Sencor tank mixes, apply 1.5 to 3.0 lbs a.i./acre of Lasso + 0.375 to 0.75 lbs a.i./acre of metribuzin in 15 or more gallons of water before weeds are 1 inch tall and before the crop has completly filled the rows. Rates depend on soild texture and weed infestation.'

Toxicity Data Base

New Toxicity Data

The following studies have been submitted (in replacement of the corresponding studies conducted by Industrial Biotest Laboratory) and reviewed by Amal Mahfouz:

Study	IBT No.	Study No.	Date Submitted	Accession Number	Review Date
Rabbit teratology	J-1183	IR-79-022	2/3/81	244369	6/23/81
Mouse carcinogenicity	621-01182	BD-77-423	7/1/81	70168, 70169	6/16/82
Three-Generation Reproduction in Rats	622-01185	BD-77-422	6/30/81	70177	1/2/82
Six-Month Subchronic Feeding in Dogs	C-1181	PR-80-015	12/1/81	246292, -93 and 247376	6/25/82
Two-Year Chronic Feeding in Rats	621-01180	BD-77-421	1/5/82	70586 to 90	6/16/82

Except for the mouse carcinogenicity study and the 3-generation reproduction study, two of the remaining studies need to be repeated because a NOEL for each of these studies could not be determined; and the third study, the rabbit teratology study, was found to be invalid, see toxicity summary on pages 23 & 24.

Two other studies were submitted on 1/5/82 with this Action: One study was performed to determine the in-vitro penetration of C-14 Alachlor formulations in human skin samples; and another study was designed to determine the rate of elimination of C-14 Alachlor in urine and feces after a single dose intramuscular injection in monkeys.

Reviews:

1) Evaluation of the Percutaneous Absorption of Alachlor Technical and Lasso Formulations in Man Using an In-Vitro Technique. UW-81-262, 11/20/81. T.J. Franz, School of Medicine, University of Washington, Seattle, Washington 98195 (Accession #070592).

Study Period: 9/2/81 to 10/29/81

Human abdominal skin was obtained at autospy from 5 male (age 52, 55, 60, 62 and 77 years) and 3 female (age 28*, 85* and 84 years) donors. The skin was mounted as a partition between two test chambers according to the method of Franz, T.J. (J. Invest. Dermat. 64:190, 1975). After the integrity of each skin sample was determined, the dermal penetration of the following labeled Lasso formulations was tested:

Table 1

Test Solutions** (treatments)	Alachlor Vol.	(mg)	uC
1. ^{14}C-Alachlor in acetone	10 ul	= 403	= 0.68
2. ^{14}C-Lasso EC [redacted]	10 ul	= 474	= 0.68
3. ^{14}C-Lasso EC 1:20 Use dilution	10 ul	= 24	= 0.68
4. ^{14}C-Lasso N (Microencapsulated)	10 ul	= 460	= 0.68
5. ^{14}C-Lasso N 1:12 Use dilution	10 ul	= 24	= 0.68

* The skin from the 28 year old female was not included in the calculation of the mean dermal penetration because this skin was judged to be a poor sample after testing with tritiated water; and the skin from the 85 old female was not tested with tritiated water due to an oversight.

** These solutions were used as supplied except for Lasso - EC spray solution (#3) which was evaporated to dryness then dissolved in water before use. We note that this treatment of the EC-spray solution before use may have contributed to the erratic data noted with this formulation in this study.

The dermis was in contact with isotonic saline and the epidermis was exposed for 24 hours to 10 microliters of the radiocarbon test material solutions. The test solution was then removed by sequential washing with water, acetone and water, the washes were analyzed for C^{14}-Alachlor concentration. The dermal bathing solution was sampled at 0.5, 1, 2, 4, 6, 8, 12, 24, 36 and 48-hours after application and the radiocarbon determined by liquid scintillation spectrophotometry (LSC). Some of the experiments on the 5 different test solutions were run in duplicates. After the 48 hours exposure, both the dermis and epidermis were analyzed for residual radioactivity.

An additional dermal penetration experiment was done with Alachlor technical and the dermis alone(after removal of the epidermis) in order to prove that only the epidermis is acting as a penetration barrier.

Results:

Six of the 7 skin samples tested with tritiated water (the 8th sample was not tested due to an oversight) were determined to be in good condition for further testing. Data from the seventh skin sample were omitted from the calculation of the mean Alachlor penetration values due to the poor condition of this sample; however data from the eighth sample were included.

Absorption is influenced by the vehicle in which Alachlor is dissolved. The five vehicles tested were ranked as follows:

Lasso EC (use dilution, 1:20) > Alachlor (acetone) > Lasso EC [redacted] surfactants) ≥, Lasso N (microencapsulated) = Lasso N (use dilution 1:12).

The 5 Lasso solutions appeared to exhibit low skin penetration values of 0.2 - 3.8% of the applied dose. However these data are not accurate, due to the encountered technical difficulty in applying Lasso EC-dilution and due to the considerable variability noted in the recovery of radiocarbon in the skin washes performed at 24-hours. Mean total recovery values for the five formulations ranged from 41 to 117% of the applied dose. With three of the five test vehicles, it appears that most of the unabsorbed Alachlor remained on the skin surface and was easily removed by washing, but an unexplained loss of ca 50% of the applied dose was noted in the data derived from Alachlor and Lasso EC use dilution treatments (#1 and #3 in table 1). Thus, this fact confounds the interpretation of the data derived from these two test solutions. Retention of radiocarbon in the dermis and epidermis at the end of the 48 hours test period was 1% or less of the applied dose for all formulations.

The rate of dermal absorption of Alachlor was slow during the first hour but gradually increased with time up to the 24-hour. The rate of penetration declined rapidly thereafter and most of the recovered radioactivity was detected in the skin wash collected after the 24-hour exposure.

Alachlor (technical) penetrated at least 10 times faster (13 % to 16% recovery) in the exposed dermis than in the whole skin (including epidermis). Thus Alachlor absorption is rate-limited by the epidermis.

Conclusions:

This study provides only supplementary information on the in-vitro dermal penetration of Alachlor. However, extrapolation of these data to in-vivo situations is not recommended due to: 1) the variability of the results; 2) low total recovery (42 - 56%) of the technical and EC-dilution products; and 3) the technical difficulty of delivering appropriate amounts of EC-dilution product to the skin.

2. Elimination of ^{14}C-Alachlor in Rhesus Monkeys Following A Single Parenteral Dose. MA-81-261, 11/28/81. H.I. Maibach, School of Medicine, University of California, San Franciso, California 94143 (Accession #070592).

Study Period: 10/5/81 to 10/24/81

Test Material: C-14 labeled Alachlor compound (specific activity of 180 microcuries per millimole; molecular weight of 269).

Vehicle: Propylene glycol

Test Solution: 1 ml solution = 3 mg Alachlor = 2 microcuries

Six male Rhesus monkeys were each injected intramuscularly (in the thigh) with a single dose of 1 ml (2.20 microcuries) of the test compound and monitored for radiocarbon elimination over 5 days.

Urine samples were collected at 4, 8 and 12-hour intervals the first day, and at 12-hour intervals thereafter for five days. Five milliliters of each urine sample were analyzed by liquid scintillation spectrophotometry (LSC) for the radiocarbon level eliminated in urine (Ref.: Fundamentals of Clinical Pharmacokinetics, first edition; Wagner, J., p. 77).

Feces samples were also collected at 24, 48 and 120 hours and analyzed for radiocarbon level (Arch. Dermatol. Res. in press).

Results were expressed as mean percents of the applied dose excreted during each interval.

Results:

^{14}C-Alachlor is mostly excreted in urine (71.4%) after 5 days of an initial single dose (intramuscular) administration. Only 5.7% of the initial dose was excreted in feces. However the remaining 22.9% of the initial dose was not accounted for in this study.

The rate of ^{14}C Alachlor elimination was highest during the first 24 hours, i.e. 60.2% in urine and 3.2% in feces. The half life (t 1/2) was 15.2 hours.

Conclusions:

The submitted study presented data only for the intramuscular injection experiment. The dermal application part of the study was not submitted. The registrant's summary of the study (part 1 of Accession No. 070592) indicated that dermal application was also performed. The summary also reported 'that a total of 15.6% of a single topical application of Alachlor was excreted in 5 days in urine. However the penetration rate was slow during the 1st 24 hours (3.2% of applied dose in urine). The half life of penetration and elimination via the kidneys of topically applied Alachlor was 31-hours'. Thus the study is classified as supplementary until the actual data for the dermal penetration section are forwarded for review.

Previously Submitted Toxicity Data:

Several studies were previously submitted and reviewed. Many of these studies were performed by IBT and later determined to be ivalid by the Canadian HPB. The following references include all the reviews of these background data:

1) Review of G.E. Whitmore (11/27/67, Acc.#091278), PP#7F0622, establishing a PADI for man of 0.0025 mg/kg/day and approving tolerances of 0.2 ppm in or on corn grain, corn forage, and soybeans.

2) Review of W. Greear (1/20/78, Acc. Nos. 091277 & 091278), PP#7F2002, approving a tolerance of 10 ppm in or on peanut forage and hay; also 524-EUP-39.

3) Review by L. Anderson (3/9/78, Acc. Nos. 091278 and 234629) for PP#9F2144, a proposed tolerance of 0.2 ppm in sugarcane and forage and fodder, not approved.

4) Review by L. Anderson (8/26/78, Acc. Nos. 234629 and 234630) of additional data submitted in support of EPA Reg. No. 524-314, -285, -296, and -304.

5) Review by R. Gessert (1/16/81) of possible opthalmological effects of Alachlor.

Repeated IBT Acute Toxicity Studies on Lasso products, EPA Reg. No. #526-316, -314, -285 and -296, (these new studies were performed by Bio/dynamics for Monsanto, report#MSL-0931, 10/2/79; Accession#241273) were reviewed by M.L. Alexander on 1/7/80 and summarized in a 9/18/80 review by A. Arce for PP#G2335, a proposed temporary tolerance of 0.1 ppm in or on sorghum grain and 0.5 ppm in or on forage and fodder, not approved.

Repeated IBT Chronic (rat & mouse), Reproduction (rat), Teratology (rat & rabbit), and Subchronic (dog) studies were submitted during 1981-1982 and reviewed for this Action by Amal Mahfouz (see section above on new toxicity data) except for the rat teratology study (IR-79-020, 3/21/80) which was reviewed by R. Gessert on 3/24/81.

Summary of relevant toxicity data on Alachlor/Lasso products (Lasso 43% EC, 524-285; Lasso 45% EC, 524-296; Lasso 15% G, 524-296; and Lasso Technical 92-94%, 524-316) are listed in the following table:

Alachlor (Lasso) Toxicity Summary

I. Acute Studies

A. Technical, 524-316

Study/Lab/Study #/Date	Material	Number	Results	Category	Classification
Acute oral LD_{50}, rat Biodynamics, Inc. #4899-77; 6/28/78	Technical	241273	LD_{50} = 930 mg/kg	III	Minimum Doc.#000055
Acute dermal LD_{50}, rabbits, Biodynamics, Inc.; 4900-77; 4/30/79	Technical	241273	LD_{50} = 13,300 mg/kg	III	Minimum Doc.#000055
Primary eye irritation rabbit, Biodynamics, Inc.; #4902-77; 8/6/79	Technical	241273	PIS = 1	IV	Minimum Doc.#000055
Primary dermal irritation, rabbit; Biodynamics, Inc.; #4902-77; 8/6/79	Technical	241273	PIS = 1.9	IV	Minimum Doc.#000055

B. Lasso 43% EC, 524-285

Acute oral LD_{50}, rats Biodynamics, Inc. #4943-77; 6/28/78	43% a.i. EC	421273	LD_{50} = 1,000 mg/kg	III	Minimum Doc.#000055
Acute dermal irritation, rabbit, Biodynamics, Inc. #4944-77; 12/15/78	43% a.i. EC	421273	LD_{50} = 8,000 mg/kg Erythema, edema at 5600 mg/kg	III	Minimum Doc.#000055
Primary dermal irritation, rabbit, Biodynamics, Inc.; #4946-77; 6/28/78	43% a.i. EC	421273	PIS = 3.2	III	Minimum Doc.#000055

(continued)

Primary eye irritation, rabbit, Biodynamics, Inc. #4945-77; 6/9/78	43% a.i. EC	421273	Severe (Pannus)	III	Minimum Doc.#000055
Repeated insult patch test dermal - human Industrial Biology Lab. #M-7; 3/5/68	43% a.i. EC	421273	Skin sensitizer	I	Minimum Doc.#000047 #000049

C. Lasso 45% EC, 524-314

Study/Lab/Study #/Date	Material	Accession Number	Results	Toxicity Category	Core Classification
Acute oral LD_{50}, rat Biodynamics, Inc. #4903-77; 5/7/79	45.1% a.i. EC	421273	LD_{50} = 2000 mg/kg	III	Minimum Doc.#000055
Acute dermal LD_{50}, rabbits, Biodynamics, Inc.; 4904-77; 11/17/78	45.1% a.i. EC	421273	LD_{50} = 7800 mg/kg Erythema, edema, weight loss at 5700 mg/kg	III	Minimum Doc.#000055
Primary eye irritation rabbit, Biodynamics, Inc.; #4905-77; 6/28/78	45.1% a.i. EEC	421273	Severe (Pannus)	I	Minimum Doc.#000055
Primary dermal irritation, rabbit; Biodynamics, Inc.; #4906-77; 6/28/78	45.1% a.i. EC	421273	PIS = 4.8	III	Minimum Doc.#000055

D. Lasso 15% G, 524-296

Acute oral LD_{50}, rats Biodynamics, Inc. #4907-77; 6/28/78	15%, Granular	421273	LD_{50} = 5800 mg/kg	IV	Minimum Doc.#000055
Acute dermal irritation, rabbit, Biodynamics, Inc. #4908-77; 8/11/78	15%, Granular	421273	LD_{50} = 16,000 mg/kg	III	Minimum Doc.#000055
Primary eye irritation, rabbit, Biodynamics, Inc.; #4909-77; 6/28/78	15%, Granular	421273	Corneal opacity	I	Minimum Doc.#000055
Primary dermal irritation, rabbit, Biodynamics, Inc.; #4910-77; 3/22/78	15%, Granular	421273	PIS = 1.2	IV	Minimum Doc.#000055

II. Chronic and Special Studies

Study/Lab/Study #/Date	Material	Number	Results	Category	Classification
Teratology - rabbit International Research & Development Corp. #IR-79-022; IRDC-401-060 11/24/80	Technical 92.19% Lot#MHK-6	244369			Invalid 000610
Teratology - rat International Research & Development Corp. #IR-79-020; 3/21/80	Technical	243506	Negative for teratogenic effect at 400 mg/kg/day (HDT). NOEL for maternal toxicity and fetotoxicity = 150 mg/kg/day		Core Guideline
Three-Generation Reproduction in Rats Biodynamics; BD-77-442 2/20/81	Technical	70177	NOEL = 10 mg/kg/day LEL = 30 mg/kg/day (HDL) Effect noted on kidneys in F_2 generation and F_{3b} pups; this effect is more remarkable in males.		

Six-Month Subchronic Feeding in Dogs Pharmacopathics Research Lab. PR-80-015; 10/9/81	Technical	246292,-93 and 247376	NOEL < 5 mg/kg/day (LDT) based on hepatotoxicity	Core-Minimum
18-Month Feeding Oncogenic in Mice Biodynamics; BD-77-423 6/18/81	Technical	70168 and 70169	Positive oncogen causes lung tumors in females at 260 mg/kg/day (bronchiolar-alveolar tumors)	Core-Minimum
Two-Year Chronic Feeding/Oncogenicity in Rats Biodynamics; BD-77-421	Technical	70586, 87 88, 89 & 90	NOEL < 14 mg/kg/day (LDT) ocular lesions (uveal degeneration syndrome) and hepatotoxicity. Also Positive oncogen at 42 mg/kg/day: Nasal turbinate tumors in both sexes. 126 mg/kg/day: Stomach and nasal tumors in both sexes; and thyroid follicular adenoma/carcinoma in males	Core-Minimum

TMRC Evaluations:

The existing TMRC is 0.0342 mg/day/1.5 kg food, which is equivalent to an estimate environmental human dose of:

$$\frac{0.0342 \text{ mg/day/1.5 kg food}}{60 \text{ kg man}} = 0.57 \times 10^{-3} \text{ mg/kg bw/day}$$

The level of existing oncogenic risk due to oral exposure (Mantel-Bryan Model) is lower than 10^{-8}.

The proposed tolerances would increase the existing TMRC as follows:

Commodity	Proposed Tolerance or Increase in tolerance (ppm)	TMRC mg/day/1.5 kg	TMRC mg/kg bw/day	TMRC % Increase	Level of Oncogenic Risk Mantel-Bryan Model
Peanuts	0.05	0.00027	0.45×10^{-5}	0.79	$<10^{-8}$
Sorghum	0.1	0.00057	0.80×10^{-6}	0.15	$<10^{-8}$
Cabbage, sauerkrant	0.3	0.00331	0.552×10^{-4}	9.68	$<10^{-8}$
Sugar, cane & beet	0.2	0.01091	0.182×10^{-3}	31.90	$<10^{-8}$
Sunflower	0.5	0.00023	0.38×10^{-5}	0.67	$<10^{-8}$
Potatoes	0.9	0.07326	0.122×10^{-2}	214.21	$<10^{-7}$
New TMRC as a result of the above uses		0.12220	0.204×10^{-2}	257.0	$= 5 \times 10^{-7}$

Both the existing and proposed TMRC are lower than the lowest safe dose, 0.42×10^{-2} mg/kg/day which reflects a risk level of 10^{-6} (see table 9 in the quantitative risk analysis report by Dynamac Corporation).

PADI Calculations:

A review by G.E. Whitmore (11/27/67) for PP#7F0622 did establish a PADI for man of 0.0025 mg/kg/day. This PADI was based upon a 90-day dog oral feeding study, IBT#C4478, 10/21/68. The NOEL in this study was 200 ppm = 5.0 mg/kg/day. With the imposition of a 2000 fold safety factor, the PADI was calculated as follows:

$$5.0 \text{ mg/kg/day} \times \frac{1}{2000} = 0.0025 \text{ mg/kg/day}$$

The Maximum Permissible Intake (MPI) based on this PADI was calculated as follows (based on a 60 kg man):

0.0025 mg/kg/day x 60 kg man = 0.1500 mg/day/60 kg man

We note that this 90-day dog oral feeding study was found to be invalid (see memo of Robert Taylor to Monsanto 11/14/80) and a six-month dog feeding study, PR-80-015, 10/19/81, was submitted as a replacement, and reviewed by A. Mahfouz on 6/25/82. The NOEL in this study appears to be less than 5 mg/kg/day (LDT).

At present, no chronic or subchronic NOEL is available to compute a new PADI.

Conclusions:

The proposed tolerances cannot be toxicologically supported.

A NOEL for chronic toxicity was not demonstrated in the new rat study. Also a NOEL was not determined in the new 6-month dog study. Consequently, an ADI/PADI cannot be calculated at the present time. Thus the following two studies are requested to support the proposed tolerances:

1) A 2-year chronic feeding study in rat, and 2) a one-year feeding study in dog.

The following studies are also noted as data gaps should be submitted for review within a reasonable time:

3) A teratology study in rabbit
4) Mutagenicity studies
   (a) Dominant Lethal in Mice (IBT determined to be valid, but evaluated as Core Supplementary)
   (b) Host-Mediated Assay (IBT determined to be valid, but evaluated as Core Supplementary)
   (c) Reverse Mutation (Invalid IBT)
   (d) Recombination Assay (Invalid IBT)
5) Skin sensitization - guinea pig - with the technical compound.

6) A metabolism study in rats.

We also note that study #IR-81-015, a 21-day dermal toxicity in rabbit, has not yet been submitted for review, although the registrant stated in the 1/5/82 submission package that this study would be filed in the first quarter of 1982. Thus this study is still considered as a data gap.

RPAR criteria have been exceeded due to an oncogenicity trigger.

The existing TMRC is 0.0342 mg/day/1.5 kg food or 0.57 x 10^{-3} mg/kg bw/day. This TMRC reflects an oncogenic risk less than 10^{-8} based on the Mantel-Bryan model. This risk is calculated based on the most sensitive site, nasal turbinate tumor incidence in males in the rat study (BD-77-421). The new TMRC calculated for all the proposed new tolerances is 0.1222 mg/day/1.5 kg food or 0.204 x 10^{-2} mg/kg bw/day, this level reflects an oncgenic risk of 5 x 10^{-7}. We shall defer to the Administrator the decision on the proposed tolerances associated with this level of oncogenic risk. However, at present no decision will be taken on these proposed tolerances until the requested studies are submitted and an appropriate NOEL is determined for the chronic effects.

Other needed data are 1) the missing dermal penetration experiment in the monkey metabolism study, MA-81-261, 11/28/81, submitted with the 1/5/82 data package; and 2) an adequate dermal penetration study to determine the applicator exposure. The submitted in vitro dermal penetration study in human skin (UW-81-286) was not useful in our calculation of the applicator exposure due to the low recovery level (approximately 50%) of Alachlor when applied as technical product or as EC-dilution.

At present the worst case estimate of the applicator exposure indicates that the flagman for aerial application of EC formulaton is exposed at a relatively high risk of 5 x 10^{-4} followed by the ground applicator (for combined mixing/loading and application operations) exposed at an estimated risk of 2 x 10^{-6} to 6 x 10^{-5} assuming a 10% to 50% dermal absorption respectively. Other applicator categories are at a risk level of 10^{-5} to 10^{-6} when a 50% dermal absorption is assumed, see discussion section on oncogenic risk p. 5 to 7.

A new estimate of the applicator exposure will be calculated when adequate dermal penetration studies are submitted.

Attachments

Amal Mahfouz 7/19/82 FDC 7/19/82

Amal Mahfouz, Ph.D 7/19/82
Toxicology Branch
Hazard Evaluation Division (TS-769)

TS-769:th:TOX/HED:7-8-82:AMahfouz:card 6
REVISED:DCR-23449:TS-769:efs:TOX/HED:7-8-82:AMahfouz:card 6

CFR 180.249 Alachlor 7/8/82

outdated as of 7/19/82

File last updated 5/4/82

ACCEPTABLE DAILY INTAKE DATA

Dog* NOEL mg/kg	ppm	S.F.	ADI mg/kg/day	MPI mg/day(60kg)
5.000	200.00	2000	0.0025	0.1500

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Corn,all types(36)	0.200	2.51	0.00753
Soybeans (oil)(148)	0.200	0.92	0.00275
Beans,dry edible(10)	0.100	0.31	0.00047
Beans,lima(11)	0.100	0.19	0.00029
Peas(117)	0.100	0.69	0.00104
Potatoes(127)	0.100	5.43	0.00814
Cottonseed (oil)(41)	0.050	0.15	0.00011
Peanuts(115)	0.050	0.36	0.00027
Milk&Dairy Products(93)	0.020	28.62	0.00858
Meat,inc poultry(89)	0.020	13.85	0.00415
Eggs(54)	0.020	2.77	0.00083

MPI	TMRC	% ADI
0.1500 mg/day(60kg)	0.0342 mg/day(1.5kg)	22.78

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Current Action PLAY

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Peanuts(115)	0.050	0.36	0.00027
Sorghum(147)	0.100	0.03	0.00005
Sunflower(156)	0.500	0.03	0.00023
Potatoes(127)	0.900	5.43	0.07326
Cabbage,sauerkraut(22)	0.300	0.74	0.00331
Sugar,cane&beet(154)	0.200	3.64	0.01091

MPI	TMRC	% ADI
0.1500 mg/day(60kg)	0.1222 mg/day(1.5kg)	81.46

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* Note that the PADI was based on an IBT 90-day subchronic study, this study was determined to be invalid by the Canadian HPB. At present an ADI/PADI cannot be calculated because a NOEL could not be determined at the highest dosage tes[illegible] (NOEL ≤5 mg/kg/day) a rat subchronic