5-16-94

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

MAY 16 1994

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

~~May 5, 1994~~

MEMORANDUM

SUBJECT: The HED Chapter of the Reregistration Eligibility Decision Document (RED) for Picloram, Case #0096

FROM: Jane Smith, Chemist
Chemical Coordination Branch
Health Effects Division (7509)

THRU: Debra Edwards, Ph.D., Branch Chief
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Health Effects Division (7509)
and
Penelope Fenner-Crisp, Ph.D, Director
Health Effects Division (7509)

TO: Lois Rossi, Chief
Reregistration Branch
Special Review and Reregistration Branch (7508)

The Human Health Assessment for the Reregistration Eligibility Document for Picloram and the salts is attached. This chapter includes the Hazard Assessment from Brian Dementi in Toxicology Branch I, the Occupational/Residential Exposure Assessment from Shanaz Bacchus in OREB, the Dietary Exposure Assessment, Product Chemistry and Tolerance Reassessment from Bill Smith in CBRS, and the Dietary Risk Assessment from John Bazuin in DRES.

Formulations of picloram include an isooctyl ester, and potassium and amine salts. There are no registered products containing the triethylamine salt and the last registered product was cancelled in 1984. Picloram is a systemic herbicide used to control deeply rooted herbaceous weeds and woody plants in rights-of-ways, rangelands, pastures and small grains.

The *Tolerance Reassessment and Codex Harmonization* that is part of this document should be included in the final RED document under Section IV, part B, entitled Regulatory position.

Dietary Risk Assessment

The Picloram chronic dietary exposure/risk TMRC and ARC estimates are exceedingly low, about 1/200th of the RfD for each of the groups and subgroups. There appears to be no reason for concern in regard to chronic dietary exposure to Picloram at this time.

The refined, ARC dietary carcinogenicity risk estimate for the U.S. population as a whole for the impurity, hexachlorobenzene, is 0.7 E-6, which is less than the 1.0 E-6 point below which risk is

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impurity, hexachlorobenzene, is 0.7 E-6, which is less than the 1.0 E-6 point below which risk is generally considered to be negligible. It should be noted that HCB also occurs as an impurity in several other pesticide technical products, so overall dietary exposure to HCB is likely to be appreciably higher than HCB considered simply as a picloram impurity as considered in this analysis.

Occupational Risk Assessment

For regulatory purposes the toxicological endpoint of concern is systemic toxicity occurring at 500 mg/kg/day (LOEL) based on the 21-day dermal rabbit study conducted with the picloram isooctyl ester (MRID#s 421716-01, 428707-01). The highest potential worker exposure by the dermal and inhalation routes is represented by the mixer/loader of the high pressure handwand scenario at 5.40 mg/kg/day exposure; and the lowest by the mixer/loader of the groundboom scenario at 1.2×10^{-2} mg/kg/day exposure. Therefore, the range of MOE's for workers involved in mixer/loader and/or application activities is between 93 and 4.2×10^{4}. The risk to mixers/loaders/applicators is considered to be minimal even for the high pressure handwand; an MOE of 93 is similar to an MOE of 100 because the dose-response is a log curve and, therefore, is not of concern in this case.

The Agency has classified hexachlorobenzene (HCB) as a probable human carcinogen (Group B_2) having a Q_1^* of 1.7 $(mg/kg/day)^{-1}$. Picloram isooctyl ester (also referred to as picloram ethylhexyl ester) bears structural similarity to di(2-ethylhexyl)phthalate (DEHP) in possessing a 2-ethylhexyl moiety. DEHP and certain other substances containing the 2-ethylhexyl moiety have been found to be positive for carcinogenicity in rodent bioassays. The recommended toxicological endpoint (cancer) for DEHP is characterized by the Q_1^* value of 3.29×10^{-4} $(mg/kg/day)^{-1}$. All exposure scenarios are appropriate for risk assessment for HCB and picloram isooctyl ester. The highest potential worker exposure by the dermal and inhalation routes is represented by the mixer/loader of the high pressure handwand scenario at 5.40 mg/kg/day exposure; and the lowest by the mixer/loader of the groundboom scenario at 1.2×10^{-2} mg/kg/day exposure. The upper bound excess carcinogenic risk estimates for workers from exposure to HCB are between 5.0×10^{-5} and 1.0×10^{-7} and for picloram isooctyl ester are between 9.7×10^{-5} and 2.2×10^{-7}. The actual risk could be as low as zero.

This is a restricted use chemical that has no residential uses at this time; therefore, there are no human risks associated with residential uses.

The risk associated with post-application exposure is not a major concern since exposure to workers is minimal due to the use patterns defined by the picloram labels and the cultural practices typically associated with a broad spectrum herbicide of this type as indicated above. The Agency recommends the REIs of 12 hours for all end use products containing picloram as required by the Worker Protection Standard PR Notice 93-7 for in-scope uses be retained.

Data Requirements

Outstanding data requirements for product chemistry include guidelines 61-3(discussion of impurities), 62-1 (preliminary analysis), 63-8 (solubility) and 63-11 (octanol/water coefficient) for picloram triisopropanolamine TGAI (005102); 62-1 for picloram isooctylester TGAI (005103); 61-1 (product identity and disclosure of ingredients), 62-1, 62-2 (certification of ingredients limits), 63-11 for picloram potassium salt FI (005104). All pertinent data requirements are satisfied for the picloram acid TGAI. Provided the registrant submits these data, the Agency has no objection to the reregistration of picloram with respect to the product chemistry. These data are considered confirmatory.

Although data are available to estimate the worker exposure for the maximum exposure scenarios for the purposes of risk assessment, the data sets available are limited in both quantity and quality as shown in Table VI. In order to reduce the uncertainty associated with the exposure assessments and thus the risk assessment and because the following scenarios lack exposure data and have a potential for as high a worker exposure as the high pressure handwand scenario, these data must

be submitted for confirmation purposes:

1) Guideline 231: Estimation of Dermal Exposure at Outdoor Sights for mixer/loaders and applicators using the hand cannon equipment.

2) Guideline 232: Estimation of Inhalation Exposure at Outdoor Sites for mixer/loaders and applicators using the hand cannon equipment.

3) Guideline 231: Estimation of Dermal Exposure at Outdoor Sights for mixer/loaders and applicators using the backpack/knapsack equipment.

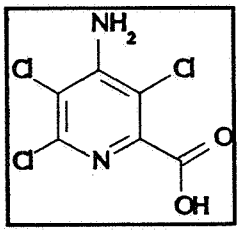
4) Guideline 232: Estimation of Inhalation Exposure at Outdoor Sites for mixer/loaders and applicators using the backpack/knapsack equipment.

ATTACHMENTS

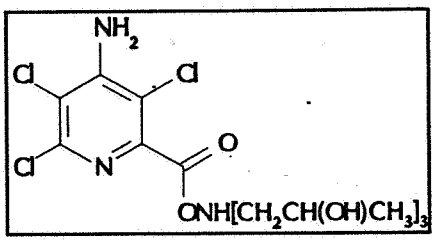
A. Product Chemistry

DESCRIPTION OF CHEMICAL

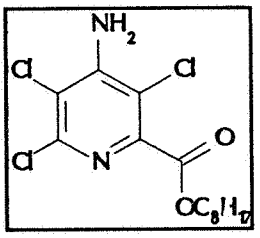
Picloram (4-amino-3,5,6-trichloropicolinic acid) is a selective herbicide for a wide variety of deep-rooted broadleaf weeds and woody plants, used for brush control on roadways, pastures, rangeland, and small grains. Formulations of picloram include an isooctyl ester, and potassium and amine salts.



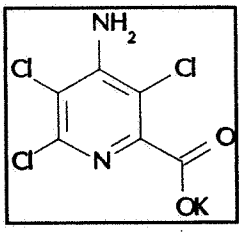
Picloram acid
Empirical Formula: $C_6H_3Cl_3N_2O_2$
Molecular Weight: 241.5
CAS Registry No.: 1918-02-1
Shaughnessy No.: 005101



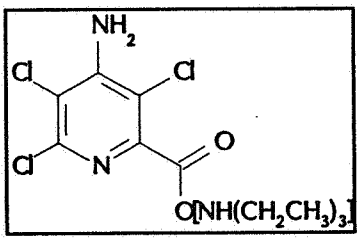
Picloram triisopropanolamine salt (TIPA)
Empirical Formula: $C_{15}H_{24}Cl_3N_3O_5$
Molecular Weight: 432.6
Shaughnessy No.: 005102



Picloram isooctyl ester (IOE aka EHE)
Empirical Formula: $C_{14}H_{19}Cl_3N_2O_2$
Molecular Weight: 353.5
Shaughnessy No.: 005103



Picloram potassium salt (K-salt)
Empirical Formula: $C_6H_2Cl_3KN_2O_2$
Molecular Weight: 280.6
Shaughnessy No.: 005104



Picloram triethylamine salt (TEA)
Empirical Formula: $C_{12}H_{18}Cl_3N_3O_2$
Molecular Weight: 342.5
Shaughnessy No.: 005105

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IDENTIFICATION OF ACTIVE INGREDIENT

The picloram acid technical is an off-white to brown powder which decomposes at 215°C, photodegrades, and is non-volatile. The acid is only slightly soluble in water at 430 ppm at 25°C, and is more soluble in ethanol, acetone, and methanol. The picloram salt formulations are water soluble; the isooctyl ester is not water soluble.

MANUFACTURING-USE PRODUCTS

A search of the Reference Files System (REFS) conducted 9/2/93 identified two picloram manufacturing-use products (MPs) registered to DowElanco Company under Shaughnessy Nos. 005101 and 005104: the 72% picloram acid technical (T; EPA Reg. No. 62719-179) and the 34.7% picloram K-salt formulation intermediate (FI; EPA Reg. No. 62719-30). For Shaughnessy Nos. 005102 and 005103 there are no registered MPs, only end-use products (EPs) manufactured by integrated systems. There are no active products containing picloram triethylamine salt as the active ingredient registered under Shaughnessy No. 005105; the sole registered product was canceled in January 1984.

At the time of the Registration Standard dated 10/84 and the Final Registration Standard and Tolerance Reassessment (FRSTR) dated 5/18/88, the only registered MP was the 34.7% K-salt FI. The 72% T was registered in 1990, following issuance of the FRSTR. The DowElanco 72% T and the 34.7% K-salt FI are the only MPs subject to a reregistration eligibility decision. Data pertaining to the technical grade of the TIPA and IOE picloram formulations also are required to satisfy data requirements for reregistration.

REGULATORY BACKGROUND

The Picloram FRSTR dated 5/18/88 required that all new data be submitted in support of the reregistration of picloram and its salts and ester. After the 72% T was registered, the product chemistry database submitted since the FRSTR was re-evaluated. Additional MP data were required for the now registered picloram acid technical, and data were required for the "practical equivalent of the technical grade of the active ingredient" for the picloram salts and ester manufactured by integrated systems.

The Picloram Registration Standard dated 3/29/85 required the limiting of the level of hexachlorobenzene (HCB) in the technical to a maximum of 200 ppm and also required testing for nitrosoamines in picloram products. The sole registrant of picloram products has complied with these requirements; no nitrosoamines were detected in picloram products (< 1 ppm) and the level of HCB has been certified to be less than 100 ppm.

Outstanding data requirements for product chemistry include guidelines 61-3(discussion of impurities), 62-1 (preliminary analysis), 63-8 (solubility) and 63-11 (octanol/water coefficient) for picloram triisopropanolamine TGAI (005102); 62-1 for picloram isooctylester TGAI (005103); 61-1 (product identity and disclosure of ingredients), 62-1, 62-2 (certification of ingredients limits), 63-11 for picloram potassium salt FI (005104). All pertinent data requirements are satisfied for the picloram acid TGAI. These data are considered confirmatory.

Human Health Assessment

1. Toxicology Assessment

The toxicological data base in support of the food uses for picloram (the acid, potassium salt, isooctyl ester, and triisopropanolamine salt) is adequate and will support reregistration eligibility.

a. Acute Toxicity

Table I: Acute Toxicity - Picloram, Acid (94.1% a.i.)

Test	Result	Category
Oral LD_{50} (rat)[1]	> 5000 mg/kg (males) 4012 mg/kg (females)	IV III
Dermal LD_{50} (rabbit)[2]	> 2000 mg/kg (both sexes)	III
Inhalation LC_{50} (rat)[3]	> 0.035 mg/L (both sexes)	I
Eye Irritation[4]	Moderate eye irritant	III
Dermal Irritation[5]	Non irritant	IV
Dermal Sensitization[6]	Non sensitizer	N/A
Delayed Neurotoxicity		N/A

1-6 MRID#s 404794-13 thru -18; HED Document Number 006787

Table II: Acute Toxicity - Picloram Potassium Salt (38.8% a.i.)

Test	Result	Category
Oral LD_{50} (rat)[7]	> 5000 mg/kg (males) 3536 mg/kg (females)	IV III
Dermal LD_{50} (rabbit)[8]	> 2000 mg/kg (both sexes)	III
Inhalation LC_{50} (rat)[9]	> 1.63 mg/L (both sexes)	II
Eye Irritation[10]	Moderate eye irritant	III
Dermal Irritation[11]	Non irritant	IV
Dermal Sensitization[12]	Positive skin sensitizer	N/A
Delayed Neurotoxicity		N/A

7-12 MRID#s 404794-01 thru -06; HED Document Number 006787

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Table III: Acute Toxicity - Picloram, Isooctyl ester (IOE) (85.9% a.i.)

Test	Result	Category
Oral LD_{50} (rat)[13]	> 3500 mg/kg (both sexes)	III
Dermal LD_{50} (rabbit)[14]	> 2000 mg/kg (both sexes)	III
Inhalation LC_{50} (rat)[15]	>0.35 mg/L (both sexes)	II
Eye Irritation[16]	Moderate eye irritation	III
Dermal Irritation[17]	Mild dermal irritation	III
Dermal Sensitization[18]	Positive skin sensitizer	N/A
Delayed Neurotoxicity		N/A

13-18 MRID#s 404794-07 thru -12; HED Document Number 006787

Table IV: Acute Toxicity - Picloram, Triisopropanolamine Salt (61% a.i.)

Test	Result	Category
Oral LD_{50} (rat)[19]	> 5000 mg/kg (both sexes)	IV
Dermal LD_{50} (rabbit)[20]	> 2000 mg/kg (both sexes)	III
Inhalation LC_{50} (rat)[21]	> 0.07 mg/L (both sexes)	II
Eye Irritation[22]	Minimal irritant (both sexes)	III
Dermal Irritation[23]	Slight irritant (females) Not an irritant (males)	IV
Dermal Sensitization[24]	Positive	N/A
Delayed Neurotoxicity		N/A

19-24 MRID#s 413812-01 thru -06; HED Document Number 010173

b. Subchronic Toxicity

In a 90-day oral toxicity study, picloram, acid was administered via the diet to groups of 15 F344 rats/sex/dose at dosage levels of 0, 15, 50, 150, 300 or 500 mg/kg/day. Based upon liver weight changes and minimal microscopic changes in the liver, the systemic LOEL is 150 mg/kg/day. The NOEL is 50 mg/kg/day. (MRID# 001105-37)

In a 1982 6-months dog dietary study, picloram acid was evaluated at dosage levels of 0, 7, 35 or 175 mg/kg/day. The systemic NOEL is 35 mg/kg/day and the LOEL is 175 mg/kg/day based on decreases in the following: body weight gain, food consumption, liver weights (relative), alkaline

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phosphatase and alanine transaminase. Increased liver to body weight ratios and absolute weights were observed in only two males at the 35 mg/kg/day dosage level. (MRID# 001105-34).

In a 21-day dermal toxicity study, the potassium salt of picloram was administered dermally to groups of five New Zealand white rabbits of each sex at doses of 0 (vehicle control), 75.3, 251 or 753 mg/kg/day (0, 65, 217 or 650 mg/kg/day picloram acid equivalents) for a total of 15 applications over the 21-day period. The NOEL is greater than or equal to 753 mg/kg/day for both sexes: hence, a LOEL was not established for either sex. Although the limit dose of 1000 mg/kg/day was not achieved, practical difficulties precluded administering more test material. The study revealed the non-systemic effects of dermal irritation and very slight to well defined edema and/or erythema in both sexes at all dose levels. (MRID# 413849-01)

In a 13-week oral toxicity study in the F344 rat, picloram isooctyl ester was evaluated by dietary administration at dosage levels of 0, 22, 73, 220 or 733 mg/kg/day (0, 15, 50, 150 or 500 mg/kg/day picloram acid equivalents). There were 10 rats/sex/group employed in the study. The LOEL is 220 mg/kg/day, where the findings were increased liver weights in both sexes accompanied by slight/very slight hepatocellular hypertrophy and increased kidney weight in males only. The NOEL is 73 mg/kg/day. (MRID# 422970-01)

In a 21-day dermal toxicity study in the rabbit, picloram isooctyl ester (89.9% purity) was evaluated at dosage levels of 0 (vehicle control) 250, 500 or 1000 mg/kg/day. There were 5 rabbits/sex in each of the study groups. The LOEL is 500 mg/kg/day based upon increased bilirubin (males) and increased BUN (males/females). The NOEL is 250 mg/kg/day. There were dermal responses at the site of application, at all doses, but such do not constitute findings of systemic toxicity. There were no dose related histopathologic findings. (MRID#s 421716-01; 428707-01)

In a 21-day dermal toxicity study the triisopropanolamine salt of picloram was administered dermally to groups of five New Zealand white rabbits of each sex at doses of 0 (vehicle control), 132, 440 or 1320 mg/kg/day (0, 73.8, 246 or 738 mg/kg/day picloram acid equivalents) for a total of 15 applications over the 21-day study period. The NOEL is greater than or equal to 1320 mg/kg/day for both sexes; hence, a LOEL was not established for either sex. The study revealed dermal irritation and very slight to well defined edema and/or erythema among animals of both sexes at all doses. (MRID# 413849-02)

In a 13-week oral toxicity study in the F344 rat, picloram, triisopropanolamine salt was evaluated by dietary administration at dosage levels of 0, 25, 90, 550 or 1800 mg/kg/day. There were 10 rats/sex/group employed in the study. The LOEL is 550 mg/kg/day based on hepatocellular hypertrophy observed in males at 550 and 1800 mg/kg/day with a dose-response relationship. Hepatocellular hypertrophy and increased liver and kidney weights were observed in females at 1800 mg/kg/day. There was decreased body weight gain in both sexes at 1800 mg/kg/day. The NOEL is 90 mg/kg/day. (MRID# 414427-01)

c. Chronic

In a 1988 1-year chronic feeding study in the dog, picloram acid was administered orally via the diet at dosage levels of 0, 7, 35 or 175 mg/kg/day. The LOEL is 175 mg/kg/day based on increased liver weight (absolute and relative). The NOEL is 35 mg/kg/day. (MRID# 408343-01)

d. Combined Chronic and Carcinogenicity

The following studies were submitted prior to the Picloram Registration Standard (1988) under the same identifier (MRID# 00081275) and were referenced in the Registration Standard.

In a study performed for the NTP by Gulf South Research Institute (GSRI), Osborne-Mendel rats were fed picloram (technical grade 90% pure with 130 ppm HCB) at dosages corresponding to time weighted average (TWA) dosages of 372 mg/kg/day (7437 ppm) and 747 mg/kg/day (14,875 ppm) for 80 weeks. At the highest dose, 747 mg/kg/day, an carcinogenic effect (neoplastic nodules) was seen in females. This study was considered supplementary since the matched control groups were not adequate size, the study was conducted for a shorter than 2-year lifetime exposure limit, and the supporting data to determine if the maximum tolerated dose (MTD) was attained at 747 mg/kg/day was not provided. (MRID# 00081275)

In a second NTP study, $B_6C_3F_1$ mice were fed picloram (technical grade 90% pure with 130 ppm HCB) at dosages of 357 or 714 mg/kg/day for 79 weeks and allowed to recover for 10 weeks prior to sacrifice. Picloram did not show an carcinogenic response up to 714 mg/kg/day for 79 weeks. This study was considered deficient since available information did not assure that an MTD was attained. (MRID# 00081275)

The following studies were submitted in response to the deficiencies cited in the Registration Standard.

In a chronic toxicity/oncogenicity feeding study conducted in the F344 rat, picloram acid (technical grade 93% containing 197 ppm hexachlorobenzene as an impurity) was evaluated at 0, 20, 60 or 200 mg/kg/day for 2 years. The chronic toxicity LOEL was 60 mg/kg/day as evidenced by altered size and tinctorial properties of centrilobular hepatocytes and increased absolute and/or relative liver weights in both sexes. The NOEL was 20 mg/kg/day. The study was negative for carcinogenicity, but due to concerns that a MTD may not have been achieved and the fact that the test material contained 197 ppm hexachlorobenzene impurity, the study was not considered to fulfill adequately the oncogenicity testing requirement. (MRID# 001559-40)

In response to the deficiencies cited in the study above, an additional 2-year dietary chronic/oncogenicity study was conducted (in 1992) using F344 rats administered picloram acid at dosage levels of 0, 250 or 500 mg/kg/day for 104 weeks. Chronic toxicity was observed at 250 mg/kg/day among males only (increased incidence and severity of glomerulonephritis, blood in urine, decreased specific gravity of urine, increased size of hepatocytes that often had altered staining properties). Among females there were chronic effects only at 500 mg/kg/day (increased glomerulonephropathy, increased absolute and relative kidney weight). There was no evidence of carcinogenicity in this study. It should be noted that use of the Osborne-Mendel rat was waived due to lack of availability of the strain of rat. In addition, the level of hexachlorobenzene in the test material employed in this study was 12 ppm (personal communication with the Registrant on 9/29/93). (MRID# 426193-02) These two studies (MRID# 001559-40, 426193-02) fulfill the guidelines 83-1(a) and 83-2(a) for rats.

In a 1992 2-year dietary oncogenicity study in B6C3F1 mice, picloram acid was evaluated at doses of 0, 100, 500 or 1000 mg/kg/day. The systemic NOEL in this study is 500 mg/kg/day based on a significant increase in absolute and relative kidney weights in males (at the high dose level). No histopathological lesions were found to corroborate these changes. There was no evidence of carcinogenicity. (MRID# 426193-01)

The dose levels tested in the 1992 carcinogenicity studies in rats and mice were considered adequate for carcinogenicity testing. The treatment did not alter the spontaneous tumor profile in mice or different strains of rats tested under the testing conditions. The chemical was classified as a "Group E - Evidence of non-Carcinogenicity for humans." This classification applies to the picloram acid and potassium salt forms for which acceptable carcinogenicity studies were available for review by the HED Carcinogenicity Peer Review Committee (5/26/88). Carcinogenicity studies

had not been required for the other forms of picloram. However, subsequent to the carcinogenicity peer review meeting, it was reported that 2-ethylhexanol was detected as a metabolite of the picloram ethylhexyl ester in Fisher 344 rats. This metabolite is thought to play a role in the ability of di-(2-ethylhexyl)phthalate (DEHP) to act as a peroxisome proliferator and it has been suggested that peroxisome proliferation might be the/an underlying mechanism in DEHP carcinogenicity. It was brought to the Committee's attention that a surrogate Q_1^* for di-(2-ethylhexyl) phthalate would be used to perform an initial assessment of possible risk to workers from potential exposure to picloram ethylhexyl ester.

e. Developmental Toxicity

The HED RfD Peer Review Committee concluded that there was no evidence, based on the available data, that picloram and the salts and ester were associated with significant reproductive or developmental toxicity under the testing conditions.

In the following developmental toxicity studies, the dose levels that appear in parenthesis are picloram acid equivalents where the conversion factors employed were 0.86, 0.68 and 0.56 as applied to doses of potassium salt, isooctyl ester and triisopropanolamine salt, respectively.

Picloram potassium salt was administered to New Zealand rabbits by oral gavage at dosage levels of 0, 40, 200 and 400 mg/kg/day (picloram acid equivalents) during days 6 to 18 of gestation. The maternal NOEL is 40 (34) mg/kg/day, where the LOEL is 200 (172) mg/kg/day based on reduced maternal weight gain during gestation. The developmental NOEL is 400 mg/kg/day and the LOEL was not determined. (MRID# 410695-01, 001387-03, Accession# 252493)

The potassium salt of picloram was administered to CD rats by gastric intubation at dosage levels of 0, 35 (30), 174 (150) and 347 (298) mg/kg/day during day 6-15 of gestation. The test vehicle was distilled, deionized water. There was no evidence of developmental toxicity at doses up to and including the high dose of 347 (298) mg/kg/day. The LOEL is 347 (298) mg/kg/day is based upon excessive salivation in the dams of the high dose group. Hence, the developmental toxicity NOEL is greater than or equal to 347 (298) mg/kg/day. The maternal toxicity LEL is 347 (298) mg/kg/day and NOEL is 174 (150) mg/kg/day. (MRID# 413825-02)

Picloram isooctyl ester was administered to New Zealand white rabbits via oral gavage at dosage levels of 0, 20 (14), 100 (68) or 500 (340) mg/kg/day during days 7-19 of gestation. Developmental toxicity was not observed at any dose level. Hence, the developmental toxicity NOEL is greater than or equal to 500 (340) mg/kg/day. Maternal toxicity was observed at 100 (68) mg/kg/day manifested as an increase in the incidence of clinical signs (decreased feces at 500 (340) mg/kg/day and decreased body weight gain at 100 (68) mg/kg/day and above). Hence, for maternal toxicity, the LOEL is 100 (68) mg/kg/day and the NOEL is 20 (14) mg/kg/day. (MRID# 421211-04)

Picloram isooctyl ester was evaluated in CD rats was administered via oral gavage at dosage levels of 0, 100 (68), 500 (340) or 1000 (680) mg/kg/day during days 6-15 of gestation. There was no evidence of developmental toxicity noted at any dosage level; hence, the developmental toxicity NOEL is greater than or equal to 1000 (680) mg/kg/day. The maternal toxicity LOEL is 500 (340) mg/kg/day based on decreased body weight gain during early gestation, days 6-9. The maternal toxicity NOEL is 100 (68) mg/kg/day. (MRID# 422969-01)

Picloram triisopropanolamine salt was administered to New Zealand white rabbits via oral gavage at dosage levels of 0, 180 (101), 538 (301) or 1,000 (560) mg/kg/day during days 7-19 of gestation (phase 1) and at doses of 0, 54 (30), 180 (101), 538 (301) or 1,000 (560) mg/kg/day (phase II).

Developmental toxicity was not observed at any dose level in either of the two phases of the study. Hence, the developmental toxicity NOEL is greater than or equal to 1000 (560) mg/kg/day. Maternal toxicity was observed in both phases of the study at greater than or equal to 180 (101) mg/kg/day manifested as increased rate of abortions at 1000 (560) mg/kg/day; increased incidence of clinical signs at 538 (301) and 1000 (560) mg/kg/day; and decreased food consumption and body weight gain at 180 (101), 538 (301) and 1000 (560) mg/kg/day. The maternal toxicity LOEL is 180 (101) mg/kg/day and the NOEL is 54 (30) mg/kg/day. (MRID# 424609-01)

Picloram triisopropanolamine salt was administered to CD rats by gastric intubation at dosage levels of 0, 100 (56), 500 (280) or 1000 (560) mg/kg/day during days 6-15 of gestation. The test vehicle was distilled, deionized water. The picloram salt did not elicit evidence of developmental toxicity at doses up to and including the high dose of 1000 (560) mg/kg/day. The developmental toxicity NOEL is 1000 (560) mg/kg/day. Maternal toxicity was observed at 1000 (560) mg/kg/day manifested as excessive salivation, decreased body weight gain and decreased food consumption. The maternal toxicity LOEL is 1000 (560) mg/kg/day and the NOEL is 500 (280) mg/kg/day. (MRID# 413825-04)

f. Reproduction

Picloram acid was evaluated in a 2-generation reproduction study in the CD rat. Dosage levels employed were 0, 20, 200 or 1000 mg/kg/day. The parental LOEL is 1000 mg/kg/day based on histopathological lesions in the kidney of males of both generations and some females. In males of both generations, blood in the urine, decreased urine specific gravity, increased absolute and relative kidney weight, and increased body weight gain was observed at the high dose. The parental LOEL is 1000 mg/kg/day and the NOEL is 200 mg/kg/day. The reproductive LOEL was not identified and the NOEL is 1000 mg/kg/day. (MRID# 420787-01)

g. Mutagenicity

Picloram acid was evaluated in the Ames test using Salmonella typhimurium. Doses ranged up to 5000 ug/plate, with and without metabolic activation. The test substance did not produce a mutagenic response either in the presence or absence of activation. (MRID# 414859-02)

Picloram acid was evaluated for gene mutation in mammalian cells (HGPRT/CHO). As evaluated up to toxic levels (750 ug/ml without metabolic activation; 1250 ug/ml with metabolic activation), the compound was found to be negative for inducing forward mutation in Chinese hamster ovary (CHO) cells. (MRID# 400726-01)

Picloram acid was evaluated for cytogenetic effects on bone marrow cells of rats via intragastric administration at dosage levels of 0 (vehicle), 20, 200 or 2000 mg/kg. The test material did not produce cytogenetic effects in the study. (MRID# 000983-22)

Picloram acid was evaluated for genotoxic potential as administered to primary rat hepatocyte cultures at concentrations of 0 (vehicle), 10, 33.3, 100, 333.3 or 1000 ug/ml. The test material was negative for unscheduled DNA synthesis (UDS, a measure of DNA damage/repair) treated up to cytotoxic levels of (1000 ug/ml). (MRID# 415497-01)

Picloram isooctyl ester was evaluated in the Ames test using Salmonella typhimurium. Dosages ranged from 16.7 to 1667 ug/plate in studies with and without S9 activation. The test compound did not induce a mutagenic response in the presence or absence of metabolic activation. (MRID# 421211-06)

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Picloram isooctyl ester was evaluated in two independent Chinese Hamster Ovary Cell HGPRT forward gene mutation assays, one of these with, and the other without, S9 activation. Concentrations of the picloram isooctyl ester employed in the non-activated trial ranged 1.25 to 50 ug/ml as conducted in two assays of overlapping dosage range. The second trial, also conducted in two assays of overlapping dose and including S9 activation, utlilzed dosages ranging from 2.50 to 200 ug/ml. Concentrations $\geq$ 40 ug/ml in the non-activated trial and $\geq$ 125 ug/ml in the activated trial were severely cytotoxic. There was no evidence of a mutagenic response at any dosage level in either the S9 activated trial(s)/or the non-activated trial(s). (MRID# 424140-01)

Picloram isooctyl ester was evaluated in two independent rat lymphocyte cytogenetic assays with and without S9 activation. Concentrations ranging from 2.67 to 800 ug/ml +/-S9 were assayed in Trial 1; severe cytotoxicity was observed at levels $\geq$ 80 ug/ml +/-S9. In Trial 2, no cytotoxicity was seen in cells exposed to 8.04 or 17.4 ug/ml +/-S9 and harvested at 24 hours. However, reductions in the mitotic index (MI) were observed in cells harvested 24 or 48 hours postexposure to 26.8 ug/ml +/-S9. Although a number of minor deficiencies rendered the purported negative results of this study inadequate in initial review, subsequent re-evaluation with additional information and data supplied by the performing laboratory were adequate to upgrade this assay to fully acceptable in demonstrating no potential for inducing chromosomal aberrations. (MRID# 423687-01)

Picloram isooctyl ester was evaluated in the mouse micronucleus assay at single oral gavage doses of 0(2), 500, 1667 and 5000 mg/kg (limit dose) using 24, 48 and 72 hour sacrifice times. The material was found not to be clastogenic. No lethality was reported and there was no evidence of target tissue cytotoxicity. The picloram compound was tested at a sufficiently high level and found not to be clastogenic. (MRID# 421716-02)

Picloram triisopropanolamine salt was evaluated in the Ames test using Salmonella typhimurium. Doses ranged up to 5000 ug/plate, with and without metabolic activation. The test material did not produce a mutagenic response either in the presence or absence of activation. (MRID# 414859-01)

Picloram triisopropanolamine salt was evaluated by oral administration to mice in the mouse bone marrow micronucleus test, at dosage levels of 0, 300, 1000 and 3000 mg/kg. The test agent was determined to be non-clastogenic in mice, as determined by lack of mutagenic effect at doses up to lethality (3000 mg/kg). (MRID# 415397-01)

Picloram triisopropanolamine salt (MRID# 415397-02) was evaluated for genotoxic (DNA damage/repair) potential when administered to primary rat hepatocyte cultures at concentrations up to 1500 ug/ml. The test material was negative for inducing unscheduled DNA synthesis (UDS) at doses up to toxic levels (1500 ug/ml). (MRID# 415397-02)

h. Metabolism

The absorption, distribution, metabolism and excretion of picloram acid was evaluated in female rats administered a single i.v. or oral gavage dose of 10 mg/kg, an oral gavage dose of 1000 mg/kg ^{14}C-picloram, or 1 mg/kg/day unlabeled picloram by gavage for 14 days followed by a single oral gavage dose of 10 mg/kg ^{14}C-picloram on day 15. The study demonstrates that ^{14}C-picloram is rapidly absorbed, distributed and excreted following oral and i.v. administration. This study alone is not adequate; however, this study is acceptable when considered in conjunction with a male rat metabolism study (MRID# 00098321) which yielded similar results. (MRID# 412096-02)

The absorption, metabolism and excretion of picloram isooctyl ester (also referred to as picloram ethylhexyl ester) was studied in male F344 rats following single oral (gavage) dosing with 15 mg/kg

of ^{14}C-picloram isooctyl ester. The ester was absorbed and excreted rapidly. By 48 hours post-exposure, mean recovery of radioactivity was 96.4%. The urine was the major elimination route (68 % of administered dose). The feces and expired $^{14}CO_2$ represented 16.35% and 10.16%, respectively, of the administered dose. Elimination of picloram ethylhexyl ester was rapid, as indicated by 67% recovery at 24 hours post-dosing. The major metabolite was 2-ethyl-1, 6-hexanoic acid. This study supports that picloram ethylhexyl ester is hydrolyzed rapidly to picloram (free acid) and 2-ethyl hexanol, and that picloram ethylhexyl ester does not influence the excretion of picloram in the rat. (MRID# 421716-03)

The absorption, metabolism and excretion of picloram triisopropanolamine salt was studied in male F344 rats following administration of single oral doses (gavage) of 9.5 mg/kg of C^{14}-triisopropanolamine and 9.8 mg/kg of picloram. This level of dosing delivered 20-30 uci per animal in the forms of ^{14}C-triisopropanolamine. The ^{14}C-triisopropanolamine was absorbed readily, with peak plasma radioactivity being observed at 0.25 hours post-dosing. The administered dose of radioactivity as recovered primarily in urine, feces, expired carbon dioxide, tissue/carcass and final cage rinse was 94%. Unchanged triisopropanolamine accounted for 80% of the total radioactivity excreted in the urine. No other metabolites were identified in the 0-6 hour pooled urine sample. The data suggest that the conversion of picloram triisopropanolamine salt to picloram was not affected by the presence of triisopropanolamine. (MRID# 423431-01)

l. Reference Dose

In the meeting of September 30, 1993, the HED RfD Peer Review Committee recommended that the RfD for this chemical be based on a NOEL of 20 mg/kg/day for a dose-related increase in size and altered tinctorial properties of centrilobular hepatocytes in males and females at 60 and 200 mg/kg/day in a chronic toxicity study in rats (MRID# 00155940). An uncertainty factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.20 mg/kg/day. It should be noted that no regulatory value has been established for this chemical by the World Health Organization (WHO) up to this date.

There was no evidence, based on the available data, to suggest that the chemical was associated with significant reproductive or developmental toxicity under the testing conditions.

e. Other Toxicological Considerations

Picloram isooctyl ester (also referred to as picloram ethylhexyl ester) bears structural similarity to di(2-ethylhexyl)phthalate (DEHP) in possessing a 2-ethylhexyl moiety. DEHP and certain other substances containing the 2-ethylhexyl moiety have been found to be positive for carcinogenicity in rodent bioassays. 2-Ethylhexanol was detected as a metabolite in the metabolism studies summarized above. This metabolite is also a primary hydrolytic cleavage product of DEHP, a positive rodent liver carcinogen. This metabolite is thought to play a role in the ability of DEHP to act as a peroxisome proliferator and it has been suggested that peroxisome proliferation might be the underlying mechanism in DEHP carcinogenicity. Available data indicate that DEHP is most potent among the 2-ethylhexyl containing compounds tested. For the purposes of carcinogenicity risk assessment for occupational exposure with respect to picloram isooctyl ester, the recommended toxicological endpoint is the Q_1^* value of 3.29×10^{-4} $(mg/kg/day)^{-1}$ obtained for DEHP in a carcinogenicity risk assessment on this compound[1]. This Q_1^* is based upon a 2-year

[1] D. Turnbull and J.V. Rodricks (1985): Assessment of Possible Carcinogenic Risk to Humans Resulting from Exposure to Di(2-ethylhexyl)phthalate (DEHP). J. Am. Coll. Toxicol., 4(2), pp.111-145.

carcinogenicity bioassay of DEHP in female mice[2] and although this Q_1^* was generated by Turnbull et al., the value was generated using the same model the Agency uses.

Hexachlorobenzene (HCB), a recognized impurity in picloram compounds, is considered to be an animal carcinogen and probable human carcinogen as discussed in the 1988 Registration Standard for picloram.

2. Exposure Assessment

a. Dietary

The qualitative nature of the residue in plants is adequately understood based on a wheat metabolism study. The residue of concern in wheat forage, straw, and grain is conjugated picloram, which is hydrolyzable by acid, base, and ß-glucosidase. The minor metabolites that were identified in grain and straw were 4-amino-6-hydroxy-3,5-dichloropicolinic acid and 4-amino-2,3,5-trichloropyridine. The data support the current uses. Additional plant metabolism studies may be required if picloram uses are expanded to other crops. (MRID#s 00037880, 00041136, 00059411, 00111527, 00157171, and 42579004).

The qualitative nature of the residue in animals is adequately understood. Picloram is the residue of concern in meat, milk, poultry tissues, and eggs. The available ruminant metabolism study indicates that picloram is the major residue in animal tissues of interest and that picloram is not metabolized in ruminants to a significant degree; only minor amounts (<10% of total radioactive residues) of 4-amino-2,3,5-trichloropyridine were detected in goat fat and liver. In the submitted poultry metabolism study, 99.9% of the recovered radioactivity was found in the excreta and virtually all of the ^{14}C-residues were identified as picloram. (MRID#s 00023105, 00041125, 00161306, 00163216, and 42535301).

Adequate enforcement methods are available for the determination of residues of picloram *per se* in/on plant and animal commodities. All of these methods use GLC with electron capture detection of the methyl ester of picloram. The Pesticide Analytical Manual (PAM), Vol. II lists Methods A and III for plant commodities. DowElanco method ACR 73.3.S2 is a GC/ECD method based on Method III with substantial modifications. Method ACR 73.3.S2 was validated using samples from the wheat metabolism study and is adequate for data collection of picloram residues. Method ACR 79.7.S.1 is adequate for collection of picloram data on grass forage and hay. DowElanco Method ACR 91.4 is adequate for HCB data collection from plant commodities.

PAM Vol. II Methods I and II are used to enforce tolerances for picloram residues in animal commodities. DowElanco GC/ECD methods ACR 67.2 and ACR 67.3 are equivalent to Methods II and I, respectively, except that toluene is used in place of benzene. These animal commodity methods have been validated using samples from the goat metabolism study and are adequate for data collection and tolerance enforcement for milk and animal tissues. (MRID#s 00026748, 00026749, 00026750, 00026751, 00026752, 00026753, 00027288, 00035959, 00045363, 00045366, 00045373, 00045374, 00045375, 00045376, 00045409, 00062818, 00069973, 00073972, 00073974, 00078483, 00085060, 00111404, 00111407, 00131364. 00132986, 00156366, and 42380201).

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[2] National Toxicology Program (1982): NTP Technical Report on the carcinogenesis bioassay of di(2-ethylhexyl)phthalate (CAS No. 117-81-7) in F344 rats and B6C3F1 mice (feed study) NIH Pub. No. 82-1773.

FDA has tested picloram using the PAM, Vol. I Multiresidue Method for acids and phenols (Sec 221.1). Table 201-D of the volume reports that picloram in nonfat foods is recovered completely through PAM I 221.1 if a 100 mL ethyl ether Florisil elution is included whereas only 6-10% is recovered from fatty foods.

Adequate storage stability data on picloram are available to support the collected samples from metabolism and magnitude of the residue studies in plants and animals. Residues of picloram *per se* are stable under frozen storage conditions in/on: (i) wheat and barley grain, forage, and straw; and grasses for up to 2 years; (ii) egg whites for up to 18 months; (iii) milk for up to 15 months; and (iv) liver and muscle for up to 6 months. Adequate storage stability data for HCB residues are available for grass and small grain commodities; residues of HCB are stable in frozen storage for up to 17 months. (MRID#s 00164725, 40082701, 40435601, 40731901, 41442301, 41976701 and 42494001).

All data requirements for magnitude of picloram residues in plants have been evaluated and deemed adequate. The registered uses of picloram on barley, oats, and wheat along with the established tolerances on these commodities are supported by acceptable field residue data from trials reflecting the maximum registered use patterns. Field trial data are adequate for grasses and support the proposed tolerance of 225 ppm for grass hay; however, residues on grass forage exceed the proposed tolerance of 225 ppm. The data indicate that a value of 300 ppm would be appropriate for grass forage.

Acceptable grain dust data have been submitted for wheat, which show that residues of picloram concentrate 7x in aspirated grain dust. The registrant must propose a suitable tolerance for grain dust.

The available field residue data on HCB residues in/on plants are adequate. HCB residues were nondetectable in/on wheat grain(<0.001 ppm), grain dust(<0.001 ppm) and wheat straw (<0.002 ppm) following applications of registered formulations of picloram according to the maximum registered use patterns. Residues of HCB were <0.001 ppm in/on grass forage and hay treated using the 2 lb/gal SC/L potassium salt formulation at a rate of 2 lb ae/A, and containing residues of picloram as high as 480 ppm. One hay sample, containing 270 ppm picloram, bore 0.001 ppm HCB. Residues of HCB were shown to dissipate from grass at a greater rate than picloram residues. (MRID#s 00026753, 00036168, 00036170, 00036171, 00045369, 00085060, 00108862, 00108864, 00111404, 00111470, 00111482, 00111557, 00128714, 41905401, 42037601, 42380201, 42535303, and 42784401).

The data requirements for magnitude of the residue in processed food/feed have been evaluated and deemed adequate. Acceptable wheat grain processing data have been submitted; the wheat processing data will be translated to barley and oats. The wheat data indicate that residues of picloram concentrate up to 5x in bran. HCB residues were not detected in/on wheat grain or processed fractions. The existing feed additive tolerance of 3 ppm for picloram residues in milled products of wheat (exc. flour) is adequate. (MRID# 42535303).

The ruminant and poultry feeding studies that were reviewed in the Residue Chemistry Chapter of the Picloram Reregistration Standard, dated 10/29/84, are adequate to satisfy animal feeding study data requirements. These feeding studies indicate that the existing tolerances on animal commodities are supported by residue data from dietary intakes exceeding the maximum dietary burden. (MRID#s 00045372, 00045374, 00045376, 00073921, and 00073973).

An acceptable confined rotational crop study has been submitted. Field rotational crop studies are not required; in addition, tolerances for rotational crop commodities need not be established.

(MRID# 42641801).

b. Occupational and Residential

Picloram is labelled for use on terrestrial food and feed crops, terrestrial non-food crops, forestry sites, and terrestrial feed crops. Terrestrial uses include: industrial areas (outdoors), non-agricultural rights-of-way, fencerows/hedgerows, nonagricultural uncultivated areas/soils, pastures, rangeland, agricultural fallow/idlelands, agricultural rights-of-way/fencerows/hedgerows, agricultural uncultivated areas, barley, grass forage/fodder/hay, oats, small grains, and wheat. Forestry sites include: forest plantings (reforestation programs), and forest trees. Picloram is a broad-spectrum herbicide used to control a variety of broadleaf plants, trees and woody plants (e.g., thistles, cedar and mesquite).

Applications can be made using several types of equipment including: ground, aerial, wiper applicator, backpacks, handheld sprayers/spraywands, tree injection, and paintbrushes. Application types include the following: broadcast/spray treatments via sprayer, aerial or ground equipment; band applications via helicopter; frill, girdle, and stump treatments using unspecified equipment, paintbrush or sprayer after scoring a basal section of the target tree or shrub; injection using a "hypo-hatchet" or other tree injection equipment; high volume spray (dilute) and spot soil treatments using high volume ground, hand-held or wiper applicator equipment; spot treatments using ground, hand-held, low-pressure or wiper applicator equipment; and basal bark and soil treatments using backpack, power, or knapsack sprayers and low volume ground equipment.

Minimum application volumes range from using small amounts of undiluted end-use-products in some spot and basal bark treatments to using various formulations diluted in up to approximately 100 gallons per acre in some ground applications. Diluents include water and various petroleum based derivatives. The maximum application rate, regardless of the crop/target for all equipment categories, application targets and formulation types is 2.16 lb active ingredient/acre. All application rates are based on the acid moiety of picloram, the active agent, and not each specific salt or ester of picloram contained in each formulation. For a significant number of other application techniques, picloram essentially is applied at the discretion of the applicator to a particular target of choice (e.g., *ad libitum* or to run-off to a tree trunk in a spot or frill/girdle treatment). For these types of application scenarios, an application rate on a per acre basis was not calculated.

Exposure data requirements are triggered based on the potential for exposure and the toxicological significance of the active ingredient, metabolites and the impurity HCB. Exposure analyses for occupational and activity patterns associated with the use of picloram have been completed for each handler (i.e., mixer/loader/applicator) and post-application scenario of concern to the Agency in order to identify specific upper end exposure scenarios as well as any associated data gaps. It should be noted that all methods of application cited above (and in Table V) are applicable to the ester and there are no terrestrial food uses for this compound.

Mixer/Loader/Applicator Exposure

Mixer/loader/applicator exposure monitoring data were not required in the *Guidance for the Registration of Pesticide Products Containing Picloram as the Active Ingredient* (9/88). The picloram toxicity data did not meet the triggers at the time the registration standard was issued. Although mixer/loader/applicator data have not been submitted to the EPA, a limited exposure assessment was conducted for this RED using the Pesticide Handlers Exposure Database (PHED) and surrogate data from the open literature.

Based on the use patterns, several exposure scenarios exist as defined by the types of application equipment and procedures that might be employed by picloram handlers. Each scenario is presented in the Summary Exposure Value (Table V) along with a corresponding exposure assessment. Each scenario was defined by the types of potential mixing/loading and application equipment that could be employed based on the four major use groups for picloram: terrestrial food and feed crops, terrestrial non-food crops, forestry sites, and terrestrial feed crops. Exposure values were determined using the Pesticide Handlers Exposure Database (PHED) as well as any pertinent data available in the open literature. No chemical specific data are available for picloram. Data are not available for every scenario. Exposures for the scenarios for which there are no data are expected to be less than or equal to the maximum exposure scenario, high pressure handwand.

Additionally, to clarify the Table V, the Exposure Scenario Description (Table VI) was developed. Table VI summarizes the caveats and parameters specific to each exposure scenario. This table also includes a description of the sources for each data point as well as general information pertaining to the techniques used to calculate the corresponding exposure values. The "Data Source" is self-explanatory. The "Clothing Scenario" represents the clothing worn by the test subjects during the generation of the referenced exposure values. "Equipment" describes the application techniques used to generate the referenced data. "Formulation" is self-explanatory. "Standard Assumptions" represent the use scenarios employed by EPA to estimate daily exposure levels. The "Comments" section includes any other critical descriptions of the data including information pertaining to the quality of the exposure data. The maximum duration of any exposure for workers on a yearly basis is likely to range from 10 to 40 days for commercial applicators, i.e., rights-of-way spraying operations are likely to require 40 days.

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TABLE V: Summary Exposure Values for Picloram

Exposure Scenario (Scen. #)	Dermal Exposure[a] (mg/lb ai)	Inhalation Exposure[b] (μg/lb ai)	Maximum Label Application Rate (lb ai/cycle)	Daily Maximum[c] Treated	Daily Dermal Exposure[d] (mg/kg/day)	HCB[g] Daily Dermal Exposure[d] (mg/kg/day)	Daily Inhalation Exposure[d] (mg/kg/day)	HCB[g] Daily Inhalation Exposure[d] (mg/kg/day)
Mixer/Loader Exposure								
Open Mixing Liquids (I)	0.3	0.4	0.54 lb ai/gal	2000 gallon	2.3[h]	2.3×10^{-4}	6.2×10^{-3}	6.2×10^{-7}
Applicator Exposure								
Groundboom Application (II)	0.02	1.3	1.08 lb ai A[e]	80 acres	1×10^{-2} [h]	1×10^{-6}	1.6×10^{-3}	1.6×10^{-7}
Fixed-Wing Aerial (III)	0.005	0.2	1.08 lb ai/A[e]	500 acres	4×10^{-2}	4×10^{-6}	1.5×10^{-3}	1.5×10^{-7}
Helicopter (IV)	No Data	No Data	1.62 lb ai/A[f]	No Data	No Data	No data	No data	No Data
Paintbrush (V)	290	570 (median)	0.54 lb ai/gal[f]	1 gallon	1.1[h]	1.1×10^{-4}	4.4×10^{-3}	4.4×10^{-7}
Tree Injection/ Hypo-hatchet (VI)	No Data	No Data	0.54 lb ai/gal[f]	No Data	No Data	No data	No data	No Data
High Pressure Handwand (VII)	0.70	0.09	1.08 lb ai/gal[f]	1000 gallon	5.4[h]	5.4×10^{-4}	1.4×10^{-3}	1.4×10^{-7}
Right-of-Way Hand Cannon[i] (VIII)	No Data	No Data	2.16 lb ai/A[f]	No Data	No Data	No data	No data	No Data
Wiper Applicator (IX)	No Data	No Data	---	No Data	No Data	No data	No data	No Data
Backpack/Knapsack (X)	159.1 mg/hr (average)	36 μg/hr (average)	2.16 lb ai/A[f]	8 hours	4.5[j]	4.5×10^{-4}	4.1×10^{-3}	4.1×10^{-7}
Powered Personal Sprayer (XI)	No Data	No Data	---	No Data	No Data	No data	No data	No Data

Mixer/Loader/Applicator Exposure								
Low Pressure Handwand (XII)	103	39	2.16 lb ai/A[f]	2 acres	3.2[h]	3.2×10^{-4}	2.4×10^{-3}	2.4×10^{-7}

a Exposure units may differ from those defined in headers. Alternate units are noted where appropriate. Dermal unit exposures are reported as the best fit mean, unless noted. The best fit mean is the composite total dermal exposure based on using the geometric mean for log normal distributed data, arithmetic mean for normal distributed data, and the median for all other distribution types.

b Inhalation exposure values are reported as geometric means (log normal distributions), unless otherwise noted.

c Values represent the maximum area or the maximum volume of spray solution which can be used in a single day to complete treatments for each exposure scenario of concern.

d Daily Exposure (mg/kg/day) = $\frac{\text{Exposure (mg/lb ai) * Max. Appl. Rate (lb ai/cycle) * Max. Treated}}{\text{70 kg}}$

e Luis Report dated 1/4/93, Picloram, triisopropanolamine salt.

f Tordon 101 (EPA Reg. No. 62719-5).

g HCB is present as a 0.01% contaminant.

h These estimates for picloram and HCB are reduced by 50% for glove use. The unit exposure reflects PPE in the Exposure Scenario Descriptions Table (VI) for Picloram.

i High Pressure Handwand (Scenario VII) data can be used for Hand Cannon (Scenario VII).

j The estimate for total deposition is reduced by 75% to reflect use of long pants, long sleeved shirt, and gloves. The unit exposure reflects PPE in the Exposure Scenario Descriptions Table (VI) for Picloram.

TABLE VI: Exposure Scenario Descriptions for Picloram[a]

Exposure Scenario (Scen. #)	Data Source	Clothing Scenario	Equipment	Standard Assumptions[b] (8 hr work day)	Comments[c]
Mixer/Loader Exposure					
Open Mixing (I)	PHED	Long Pants, Long-Sleeved Shirt, No gloves	Open Mixing	25 gal/acre x 80 acres (Groundboom)	Acceptable grades; Dermal = 14 + replicates; Inhalation = 40 replicates
Applicator Exposure					
Groundboom Application (II)	PHED	Long Pants, Long-Sleeved Shirt, No gloves	Open Cab Tractor	80 acres/day	Grades A, B, C; Dermal = 6 + replicates; Inhalation = 56 replicates.
Aerial (III)	PHED	Long pants, long-sleeved shirt, no gloves	All Cab types	500 acres/day	Inhalation grades A, B, C; Dermal all grades; Dermal = 4 - 41 replicates; Inhalation = 25 replicates.
Helicopter (IV)	No Data	No Data	No Data	No Data	No Data
Paintbrush (V)	PHED	Long pants, Long sleeve shirt, no gloves	Paint brush	1 gallon undiluted	Inhalation grade C; Dermal grades B, C; Dermal and Inhalation = 15 replicates.
Tree Injection/Hypo-Hatchet (VI)	No Data	No Data	No Data	No Data	No Data
High Pressure Handwand (VII)	PHED	Long pants, Long-sleeved shirt, no gloves	High pressure portable hand wand on wheels	1000 gallons/day	Inhalation grades B and C; Dermal grade B and C; Dermal and Inhalation = 9 replicates
Right-of Way Cannon (VIII)	No Data	No Data	No Data	No Data	No Data
Wiper Applicator (IX)	No Data	No Data	No Data	No Data	No Data
Backpack/ Knapsack (X)	Abbott et al. 1987	Total Deposition	Knapsack with 1 meter boom	8 hour work day	Laboratory and field recovery available; Dermal = 6 replicates; Inhalation = 12 replicates.
Powered Personal Sprayer (XI)	No Data	No Data	No Data	No Data	No Data
Mixer/Loader/Applicator Exposure					
Low Pressure Handwand (XII)	PHED	Long pants, long-sleeved shirt, no gloves	Portable handwand	2 acres/day	Inhalation grades B and C; Dermal all grades; Dermal = 25 to 95 replicates; Inhalation = 95 replicates.

a "No Data" indicates that no data were available to complete an exposure assessment.

b Standard Assumptions based on an 8 hour work day as estimated by OREB. BEAD data were not available.

c If dermal and inhalation grades are not listed separately, then the listed grades pertain to both dermal and inhalation. "Acceptable grades," as defined by OREB SOP for meeting Subdivision U Guidelines, are grades A and B for dermal and inhalation, and grade C for hand rinse method. All grades that do not meet OREB's SOP are listed individually.

Post-Application Worker Exposure and Restricted Entry Interval (REI)

The potential for post-application exposure to picloram residues is low because of the use patterns for this chemical (i.e., herbicide used in areas where re-entry exposure is expected not to be problematic such as rights-of-way or pastures/rangeland). Additionally, picloram can be phytotoxic and the residues can be persistent enough to be identified in food products if strict label guidance is not followed (e.g., pregrazing intervals). As a result, picloram is a restricted use pesticide. The label guidance directs end-use-product users to minimize potential off-target drift during application.

Post-application exposure is not a major concern due to the use patterns defined by the picloram labels and the cultural practices typically associated with a broad spectrum herbicide of this type as indicated above. As a result, the Agency does not require that any post-application exposure monitoring or residue dissipation data be generated to support the reregistration of picloram. The Agency recommends the REIs of 12 hours for all end use products containing picloram as required by the Worker Protection Standard PR Notice 93-7 for in-scope uses be retained.

Personal Protective Equipment (PPE) Requirements

PPE selection for mixer/loader/applicators and other handlers will be based on the end use products of picloram potassium and triisopropanolanime salts and isooctyl ester. The following statements to be included on picloram labels are located on the attached Pesticide Worksheets -- Parts One and Two: Type of Respirator, Reduce PPE When Engineering Controls Used; User Safety Statements; Application Restrictions; Entry Restrictions; Early-Entry PPE; and Notification Statements.

Data Requirements

Although data are available to estimate the worker exposure for the maximum exposure scenarios for the purposes of risk assessment, the data sets available are limited in both quantity and quality as shown in Table VI. In order to reduce the uncertainty associated with the exposure assessments and thus the risk assessment and because the following scenarios lack exposure data and have a potential for as high a worker exposure as the high pressure handwand scenario, these data must be submitted for confirmation purposes:

1) Guideline 231: Estimation of Dermal Exposure at Outdoor Sights for mixer/loaders and applicators using the hand cannon equipment.

2) Guideline 232: Estimation of Inhalation Exposure at Outdoor Sites for mixer/loaders and applicators using the hand cannon equipment.

3) Guideline 231: Estimation of Dermal Exposure at Outdoor Sights for mixer/loaders and applicators using the backpack/knapsack equipment.

4) Guideline 232: Estimation of Inhalation Exposure at Outdoor Sites for mixer/loaders and applicators using the backpack/knapsack equipment.

3. Risk Assessment

a. Dietary

There are two primary dietary exposure/risk analysis considerations for picloram: (1) the chronic dietary exposure/risk to picloram *per se*, and (2) dietary carcinogenicity exposure/risk to HCB, an impurity. An acute toxicity endpoint has not been identified for picloram; therefore, neither a carcinogenicity nor an acute dietary exposure/risk analysis was conducted for picloram per se.

The routine chronic analysis for picloram used a Reference Dose (RfD) of 0.2 mg/kg bodyweight per day, based on a NOEL of 20.0 mg/kg body-weight per day from a two-year rat feeding study and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variability. The endpoint effects noted were altered size and tinctorial properties of centrilobular hepatocytes in both male and female rats. HCB is considered a Group B2 carcinogen. The carcinogenicity analysis that was performed for HCB used a Q_1* of 1.7 (mg/kg bodyweight per day)$^{-1}$. The residue values used are summarized in Table VII. The HCB values are calculated anticipated residue values. Where percent crop treated values were not available, 100% was assumed.

Table VII. Residue Values for DRES Run on Picloram and HCB. Residue values are based on the assumption of tolerance level residues of picloram on crops. Residues of HCB were estimated by assuming they are present on all crops in direct proportion to the maximum level of HCB in picloram TGAI as certified by the producer, i.e., ar 0.01% of the picloram tolerance.[a]

Commodity	Picloram Residues (ppm)	HCB Residues (ppm)	% crop treated
Barley, grain	0.5	0.00005	2
Barley, milled fractions (exc. flour)	3	0.0003	2
Oats, grain	0.5	0.00005	1
Oat, milled fractions (exc. flour)	3	0.0003	1
Wheat, grain	0.5	0.00005	2
Wheat, milled fractions (exc. flour)	3	0.0003	2
Secondary Residues			
Milk	0.05	0.000011 (whole milk) 0.000265 (milk fat only assuming 4% fat)	
Cattle, fat	0.2	0.00045	
Cattle, kidney	5	0.000023[b]	
Cattle, liver	0.5	0.000023[b]	
Cattle, mbyp (exc kidney and liver)	0.2	0.000023[b]	
Cattle, meat	0.2	0.000023[b]	
Poultry, fat	0.05	0.000007	
Poultry, mbyp	0.05	0.0000001[c]	
Poultry, meat	0.05	0.0000001[c]	
Eggs	0.05	0.000002 (yolk) 0.000000007[c] (white)	

Commodity	Picloram Residues (ppm)	HCB Residues (ppm)	% crop treated
Hogs, fat	0.2	0.000008	
Hogs, kidney	5	0.0000004[c]	
Hogs, liver	0.5	0.0000004[c]	
Hogs, mbyp (exc kidney and liver)	0.2	0.0000004[c]	
Hogs, meat	0.2	0.0000004[c]	
Horses, fat	0.2	0.00045	
Horses, kidney	5	0.000023[b]	
Horses, liver	0.5	0.000023[b]	
Horses, mbyp (exc kidney and liver)	0.2	0.000023[b]	
Horses, meat	0.2	0.000023[b]	
Sheep, fat	0.2	0.00045	
Sheep, kidney	5	0.000023[b]	
Sheep, liver	0.5	0.000023[b]	
Sheep, mbyp (exc kidney and liver)	0.2	0.000023[b]	
Sheep, meat	0.2	0.000023[b]	
Goats, fat	0.2	0.00045	
Goats, kidney	5	0.000023[b]	
Goats, liver	0.5	0.000023[b]	
Goats, mbyp (exc kidney and liver)	0.2	0.000023[b]	
Goats, meat	0.2	0.000023[b]	

a Tolerances are established for residues of picloram per se.
b These residue values were rounded up to the usable six decimal limit for the analysis resulting in a very slight overestimation of the risk.
c These residue values were so small, they rounded to less than 0.000000, the decimal places allowed iin the analysis which lowered tbe risk just slightly.

The routine *chronic dietary exposure/risk estimates for picloram* are extremely low. For the United States population as a whole, the Theoretical Maximum Residue Contribution (TMRC) is 0.001845 mg/kg bodyweight per day, only 0.9% of the RfD. For this same group, the Anticipated Residue Contribution (ARC) is 0.001053 mg/kg bodyweight per day, only 0.5% of the RfD. The subgroup with the greatest routine chronic exposure/risk is Non-nursing Infants (Less Than One Year Old), which has a TMRC of 0.004753 mg/kg bodyweight per day (2.4% of the RfD) and an ARC of 0.003805 mg/kg bodyweight per day (1.9% of the RfD). All of the exposure/risk for the U.S. population as a whole and each of the 22 subgroups are contributed by published tolerances.

The *HCB upper-bound carcinogenicity exposure/risk estimate*, which is performed only for the U.S. population as a whole, was an ARC of 0.000000394 mg/kg bodyweight per day and produced a calculated ARC upper-bound carcinogenicity risk estimate of 0.67×10^{-6}. As a note, the estimated chronic toxicity ARC exposures and risks for HCB, using an RfD of 0.0008 mg/kg bodyweight per day and the same residue figures that were used in the carcinogenicity analysis, were very low. For all groups and subgroups, the exposure was 0.000001 mg/kg bodyweight per day or less and the calculated risk was less than 0.14% of the RfD. The following commodities contributed the large majority of the HCB carcinogenicity exposure/risk estimate:

Commodity	Carcinogenic ARC Exposure*	Carcinogenic ARC Risk**
Cattle (Beef)	0.000000195	0.33 (49.5%)
Milk	0.000000193	0.33 (49.0%)
TOTALS for both	0.000000388	0.66 (98.5%)

*In units of mg/kg bodyweight per day
**In units of E-6 (percent of the total risk--and exposure)

The Picloram chronic dietary exposure/risk TMRC and ARC estimates are exceedingly low, about 1/200th of the RfD for each of the groups and subgroups. There appears to be no reason for concern in regard to chronic dietary exposure to Picloram at this time.

The refined, ARC upper-bound dietary carcinogenicity risk estimate for the U.S. population as a whole for Picloram's impurity Hexachlorobenzene is 0.7 E-6, which is less than the 1.0 E-6 point below which risk is generally considered to be negligible. It is also likely that this upper-bound risk estimate is a substantial overestimate because the absolute worst-case scenarios and assumptions were used for determining HCB residues. The rounding of the residue level numbers also may have contributed to overestimation of the HCB exposure/risk because more of the rounding was in an upward direction than in a downward direction. The estimated dietary carcinogenicity risk from HCB, when dietary exposure to HCB is considered only for its occurrence as an impurity of picloram, is within Agency acceptability guidelines. It should be noted that HCB also occurs as an impurity in several other pesticide technical products, so overall dietary exposure to HCB is likely to be appreciably higher than HCB considered simply as a picloram impurity as considered in this analysis.

b. Occupational and Residential

Picloram acid, potassium salt, triisopropanolamine and isooctyl ester

In order to adequately determine the risk associated with a chemical the toxicological end-points of concern must be identified in relation to the duration of these exposures. The toxicological endpoints of significance for occupational exposure are as follows:

1) There are no short term (one to seven day exposures) toxicological concerns indicated for occupational exposure.

2) The intermediate term exposure (1 week to several months) toxicological endpoints are indicated by the 21-day dermal rabbit studies based upon increased bilirubin (males) and BUN (males/females). The NOELs range from 250 to 1320 mg/kg/day for the picloram compounds. For the purposes of risk assessment, the lowest LOEL of 500 mg/kg/day should be used as the toxicological end-point (rather than 250 mg/kg/day). The effects observed at the LOEL of 500 mg/kg/day from the 21-day dermal rabbit study using picloram isooctyl ester were minimal and of questionable biological significance. In addition, studies conducted over a longer period of time by the oral route do not show effects until a dose level of 500 mg/kg/day.

3) Longterm non-cancer toxicological endpoints for worker exposure are not required based on the use patterns of this chemical (<90 days/year worker exposure).

The Margins of Exposure (MOE) for workers involved with mixing/loading and applying these chemicals for 7 to 40 days/year may be estimated by the following equation:

$$MOE = \frac{\text{NOEL (mg/kg/day)}}{\text{Exposure (mg/kg/day)}}$$

For regulatory purposes the toxicological endpoint of concern is 500 mg/kg/day (LOEL) based on the 21-day dermal rabbit study conducted with the picloram isooctyl ester (MRID#s 421716-01, 428707-01). The highest potential worker exposure by the dermal and inhalation routes is represented by the mixer/loader of the high pressure handwand scenario at 5.40 mg/kg/day exposure; and the lowest by the mixer/loader of the groundboom scenario at 1.2×10^{-2} mg/kg/day exposure. Therefore, the range of MOEs for workers involved in mixer/loader and/or application activities is between 93 and 4.2×10^{4}. The risk to mixers/loaders/applicators is considered to be minimal even for the high pressure handwand; an MOE of 93 is similar to an MOE of 100 because the dose-response is a log curve, and, therefore, there is no concern in this case. The MOEs for picloram are summarized in the Table VIII below:

TABLE VIII: The Margins of Exposure (MOE) for Picloram *per se*

Scenario / Mixer(M), Loader (L), Applicator (A)	Daily Dermal and Inhalation Exposure (mg/kg/day) Picloram	Margin of Exposure (MOE) Picloram
Open Mixing Liquids (I) / M,L	2.31	216
Groundboom Application (II) / A	1.2×10^{-2}	4.2×10^{4}
Fixed-Wing Aerial (III) / A	4.2×10^{-2}	1.2×10^{4}
Helicopter (IV) / A	-	-
Paintbrush (V) / A	1.10	455
Tree Injection/Hypo-hatchet (VI) / A	-	-
High Pressure Handwand (VII) / A	5.40	93
Right-of-Way Hand Cannon (VIII) / A	-	-
Wiper Applicator (IX) / A	-	-
Backpack/Knapsack (X) / A	4.50	111
Powered Personal Sprayer (XI) / A	-	-
Low Pressure Handwand (XII) / M,L,A	3.20	156

* No Data. Exposures for the scenarios for which there are no data are expected to be less than or equal to the maximum exposure scenario, high pressure handwand.

Hexachlorobenzene (HCB) and Picloram Isooctyl Ester

The Agency has classified HCB as a probable human carcinogen (Group B_2) based on an increased incidence of malignant tumors in two species; haemangioendothelioma in hamsters and heptocellular carcinoma in rats as well as confirmed reports of hepatoma in both of these species. A Q_1^* of 1.7 $(mg/kg/day)^{-1}$ was derived using data regarding the incidence of hepatocellular carcinoma in female rats. For these reasons, an occupational carcinogenic risk assessment associated with picloram is required since HCB could be present up to 100 ppm.

Picloram isooctyl ester (also referred to as picloram ethylhexyl ester) bears structural similarity to di(2-ethylhexyl)phthalate (DEHP) in possessing a 2-ethylhexyl moiety. DEHP and certain other substances containing the 2-ethylhexyl moiety have been found positive for carcinogenicity in rodent bioassays. 2-ethylhexanol was detected as a metabolite in the metabolism studies summarized above. This metabolite is also a primary hydrolytic cleavage product of DEHP, a known rodent liver carcinogen. This metabolite is thought to play a role in the ability of DEHP to act as a peroxisome proliferator and it has been suggested that peroxisome proliferation might be the underlying mechanism in DEHP carcinogenicity. Available data indicate that DEHP is most potent among the 2-ethylhexyl containing compounds tested. For the purposes of carcinogenicity risk assessment for occupational exposure with respect to picloram isooctyl ester the recommended toxicological endpoint is the Q_1^* value of 3.29×10^{-4} $(mg/kg/day)^{-1}$ obtained for DEHP in a carcinogenicity risk assessment on this compound[3]. This Q_1^* is based upon a 2-year carcinogenicity bioassay of DEHP in female mice[4] and although this Q_1^* was generated by Turnbull et all., the value was generated using the same model the Agency uses.

The estimated excess carcinogenic risk to agricultural workers from HCB and picloram isooctyl ester based on the use patterns (Tables V, VI, and VII) for picloram are calculated at follows:

$$\text{Excess Carcinogenic Risk} = Q_1^* \times \text{LADD}$$

where LADD represents the lifetime (35 work years/ 70 average Lifetime years) *times* the Average number of work days over a year (40 work days/365 days) *times* the Daily Dose for each exposure scenario (mg/kg/day) from Table VII. For the purposes of risk assessment, the daily dose includes the dermal and inhalation exposures combined. A dermal absorption factor of 100% was assumed for both chemicals. There are limited dermal absorption data available on HCB, but the test material in the study was HCB mixed with a pesticide other than picloram; therefore, the absorption factor is inappropriate to use for this risk assessment.

All exposure scenarios are appropriate for risk assessment for HCB and picloram isooctyl ester. The highest potential worker exposure by the dermal and inhalation routes is represented by the mixer/loader of the high pressure handwand scenario at 5.40 mg/kg/day exposure; and the lowest by the mixer/loader of the groundboom scenario at 1.2×10^{-2} mg/kg/day exposure. The excess carcinogenic risk estimates for workers from exposure to HCB are between 5.0×10^{-5} and 1.0×10^{-7} and for picloram isooctyl ester are between 9.7×10^{-5} and 2.2×10^{-7}.

These risk assessments are considered very conservative since a 100% dermal absorption factor

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[3] D. Turnbull and J.V. Rodricks (1985): Assessment of Possible Carcinogenic Risk to Humans Resulting from Exposure to Di(2-ethylhexyl)phthalate (DEHP). J. Am. Coll. Toxicol., 4(2), p.p.111-145.

[4] National Toxicology Program (1982): NTP Technical Report on the carcinogenesis bioassay of di(2-ethylhexyl)phthalate (CAS No. 117-81-7) in F344 rats and B6C3F1 mice (feed study) NIH Pub. No. 82-1773.

was used and a Q_1^* from DEHP was used for the picloram isooctyl ester which assumes the peroxisome proliferator mechanism of carcinogenicity to be valid. There is a degree of uncertainty associated with this risk assessment which is highly dependent on the quality and quantity of the exposure values summarized in Table VI. Additional exposure data for the most highly exposed workers would reduce the uncertainty significantly. Since the risk estimates are fairly conservative at this time the uncertainty associated with the determinations is not unreasonable.

This is a restricted use chemical that has no residential uses at this time; therefore, there are no human risks associated with residential uses.

The risk associated with post-application exposure is not a major concern since exposure to workers is minimal due to the use patterns defined by the picloram labels and the cultural practices typically associated with a broad spectrum herbicide of this type as indicated above. The Agency recommends the REIs of 12 hours for all end use products containing picloram as required by the Worker Protection Standard PR Notice 93-7 for in-scope uses be retained.

- *Data Requirements*

Outstanding data requirements for product chemistry include guidelines 61-3(discussion of impurities), 62-1 (preliminary analysis), 63-8 (solubility) and 63-11 (octanol/water coefficient) for picloram triisopropanolamine TGAI (005102); 62-1 for picloram isooctylester TGAI (005103); 61-1 (product identity and disclosure of ingredients), 62-1, 62-2 (certification of ingredients limits), 63-11 for picloram potassium salt FI (005104). All pertinent data requirements are satisfied for the picloram acid TGAI.

The following occupational exposure data must be submitted for confirmation purposes:

1) Guideline 231: Estimation of Dermal Exposure at Outdoor Sights for mixer/loaders and applicators using the hand cannon equipment.

2) Guideline 232: Estimation of Inhalation Exposure at Outdoor Sites for mixer/loaders and applicators using the hand cannon equipment.

3) Guideline 231: Estimation of Dermal Exposure at Outdoor Sights for mixer/loaders and applicators using the backpack/knapsack equipment.

4) Guideline 232: Estimation of Inhalation Exposure at Outdoor Sites for mixer/loaders and applicators using the backpack/knapsack equipment.

TOLERANCE REASSESSMENT SUMMARY

Tolerances Listed Under 40 CFR §180.292:

The tolerances listed in 40 CFR §180.292 are for residues of picloram *per se*. Sufficient data are available to ascertain the adequacy of the established tolerances listed in 40 CFR §180.292 for the following commodities: barley grain; barley forage; barley straw; oat grain; oat forage; oat straw; wheat grain; wheat forage; wheat straw; fat, meat, kidney, liver, and meat by-products of cattle; goats, hogs, horses, and sheep; and fat, meat, and meat by-products of poultry, milk, and eggs. See Table IX for modifications in commodity definitions.

Sufficient field residue data are available for grasses, although the data indicate that the established tolerance of 80 ppm for picloram residues in/on grass forage is not adequate. Tolerances of 225 ppm have been proposed for picloram residues in/on grass forage and hay. The available data support the proposed tolerance for grass hay but show that a higher tolerance must be proposed for grass forage. The data indicate that a level of 300 ppm would be appropriate.

A wheat grain dust study has shown that a tolerance must be proposed. The available data indicate that a tolerance of 4 ppm would be appropriate for grain dust.

The established tolerances for picloram residues in/on flax seed and flax straw should be revoked, as there is no registered use of picloram on flax.

Tolerances Listed Under 40 CFR §185.4850 and 40 CFR §186.4850:

The tolerances listed in 40 CFR §185.4850 and 40 CFR §186.4850 are for residues of picloram *per se*. Sufficient data are available to ascertain the adequacy of the established food/feed additive tolerances listed in 40 CFR §185.4850 and 40 CFR §186.4850 for barley, oat, and wheat milled fractions (excluding flour).

CODEX HARMONIZATION

There are no Codex MRLs established or proposed for residues of picloram. Therefore, there are no questions with respect to compatibility of U.S. tolerances with Codex MRLs.

Table IX. Tolerance Reassessment Summary for Picloram

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/*Correct Commodity Definition*
Tolerances listed under 40 CFR §180.292:			
Barley, grain	0.5	0.5	
Barley, green forage	1	1	*Barley, forage*
Barley, straw	1	1	
Cattle, fat	0.2	0.2	
Cattle, kidney	5	5	
Cattle, liver	0.5	0.5	
Cattle, mbyp (exc kidney and liver)	0.2	0.2	*Cattle, mbyp (exc. liver and kidney)*
Cattle, meat	0.2	0.2	
Eggs	0.05	0.05	
Flax, seed	0.5	Revoke	No registered use
Flax, straw	0.5	Revoke	No registered use
Goats, fat	0.2	0.2	
Goats, kidney	5	5	
Goats, liver	0.5	0.5	
Goats, mbyp (exc kidney and liver)	0.2	0.2	*Goats, mbyp (exc. liver and kidney)*
Goats, meat	0.2	0.2	
[Grain dust]	none	4	Registrant must propose tolerance
Grasses, forage	80	300	Revised tolerance proposal of 225 ppm pending (PP#6F3367); registrant must propose higher tolerance/*Grass, forage*
[Grass, hay]	none	225	Tolerance pending (PP#6F3367)/*Grass, hay*
Hogs, fat	0.2	0.2	
Hogs, kidney	5	5	
Hogs, liver	0.5	0.5	
Hogs, mbyp (exc kidney and liver)	0.2	0.2	*Hogs, mbyp (exc. liver and kidney)*
Hogs, meat	0.2	0.2	
Horses, fat	0.2	0.2	
Horses, kidney	5	5	
Horses, liver	0.5	0.5	
Horses, mbyp (exc kidney and liver)	0.2	0.2	*Horses, mbyp (exc. liver and kidney)*

(continued)

Table C *(continued)*.

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/*Correct Commodity Definition*
Horses, meat	0.2	0.2	
40 CFR §180.292 continued:			
Milk	0.05	0.05	
Oats, grain	0.5	0.5	
Oats, green forage	1	1	*Oats, forage*
Oats, straw	1	1	
Poultry, fat	0.05	0.05	
Poultry, mbyp	0.05	0.05	
Poultry, meat	0.05	0.05	
Sheep, fat	0.2	0.2	
Sheep, kidney	5	5	
Sheep, liver	0.5	0.5	
Sheep, mbyp (exc kidney and liver)	0.2	0.2	*Sheep, mbyp (exc. liver and kidney)*
Sheep, meat	0.2	0.2	
Wheat, grain	0.5	0.5	
Wheat, green forage	1	1	*Wheat, forage*
Wheat, straw	1	1	
Tolerances listed under 40 CFR §185.4850			
Barley, milled fractions (exc. flour)	3	3	
Oat, milled fractions (exc. flour)	3	3	
Wheat, milled fractions (exc. flour)	3	3	
Tolerances listed under 40 CFR §186.4850			
Barley, milled fractions (exc. flour)	3	3	
Oat, milled fractions (exc. flour)	3	3	
Wheat, milled fractions (exc. flour)	3	3	

ACTIVE INGREDIENT WORKSHEET – PART ONE

This two-page Worksheet lists possible label statements to require based on the characteristics of the a.i.

ACTIVE INGREDIENT: Picloram, potassium salt, triisopropanolamine salt, and isooctyl ester

Uses Covered by Worksheet ☒ WPS ☐ NonWPS ☐ Both ☐ Home Use

PERSONAL PROTECTIVE EQUIPMENT

(Fill in sections A and B for an active ingredient ONLY if unusual risk concern, such as delayed-effect or sensitization. PPE requirements for each end-use product will be set based on the acute toxicity of that product.)

A APPLICATOR PPE

Applicators and other handlers ▲ must wear:
☐ (except mixers, loaders, and others exposed to the concentrate)
(Choose this insert if Section B is filled in.)

Choose one item (or none) from each grouping:

16 ☐ Chemical-resistant protective suit ..... EXT
16 ☐ Coveralls over long-sleeved shirt and long pants
17 ☐ Coveralls over short-sleeved shirt and short pants
18 ☐ Long-sleeved shirt and long pants

20 ☐ Chemical-resistant gloves, such as ___

21 ☐ Chemical-resistant footwear plus socks
21 ☐ Shoes plus socks

24 ☐ Goggles
24 ☐ Protective Eyewear

23 ☐ Chemical-resistant headgear for overhead exposure

19 ☐ Chemical-resistant apron when cleaning equipment, ▲
(Select insert if not checked below in B) ☐ mixing, or loading

26 ☐ Respirator (specify type in section C)

B MIXER AND LOADER PPE

Mixers and loaders ▲ must wear:
☐ (and others exposed to the concentrate)
(Choose this insert if all persons exposed to the concentrate must wear this PPE and not the PPE selected in section A.)

Choose one item (or none) from each grouping:.

6 ☐ Chemical-resistant protective suit ..... EXT
6 ☐ Coveralls over long-sleeved shirt and long pants
7 ☐ Coveralls over short-sleeved shirt and short pants
8 ☐ Long-sleeved shirt and long pants

0 ☐ Chemical-resistant gloves, such as _____

1 ☐ Chemical-resistant footwear plus socks
1 ☐ Shoes plus socks

4 ☐ Goggles
4 ☐ Protective Eyewear

3 ☐ Chemical-resistant headgear for overhead exposure

) ☐ Chemical-resistant apron when mixing or loading

; ☐ Respirator (specify type in section C)

C TYPE OF RESPIRATOR

[Select respirator type(s) for each active ingredient in category I or II for acute inhalation toxicity OR if respirator chosen in A or B. See Appendix B for instructions about selecting respirator type(s).]

☐ In enclosed areas only
26 ☐ ▲ A supplied-air respirator (MSHA/NIOSH approval number prefix TC-19C) OR (b) a self-contained breathing apparatus (SCBA) (MSHA/NIOSH approval number prefix TC-13F).

☐ In enclosed areas only OR ☐ In outdoor areas only
27 ☐ ▲ A respirator with either an organic-vapor-removing ..... EXT cartridge with a prefilter approved for pesticides (MSHA/ NIOSH approval number prefix TC-23C), or a canister approved for pesticides (MSHA/NIOSH approval number prefix TC-14G).
☐ In enclosed areas only OR ☐ In outdoor areas only
29 ☒ ▲ A dust/mist filtering respirator (MSHA/NIOSH approval number prefix TC-21C).

D REDUCE PPE WHEN ENGINEERING CONTROLS USED

(Already allowed in WPS; Select to allow for NonWPS uses)

31 ☐ When handlers use closed systems, enclosed cabs, or aircraft in a manner that meets the requirements listed in the Worker Protection Standard (WPS) for agricultural pesticides [40 CFR 170.240(d)(4-6)], the handler PPE requirements may be reduced or modified as specified in the WPS.

E USER SAFETY STATEMENTS

(See Appendix F in the GUIDE for other user safety requirements to consider for special situations.)

REQUIREMENTS:

40 ☒ Follow manufacturer's instructions for cleaning/ ..... ALL WPS
maintaining PPE. If no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.

(Consider the statement below if delayed- or allergic-effect concerns AND formulated as a concentrate.)

40 ☐ Discard clothing and other absorbent materials that have been drenched or heavily contaminated with this product's concentrate. Do not reuse them.

RECOMMENDATIONS:

39 ☒ Users should wash hands before eating, drinking, ... ALL
chewing gum, using tobacco, or using the toilet.

39 ☒ Users should remove clothing immediately if pesticide ..... ALL
gets inside. Then wash thoroughly and put on clean clothing.

39 ☒ Users should remove PPE immediately after handling ..... ALL
this product. ▲ As soon as possible, wash thoroughly and change into clean clothing.

☒ [redacted]
(Select this insert if gloves are required PPE.)

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ACTIVE INGREDIENT WORKSHEET – PART TWO

ACTIVE INGREDIENT: . . . . . **Uses Covered by Worksheet** ☐ WPS ☐ NonWPS ☐ Both

F ENGINEERING CONTROLS

(See Appendix E if considering mandatory engineering controls, such as closed systems, enclosed cabs, or aircraft.)

G APPLICATION RESTRICTIONS

(See p. 46 in the Guide for other application restrictions, such as setback restrictions, to consider for special situations.)

15 Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application.
✓ WPS uses This is a WPS requirement.

~~☐ All NonWPS uses ☐ All NonWPS uses, except~~
Consider for most nonWPS uses, other than wide-area mosquito control, insect repellents, etc.)

H ENTRY RESTRICTIONS

WPS ENTRY RESTRICTIONS

(Set one REI for whole product OR different REI's for different uses. If subpart K data are not available, use acute toxicity of active ingredient to set REI. If delayed-effect concern, consider raising REI one level.)

Choose this item if only one REI for entire product:

☒ Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of ▲
- ☐ ____ days. . . . . NOT WPS, EPA SET
- ☐ 72 hours. . . . . NOT WPS, EPA SET
- ☐ 48 hours. . . . . I-D/S/EYE
- ☐ 24 hours. . . . . II-D/S/EYE
- ☒ 12 hours. . . . . III/IV-D/S/EYE

Choose this item if two REI's for product:

☐ Do not enter or allow worker entry into treated areas during the restricted-entry interval (REI) of ____ ☐ hours ☐ days, except for _____ (crop with different REI). The REI for _____(crop with different REI) is ____ ☐ hours ☐ days.

Choose this item if more than two REI's for product:

☐ Do not enter or allow worker entry into treated areas during the restricted entry interval (REI).
- ☐____ ☐hours ☐days REI for _____(specify uses)
- ☐____ ☐hours ☐days REI for _____(specify uses)
- ☐____ ☐hours ☐days REI for _____(specify uses)
- ☐____ ☐hours ☐days REI for _____(specify uses)
- ☐____ ☐hours ☐days REI for _____(specify uses)

Longer REI for organophosphates in arid areas:

☐ Each 48-hour REI is increased to 72 hours . . . . . I-D/S/EYE-OP in outdoor areas where average annual rainfall is less than 25 inches a year.

NON-WPS ENTRY RESTRICTIONS

(See p. 50 in the Guide for entry restrictions, ventilation criteria, and notifiction requirements to consider for nonWPS uses.)

I EARLY ENTRY PPE

(Use the acute toxicity of active ingredient, then adjust if delayed-effects, allergic-effects, or other special concerns.)

☒ PPE required for early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil, or water is: . . . . . WPS

☐ PPE required for early entry to treated areas that involves contact with anything that has been treated is: . . . . . NonWPS

Choose one item (or none) from each grouping:

16 ☐ Chemical-resistant protective suit . . . . . EXT
16 ☐ Coveralls over long-sleeved shirt and long pants . . . . . I-D/S
17 ☐ Coveralls over short-sleeved shirt and short pants . . . . . II-D/S
17 ☒ Coveralls . . . . . III/IV-D/S
18 ☐ Long-sleeved shirt and long pants . . . . . NonWPS Only
(WPS requires at least coveralls for early entry.)

20 ☒ Chemical-resistant gloves, such as ____ . . . . . I/II/III/IV-D/S
21 ☐ Chemical-resistant footwear plus socks . . . . . I/II-D/S
21 ☒ Shoes plus socks . . . . . III/IV-D/S
24 ☐ Goggles . . . . . EXT
24 ☐ Protective Eyewear . . . . . I/II-EYE
23 ☐ Chemical-resistant headgear for overhead exposure
26 ☐ Respirator (specify type in section C) . . . . . N
(WPS allows only handlers (not early-entry workers) t
enter during an REI if inhalation is a concern. See p.

J NOTIFICATION

62 **WPS Only:** (WPS requires oral warning OR treated ar
WPS uses – select this statement to require both.)
☐ Notify workers of the application by warning them orally and by posting warning signs at entrances to tre

62 **NonWPS:** (Do not select the above statement– a custo
required.)

Entered into RED system

KEY TO PESTICIDE WORKSH

▲	= Insert shaded text here, if sele
▒	= Text must be selected or crossed out
I, II, III, IV	= Toxicity Categories
1, 2, 3, etc	= Page numbers where discussed in GUIDE
ALL	= Consider for all products
D	= Acute Dermal Toxicity (oral=surrogate)
EXT	= Extraordinary PPE (heat/stress concern)
EYE	= Eye Irritation Potential
INH	= Acute Inhalation Toxicity (oral=surrogate)
NonWPS	= Uses outside Worker Protection Standard
NonWPS only	= Select for NonWPS only; not for WPS
OP	= Organophosphate Pesticide
S	= Skin Irritation Potential
WPS	= Uses under Worker Protection Standard