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WASHINGTON, D.C. 20460

Attachment 1

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: June 2, 1999

MEMORANDUM

SUBJECT: *Clodinafop-propargyl (CGA 184927)*: Report of the Hazard Identification Assessment Review Committee.

FROM: Yung G. Yang, Ph.D. *Yung G. Yang 6/2/99*
Toxicology Branch
Health Effects Division (7509C)
and
Brenda Tarplee, Executive Secretary *B.T. 6/2/99*
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair *Jess Rowland 6/9/99*
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Pauline Wagner, Co-Chair *Pauline Wagner 6/9/99*
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Mary Rust, Risk Assessor
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PC Code: 125203

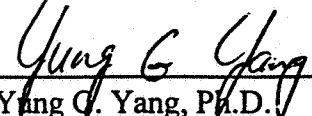
On April 29, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database of clodinafop-propargyl (CGA 184927), established a Reference Doses (RfDs), selected toxicological endpoints for acute dietary as well as occupational and residential exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity to infants and children as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

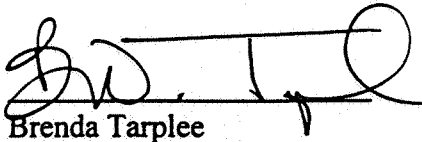
Members present were Dave Anderson, William Burnam, Virginia Dobozy, Karen Hamernik, Pam Hurley (acting Chair), Tina Levine, Sue Makris, Nicole Paquette, Kathleen Raffaele, and Brenda Tarplee (Executive Secretary). Data was presented by Yung Yang of Toxicology Branch. Also, in attendance were Mary Rust, Nancy Dodd, and Kelly O'Rourke.

Members not present were Mike Ioannou, Nancy McCarroll, Jess Rowland, P.V. Shah, and Pauline Wagner.

Data Presentation &
Report Preparation:


Yung C. Yang, Ph.D.
Toxicologist

Report Concurrence:


Brenda Tarplee
Executive Secretary

I. INTRODUCTION

Clodinafop-propargyl (CGA 184927) is the active ingredient of Clodinafop 2E herbicide for use on wheat. Clodinafop-propargyl is registered in Canada. As part of the Agency's continued efforts at harmonization with Canada under NAFTA, OPP management has agreed to use Canada's reviews to the extent possible in making a U.S. registration decision. The EPA reviewers had reviewed and made comments on these Canadian reviews. On April 29, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database of clodinafop-propargyl (prepared by the EPA reviewers), established a reference dose (RfD), and selected toxicological endpoints for acute dietary as well as occupational and residential exposure risk assessments pursuant to the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

II. HAZARD IDENTIFICATION

A. Acute Dietary

a. For Females 13+

Study Selected: Developmental Toxicity Study in Rats Guideline #: §83-3a

MRID No. 44399145

Executive Summary: In a developmental toxicity study (MRID 44399145), pregnant Ico: OFA SD. (IOPS Caw) rats were dosed by gastric gavage with CGA 184927 (purity 93.70%), as a suspension in aqueous hydroxypropyl methylcellulose, at dose levels of 0 (vehicle control), 5, 40 and 160 mg/kg/day, 25 mated females per group, on days 6 to 15 of gestation, inclusive.

There were no mortality or treatment-related toxicity observed. At 160 mg/kg/day, a statistically non-significant decrease in mean maternal body weight gain was seen during GD 6-11 (21%) and during GD 6-16 (9%) of the dosing period. However, the corrected body weight gain was comparable to that of the control group. Therefore, the observed effect on body weight gain during GD 6-11 and 6-16 was most likely caused by the intrauterine effect. In the absence of any other maternal effects, this was not considered toxicologically significant. **Therefore, the maternal LOAEL is >160 mg/kg/day based on lack of effect and the maternal NOAEL is 160 mg/kg/day.**

Fetal anomalies considered to be treatment-related, consisted of increased incidences of the following: bilateral distension of the ureter and bilateral torsion of the ureter, 40 and 160 mg/kg/day; hematoma to the head, 160 mg/kg/day; absence of ossification in the sternbrae, 160 mg/kg/day; incomplete ossification of the thoracic vertebral centra, 160 mg/kg/day; absence of ossification in the caudal vertebral arches, 160 mg/kg/day; unilateral 14th ribs, 40 and 160 mg/kg/day; incomplete ossification of the metacarpals, 40 and 160 mg/kg/day; and incomplete ossification of various cranial bones (parietal, interparietal, occipital, and squamosal) at 40 and 160 mg/kg/day. Also there was a significant but slight reduction (7%) in mean fetal body weights at 160 mg/kg/day compared to the control. **Therefore, the developmental LOAEL is 40**

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mg/kg/day, based on increased incidences of bilateral distension and torsion of the ureters, unilateral 14th ribs, and incomplete ossification of the metacarpals and various cranial bones (parietals, interparietals, occipital, and squamosal). The developmental NOAEL is 5 mg/kg/day.

Dose and Endpoint for Risk Assessment: 5 mg/kg (NOAEL) based on increased incidences of bilateral distension and torsion of the ureters, unilateral 14th ribs, and incomplete ossification of the metacarpals and various cranial bones (parietals, interparietals, occipital, and squamosal) at 40 mg/kg/day (LOAEL).

Comments about Study and Endpoint: This endpoint is appropriate for acute risk assessment for females 13+ because developmental effects could occur following a single exposure.

Uncertainty Factor (UF): 100 (10x for inter-species extrapolation and 10x for intra-species variability).

$$\text{Acute RfD (for females 13+)} = \frac{5 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.05 \text{ mg/kg/day}$$

b. For General Population

Study Selected: Developmental Toxicity Study in Rabbits Guideline #: §83-3b

MRIDNo. 44399144

Executive Summary: In a developmental toxicity study (MRID 44399144), hybrid albino (HyCr) rabbits were dosed by gavage with CGA 184927 (purity 93.7%), as a suspension in aqueous hydroxypropyl methylcellulose, at dose levels of 0 (vehicle control), 5, 25 and 125 mg/kg/day, 18 mated females per group, and 175 mg/kg/day, 14 mated females, on days 7 to 19 of gestation, inclusive.

Maternal toxicity was evident at 125 and 175 mg/kg/day which consisted of mortality (5/18 during GD 14-22 and 11/14 during GD 11-15, respectively), clinical signs (labored breathing, reduced activity, ataxia, pallor and nasal discharge) and body weight loss (in nonsurvivors only). Clinical signs of intoxication were first evident on day 9 in females at 125 mg/kg/day. Necropsy revealed ulceration of the stomach and hemorrhagic contents of the caecum and colon. One doe from 175 mg/kg/day group aborted on GD 23. Mortality and clinical signs were also noted in the range-finding study at 160 mg/kg/day. Consequently, the observed effect seen in this study were considered to be treatment-related. **Therefore, the maternal LOAEL is 125 based on mortality, clinical signs and body weight loss and the maternal NOAEL is 25 mg/kg/day.**

Due to high rate of mortality at 175 mg/kg/day, the fetal data for this group was excluded from analyses. There was no treatment-related developmental toxicity observed in other dose groups. **Therefore, the developmental LOAEL is >125 mg/kg/day based on lack of developmental toxicity. The developmental NOAEL is 125 mg/kg/day.**

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Dose and Endpoint for Risk Assessment:: 25 mg/kg (NOAEL) based on observed maternal toxicity (increased mortality, clinical signs and body weight loss) at 125 mg/kg/day.

Comments about Study and Endpoint: This study is suitable for general population because mortality, clinical signs, and maternal body weight loss occurred on the first measurement time point (days 2 after dosing). It is reasonable to assume that the effects could occur after a single dose.

Uncertainty Factor (UF): 100 (10x for inter-species extrapolation and 10x for intra-species variability).

$$\text{Acute RfD (for general population)} = \frac{25 \text{ mg/kg/day}}{100} = 0.25 \text{ mg/kg/day}$$

This risk assessment is required.

B. Chronic Dietary [Reference Dose (RfD)]

Study Selected: 2-Year Chronic Toxicity/Carcinogenicity in Rats

Guideline#: §83-5

MRID No.

44399147

Executive Summary: In a combined chronic toxicity/carcinogenicity study (MRID# 44399147), CGA 184927 (93.7% a.i.) was administered in diet to male and female Tif: RAIf (SPF) albino rats (80/sex/group) for a period of 24 months. The test diets contained technical CGA 184927 at dietary concentrations of 0, 1, 10, 300 or 750 ppm (0, 0.031, 0.32, 10.18, 26.28 mg/kg/day for males; and 0, 0.034, 0.36, 11.31, 29.48 mg/kg/day for females, respectively). At interim sacrifice, week 53, 10 rats/sex/dose were sacrificed.

An increase in liver enzyme levels was noted in both sexes at ≥ 300 ppm. At interim and final sacrifices, absolute and/or relative liver and kidney weights increased in one or both sexes at ≥ 300 ppm. Necropsy revealed increased incidence of enlarged, or mottled liver in males at ≥ 300 ppm and in females at 750 ppm. In addition, there was a dose-related increase in the incidence of microscopic changes in the liver including hepatocytic hypertrophy in males at ≥ 10 ppm as well as focal or nodular hyperplasia and fibrosis in one or both sexes at ≥ 300 ppm. At 750 ppm, one of 80 males developed hepatocarcinoma. Hypertrophy of follicular epithelium in the thyroid was noted in females at 750 ppm. Kidney changes noted in both sexes consisted of increased incidence of chronic progressive nephropathy and tubular pigmentation at ≥ 10 ppm. Increased incidence of ovarian medullary tubular hyperplasia was noted at ≥ 300 ppm.

Under the conditions of this study, treatment with CGA 184927 increased the incidence of prostate and ovarian tumors in rats at 750 ppm. For males, an increased incidence of prostate adenoma was seen in the high-dose group, i.e., incidence rates were 8/80 (10.0%), 9/80 (11.25%), 12/80 (15.0%), 13/80 (16.25%) and 19/80 (23.75%) in the 0, 1, 10, 300 and 750 ppm groups, respectively. For females, an increased incidence of tubular adenomas of the ovary was noted in the high-dose group, i.e., incidence rates of 2/80 (2.5%), 1/80 (1.25%), 1/80 (1.25%), 1/80

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(1.25%) and 9/80 (11.25%) for the 0, 1, 10, 300 and 750 ppm groups, respectively.

The test material was administered at a dose sufficient to test its carcinogenic potential.

The LOAEL for systemic toxicity is 10 ppm (0.32 and 0.36 mg/kg/day in males and females, respectively) based on hepatocytic hypertrophy, chronic progressive nephropathy and tubular pigmentation. The systemic NOAEL is 1 ppm (0.031 and 0.034 mg/kg/day in males and females, respectively). There were increased incidences of prostate adenomas and tubular adenomas of the ovary in rats fed CGA 184927.

Dose/Endpoint for establishing the RfD : 0.03 mg/kg/day (NOAEL) based on observations of hepatocytic hypertrophy, chronic progressive nephropathy and tubular pigmentation at 0.3 mg/kg/day (LOAEL).

Comments about Study and Endpoint: The lowest NOAEL in the most sensitive species with common endpoints of liver toxicity in both sexes.

Uncertainty Factor (UF): 100 (10x for inter-species extrapolation and 10x for intra-species variability).

$$\text{Chronic RfD} = \frac{0.03 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.0003 \text{ mg/kg/day}$$

This risk assessment is required

C. Occupational/Residential Exposure

There are no residential uses; however, there is potential for residential exposure to spray drift resulting from aerial application. Based on the use pattern, there is potential for short-term exposures (private- one field) and intermediate-term exposure (commercial- several fields) during mixing, loading, application, and post-application activities. Long-term exposure is not expected to occur.

1. **Dermal Absorption**

No dermal absorption study is submitted. The HIARC estimated the % dermal absorption for CGA 184927 to be 2.5%. This dermal absorption rate was derived by taking the ratio of the LOAEL from the 28-day oral (gavage) toxicity study in rats (5 mg/kg/day) and the 28-dermal toxicity study in rats (200 mg/kg/day) based on the common endpoint of liver toxicity. However, a dermal absorption factor is not required since dermal NOAEL was selected for dermal risk assessment.

2. Short-Term Dermal - (1-7 days)

Study Selected: 28-Day Dermal Toxicity Study in Rats

Guideline #: §82-2

MRID No. 44399141

Executive Summary: In this 28-day dermal toxicity study, forty rats (5/sex/dose) were assigned to four groups. Groups 1, 2, 3, and 4 received topical application of either 0, 50, 200, or 1000 mg/kg/day of CGA 184927 (2 mL/kg/day) to the shaved area six hours per day, 5 days/week for 4 weeks. No treatment-related mortality or dermal signs were observed. Dose-related clinical signs included piloerection and hunched posture at ≥ 200 mg/kg/day (males only) mainly during weeks 2, 3, and 4. Post-mortem examination revealed an increase in absolute and relative liver weight as well as in liver:brain weight ratio in males at ≥ 200 mg/kg/day and centrilobular hypertrophy in male rats treated at 1000 mg/kg/day. There was a decrease in thymus weight in males and females receiving 1000 mg/kg/day and atrophy of the thymus in male rats receiving this dosage.

The systemic toxicity LOAEL is 200 mg/kg/day based on dose-related increases in liver weights and clinical signs (piloerection and hunched posture) in male rats. The systemic toxicity NOAEL is 50 mg/kg/day. The dermal toxicity NOAEL is 1000 mg/kg/day.

Dose and Endpoint for Risk Assessment: 50 mg/kg/day (NOAEL) based on dose-related increases in liver weights and clinical signs (piloerection and hunched posture) in male rats at 200 mg/kg/day (LOAEL).

Comments about Study and Endpoint: This study is selected because its duration and route of exposure are appropriate for short and intermediate term dermal exposure.

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 28-Day Dermal Toxicity Study in Rats

Guideline #: §82-2

MRID No.: 44399141

Executive Summary: See previous short-term dermal section.

Dose and Endpoint for Risk Assessment: See previous section.

Comments about Study and Endpoint: See previous section.

This risk assessment is required.

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4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: None

MRID No. None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable

Comments about Study and Endpoint: Based on the current use pattern, no long-term dermal exposure is expected to occur.

This risk assessment is NOT required.

5. Short-Term Inhalation (1-7 days)

Study Selected: Developmental Toxicity Study in Rats

Guideline #: §83-3a

MRID No. 44399145

Executive Summary: See previous acute dietary section.

Dose and Endpoint for Risk Assessment: 5 mg/kg (NOAEL) based on increased incidences of bilateral distension and torsion of the ureters, unilateral 14th ribs, and incomplete ossification of the metacarpals and various cranial bones (parietals, interparietals, occipital, and squamosal) at 40 mg/kg/day (LOAEL).

Comments about Study and Endpoint: Only an acute inhalation toxicity study has been submitted to the Agency. There were no inhalation toxicity studies appropriate for risk assessment in the toxicology database. Consequently, the oral values should be used for inhalation exposure risk assessment; the route-to-route extrapolation should be done as follows:

Convert the inhalation exposure component (i.e. $\mu\text{g a.i./day}$) using a 100% absorption rate (default value) and an application rate to an equivalent oral dose (mg/kg/day) and compare it to the oral value of 5 mg/kg/day for short-term and oral values of 0.9 mg/kg/day for intermediate-term exposure to calculate the MOEs.

This risk assessment is required.

6. Intermediate-Term Inhalation (7 days to several months)

Study Selected: Subchronic Oral Toxicity Study in Rats

Guideline #: §82-1

MRID No. 44399132

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Executive Summary: In a subchronic toxicity study (MRID# 44399132), CGA 184927 was administered to male and female Tif: RAIf (SPF) albino rats. The test diets contained technical CGA 184927, purity 93.7%, at dietary concentrations of 0, 2, 15, 120, and 1000 ppm (0, 0.13, 0.92, 8.24, and 70.0 mg/kg/day for males; and 0, 0.13, 0.94, 8.24, and 71.1 mg/kg/day for females, respectively) for a period of 92 to 94 days, 20 rats/sex/group. At the end of the treatment period, 10 rats/sex/group were sacrificed; the remaining rats were retained for a 28-day recovery period, i.e., fed control diet, and were then sacrificed.

At the end of the treatment period, an increase in mean absolute and relative liver weights at 120 (males only) and 1000 ppm (both sexes), and increased alkaline phosphatase activity at 120 (in males) and 1000 ppm (both sexes) were noted. The other findings at 1000 ppm were: decreased mean bodyweight and reduced mean absolute and relative thymus weight, in males. Histopathological findings considered to be treatment-related were hepatocytic hypertrophy seen in both sexes, and thymic atrophy observed in males only.

After a 28-day recovery period, it was demonstrated that the treatment-related findings were reversible.

The LOAEL was 120 ppm for males (8.24 mg/kg/day) and 1000 ppm for females (71.1 mg/kg/day), based on increased liver weights and enzyme activity in males at 120 ppm and liver hypertrophy in both sexes at 1000 ppm.

The NOAEL was 15 ppm for males (0.92 mg/kg bw/day), and 120 ppm for females (8.24 mg/kg/day).

Dose and Endpoint for Risk Assessment: 0.9 mg/kg/day (NOAEL) based on increases in liver weights and enzyme activity in males at 8.2 mg/kg/day (LOAEL).

Comments about Study and Endpoint: See previous section for the route-to-route extrapolation.

This risk assessment is required.

7. Long-Term Inhalation (several months to life-time)

Based on the current use pattern, no long-term inhalation exposure is expected to occur.

This risk assessment is NOT required.

D. Recommendation for Aggregate (Food, Water, and Dermal) Exposure Risk Assessments

For acute aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the acute RfD.

For short and intermediate-term aggregate exposure risk assessment, oral and dermal exposures can not be combined due to differences in the toxicological endpoints via these routes. Oral and

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inhalation exposure can be combined since inhalation exposure is corrected to oral equivalent doses.

Based on the current use pattern, long-term aggregate exposure risk assessment is not required.

E. Margins of Exposures for Occupational Exposure Risk Assessments

A MOE of 100 is required for occupational exposure risk assessment. The MOEs for residential exposure risk assessment will be determined by the FQPA Safety Factor Committee.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. 2-Year Chronic Toxicity/Carcinogenicity study in Rats

Guideline #: §83-5

MRID No.: 44399147

Executive Summary: See chronic dietary section.

Discussion of Tumor Data: Under the conditions of this study, treatment with CGA 184927 increased the incidence of prostate and ovarian tumors in rats at 750 ppm. For males, a statistically significantly increased incidence of prostate adenoma was seen in the high-dose group, i.e., incidence rates were 8/80 (10.0%), 9/80 (11.25%), 12/80 (15.0%), 13/80 (16.25%) and 19/80 (23.75%) in the 0, 1, 10, 300 and 750 ppm groups, respectively. At 750 ppm, one of 80 males developed hepatocarcinoma. For females, a statistically significantly increased incidence of tubular adenomas of the ovary was noted in the high-dose group, i.e., incidence rates of 2/80 (2.5%), 1/80 (1.25%), 1/80 (1.25%), 1/80 (1.25%) and 9/80 (11.25%) for the 0, 1, 10, 300 and 750 ppm groups, respectively.

Adequacy of the Dose Levels Tested: The chemical was administered at doses sufficient to test its carcinogenic potential.

2. Carcinogenicity Study in Mice

Executive Summary:

In an 18-month carcinogenicity study (MRID# 44399143), male and female Tif:MAGf (SPF) albino mice (60/sex/group) were fed diets containing 0, 1, 10, 100 or 250 ppm (0, 0.113, 1.10, 11.0 or 29.6 mg/kg bw/day for males and 0, 0.129, 1.25, 12.6 and 33.1 mg/kg bw/day for females, respectively) CGA 184927 (93.7% a.i.).

At 250 ppm, among males, there was increased mortality (12/60; 20%) during the last month of the study; a high proportion of them (38/60; 63%) developed hepatocellular tumors. The mean final body weight (5-6%) and mean overall body weight gain (11%) were lower in males only. At ≥100 ppm, there were increases in liver enzyme activity and liver weights in both sexes. At necropsy, an increased incidence of enlarged livers and liver nodules/masses were noted in males

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at 100 ppm and in males and females at 250 ppm. Histopathology revealed non-neoplastic changes including hepatocytic hypertrophy, kupffer cell pigmentation and intrahepatic bile duct hyperplasia in males at 100 ppm and in males and females at 250 ppm; hepatocytic necrosis in males at 100 and 250 ppm and necrosis in females at 250 ppm. In addition, an increased incidence of pre-neoplastic foci was noted at 100 and 250 ppm in males only; an increase in the severity of thymic atrophy was seen in both sexes.

The neoplastic changes noted consisted of dose-related increased incidence of hepatomas in males (11/60 [18%] and 30/60 [50%; $p < 0.01$] at 100 ppm and 250 ppm, respectively) and in females (4/60 [7%]) at 250 ppm; hepatocellular carcinomas in males (8/60 [13%; $p < 0.05$]) at 250 ppm and combined incidences of hepatocellular tumors in males (15/60 [25%] and 38/60 [63%; $p < 0.01$] at 100 ppm and 250 ppm, respectively), and in females (4/60 [7%]) at 250 ppm. The incidences of these findings exceeded that of concurrent controls. In addition, the incidence of pre-neoplastic hepatic lesions also increased in a dose-related manner in males at 100 and 250 ppm. Therefore, these findings were considered to be treatment-related. A slight increase in the incidence of angiosarcoma (2/60, 3%) and hemangioma (2/60, 3%; combined incidence: 4/60, 7%) in the liver of females at 250 ppm (2/60, 3%) was possibly treatment-related.

The LOAEL for systemic toxicity is 11.0 and 12.6 mg/kg/day for males and females, respectively, based on increases in liver enzyme activity and liver weights. The NOAEL was estimated to be 1.10 and 1.25 mg/kg/day for males and females, respectively.

Under the conditions of this study, CGA 184927 induced hepatocellular tumors in males at ≥ 100 ppm and in females at 250 ppm. The chemical was tested at doses sufficient to measure its carcinogenic potential.

MRID No.: 44399143

Discussion of Tumor Data: CGA 184927 induced hepatocellular tumors in males at ≥ 100 ppm and in females at 250 ppm.

Adequacy of the Dose Levels Tested: The chemical was tested at doses sufficient to measure its carcinogenic potential.

3. Mutagenic Data

The acceptable genetic toxicology studies indicate that CGA 184927 is not mutagenic in bacteria (*Salmonella typhimurium*) or cultured mammalian cells (Chinese hamster V79 lung fibroblasts). There is also no evidence of clastogenicity *in vivo*. Similarly, CGA 184927 did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes. However, the acceptable studies do not satisfy the 1991 mutagenicity guideline requirements since the submitted *in vitro* cytogenetic assay has been classified as unacceptable. It is recommended, therefore, that an *in vitro* cytogenetic assay be conducted to fulfill guideline requirements. Summaries of the acceptable studies are presented below:

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A. Gene Mutations

1) *S. typhimurium* mammalian microsome gene mutation assay (MRID No. 44399153): Independently performed trials were negative up to insoluble doses ($\geq 313 \mu\text{g}/\text{plate}$) with or without S9 activation. The study is classified as Acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for a bacterial gene mutation assay.

2) *In vitro* mammalian cell forward gene mutation assay in Chinese hamster V79 cells (MRID No. 44399152): Independently performed trials were negative up to cytotoxic concentrations ($500 \mu\text{g}/\text{mL}$ without S9 activation and $\approx 41\text{-}50 \mu\text{g}/\text{mL}$ in the presence of S9 activation). The study is classified as Acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for a mammalian cell gene mutation assay.

B. Chromosome Aberrations

In vivo micronucleus assay (MRID No. 44399151): The test was negative in male and female NMRI mice administered single doses of 1667 or 5000 mg/kg by oral gavage. Lethality was seen in the high-dose group. There was no evidence of bone marrow cytotoxicity. The study is classified as Acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for an *in vivo* cytogenetic assay.

C. Other Mutagenic Mechanisms

In vitro UDS assay in primary rat hepatocytes (MRID No. 44399156): Independently performed trials were negative up to insoluble doses ($\geq 4000 \mu\text{g}/\text{mL}$). The study is classified as Acceptable and satisfies the requirements for FIFRA Test Guideline 84-2 for a UDS assay.

4. Classification of Carcinogenic Potential:

The HIARC recommends clodinafop-propargyl (CGA 184927) to be reviewed by the Cancer assessment Review Committee based on increased incidences of prostate and ovarian tumors in rats and hepatocellular tumors in mice.

IV. FOPA CONSIDERATIONS

1. Neurotoxicity

There are no neurotoxicity studies available for clodinafop-propargyl. However, clinical signs indicative of neurotoxicity were observed in dogs, rats and rabbits. In order to further define the potential of neurotoxicity, the HIARC recommends acute and subchronic neurotoxicity studies to be conducted on this chemical.

2. Developmental Toxicity

a. Developmental toxicity study in rats (MRID 44399145)- See acute dietary (for females 13+).

b. Developmental toxicity study in rabbits (MRID 44399144)- See acute dietary (for general population) section.

3. Reproductive Toxicity

A two-generation study (MRID 44399146) was conducted using Sprague Dawley Crl: CD (SD)BR SPF rats, fed test diets containing 0, 5, 50, 500 or 1000 ppm (0, 0.33, 3.21, 31.69, and 64.24 mg/kg/day in males and 0, 0.41, 3.77, 37.54, and 73.60 mg/kg/day in females, respectively) CGA 184927 continuously throughout the study period, 25 rats per sex per group. Each female in each generation was mated to produce one litter only.

There were no treatment-related mortality or clinical signs of toxicity observed. The mean bodyweight gains were significantly but slightly lower during the pre mating/ mating period for mid- and high-dose males in both generations. The mean food consumption was decreased during the pre mating period for males in the 500 and 1000 ppm groups, and during lactation for females in the 500 and 1000 ppm groups.

Absolute and relative liver and kidney weights were increased in the 500 and 1000 ppm groups, one or both sexes, in both generations. The mean testicular weight was decreased for F1 males in the 1000 ppm group only.

Necropsy revealed an increased incidence of dilatation of the renal pelvis in the 500 and 1000 ppm groups in both sexes in F1 generation only.

Histopathological findings observed in the 1000 ppm group of both generations and sexes, and considered to be treatment-related were as follows: liver - hepatocytic hypertrophy; kidney - hyaline casts, parenchymal atrophy, pigment deposits in tubules (P), pelvis dilatation (F1), tubular dilatation (F1), and loss of tubular epithelium with gray masses in tubule lumina (F1).

There were no adverse, treatment-related effects on reproductive performance.

For F1a pups, viability index on day 21 was lower in the 1000 ppm group and the mean pup weight was decreased in the 500 and 1000 ppm groups on days 14 and 21 of lactation. For F2a pups, mean pup weight was decreased in the 1000 ppm group throughout the lactation period and in the 500 ppm group on days 7, 14 and 21 of lactation.

Minor delays noted in development of F1a and F2a pups in the 500 and 1000 ppm groups consisted of pinna unfolding and/or incisor eruption and/or eye opening. However, these were no longer evident at weaning and so were considered transient. There were no treatment-related effects on functional tests at weaning (pupillary reflex, auditory response).

An increase in the incidence of dilatation of renal pelvis was observed in the 500 and 1000 ppm groups, F2a pups only.

The LOAEL for parental systemic toxicity is 500 ppm (31.7 mg/kg/day) based on decrease in body weight gain, reduced food consumption, increased liver and kidney weights and histopathological changes in the liver (hepatocytic hypertrophy, and renal tubules (hyaline casts, parenchymal atrophy, pigment deposits, dilatation and loss of tubular epithelium).

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The NOAEL for parental systemic toxicity is 50 ppm (3.2 mg/kg/day).

The LOAEL for reproductive toxicity is ≥ 1000 ppm (≥ 64.2 mg/kg/day) based on lack of reproductive effects. The NOAEL for reproductive toxicity is 1000 ppm (64.2 mg/kg/day).

The LOAEL for offspring toxicity is 500 ppm (31.7 mg/kg/day) based on reduced viability, decreased pup body weight and dilatation of renal pelvis. The NOAEL is 50 ppm (3.2 mg/kg/day).

5. Determination of Susceptibility

The HIARC concluded that there was a concern for increased susceptibility for clodinafop-propargyl (CGA 184927) based on the developmental toxicity study in rats where increased skeletal effects were observed at doses lower than the maternal NOAEL. The HIARC also identified acute and subchronic neurotoxicity studies as data gaps to further define the potential of neurotoxicity. In addition, there is a concern for thyroid hormone effects based on observations of increased hypertrophy of follicular epithelium of the thyroid in the two-year chronic toxicity study in rats.

6. Recommendation for a Developmental Neurotoxicity Study

The HIARC recommends a developmental neurotoxicity study to be placed on "Reserve" for Clodinafop-propargyl (CGA 184927) pending submissions and reviews of acute and subchronic neurotoxicity studies.

7. Determination of the FOPA Factor

Based on the hazard assessment, the HIARC recommends that the 10x FQPA Safety Factor for the protection of infants and children (as required by FQPA) for clodinafop-propargyl (CGA 184927) be retained due to increased susceptibility and data gaps for acute and subchronic neurotoxicity studies. The final recommendation will be made by the FQPA Safety Factor Committee during risk characterization.

V. HAZARD CHARACTERIZATION

The toxicity data indicated that clodinafop-propargyl (CGA 184927) has low acute oral, dermal, and inhalation toxicity. It is not a eye or skin irritant. However, it is a skin sensitizer.

The primary target organ was the liver for dogs, mice, and rats. The liver toxicity was evidenced by increased liver weight, elevated liver enzyme activities and abnormal histopathological findings. An increased incidence of hepatoma and hepatocellular carcinoma was observed at the high dose (29.6 mg/kg/day) in a mouse carcinogenicity study.

For dogs only, skin lesions (e.g. pustules, erythema, and crusts) were observed in the subchronic and chronic dog studies. It was noted that the skin lesions were observed at doses as low as 50 ppm (1.73 mg/kg/day) in the subchronic feeding study while skin lesions were observed at higher doses (500 ppm or 15.2 mg/kg/day) in the one year feeding study.

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There was no evidence of reproductive toxicity; however, a mild fetotoxic effect was noted (in rats only). In the two-generation reproduction study, reduced fetal viability, decreased pup body weight, and dilatation of renal pelvis were observed at doses that produced maternal toxicity (decreased body weight gain, increased liver and kidney weights with histopathological changes). In the developmental toxicity study in rats, fetotoxic effects were observed at doses lower than those that produced maternal toxicity. The fetal anomalies consisted of an increased incidence of the following: bilateral distension of the ureter and bilateral torsion of the ureter, hematoma to the head, absence of ossification in the sternbrae, incomplete ossification of the thoracic vertebral centra, absence of ossification in the caudal vertebral arches, unilateral 14th ribs, incomplete ossification of the metacarpals, and incomplete ossification of various cranial bones (parietal, interparietal, occipital, and squamosal). Also there was a significant but slight reduction (7%) in mean fetal body weights at the high-dose group compared to the control.

Carcinogenicity studies indicated that treatment with clodinafop-propargyl increased the incidence of prostate and ovarian tumors in rats and hepatocellular tumors in mice. The genetic toxicology studies indicate that clodinafop-propargyl is not mutagenic in bacteria (*Salmonella typhimurium*) or cultured mammalian cells (Chinese hamster V79 lung fibroblasts). There is also no evidence of clastogenicity *in vivo*. However, an *in vitro* cytogenetic assay was unacceptable. Clodinafop-propargyl did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes. The classification of the carcinogenic potential of CGA 184927 will be further evaluated by the Cancer Assessment Review Committee.

There are no neurotoxicity studies available for clodinafop-propargyl. However, clinical signs indicative of neurotoxicity were observed in the dog, rat and rabbit studies. In order to further define the potential of neurotoxicity, the HIARC recommends acute and subchronic neurotoxicity studies to be conducted on this chemical.

Results from metabolism studies in rats indicated that clodinafop-propargyl was well absorbed from the intestinal tract (74.7% - 94.1%) and excreted via the urine; much smaller percentage was eliminated in the feces. The excretion rate was much faster for females, i.e. more than 80% of the administered dose (AD) was excreted within the first 24 hours, whereas for males, only about 75% of the AD was excreted by 96 hours post-dosing. Significant residues were evident in most tissues of the males, with highest levels seen in the fat, bone marrow, liver, and kidney. Tissue residues in females were significantly lower than males due to the higher elimination rate of the test material. Residues in females were highest in the fat, ovaries, uterus, and kidney. In the urine, the major metabolite was (R)-2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)-phenoxy]-propionic acid (36.7-39.1% of AD). In addition, seven unidentified metabolites were isolated (0.1-5.2% of the AD). In the feces, the major metabolite corresponded to the major urinary metabolite, accounting for 15.7% to 16.9% of the AD. Six unidentified metabolites were isolated, ranging from 0.3% to 1.4% of the AD. In the fat, all metabolites were reportedly acylglycerides, the majority of which were hybrid di- and triacylglycerides (3.5 and 17% of the AD, respectively). In the liver, kidney, and carcass, the metabolite pattern reflected the transformations seen in excreta and fat.

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Acute Toxicity Profile for Clodinafop-propargyl (CGA 184927)

GDLN	Study Type	MRID	Results	Tox. Cat.
81-1	Acute Oral- Rat	44399124	LD ₅₀ = 1392(♂)/2271(♀) mg/kg	3
81-2	Acute Dermal -Rabbit -Rat	44399125	LD ₅₀ > 2000 mg/kg (rat or rabbit)	3
81-3	Acute Inhalation- Rat	44399126	LC ₅₀ > 2.3 mg/L(♂ & ♀)	4
81-4	Primary Eye Irritation- Rabbit	44399127	Slightly eye irritant	3
81-5	Primary Skin Irritation- Rabbit	44399128	Non-irritant	4
81-6	Dermal Sensitization-Rat	44399129	Skin sensitizer	NA

VI. DATA GAPS

Acute Neurotoxicity Study in Rats (81-8; OPPTS 870.6200)
Subchronic Neurotoxicity Study in Rats (82-7; OPPTS 870.6200)
In vitro cytogenetic assay (84-2; OPPTS 870.5375)

VII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected on clodinafop-propargyl (CGA 184927) for various exposure scenarios are summarized as follows.

Clodinafop-propargyl (CGA 184927)

Doses and Toxicological Endpoints Selected for Various Exposure Scenarios on Clodinafop-propargyl (CGA 184927)

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (For females 13+)	NOAEL=5 (UF=100)	Increased incidences of bilateral distension and torsion of the ureters, unilateral 14th ribs, and incomplete ossification of the metacarpals and various cranial bones.	Developmental toxicity study in rats
	Acute RfD (females 13+) = 0.05 mg/kg/day		
Acute Dietary (For general population)	NOAEL=25 (UF=100)	Maternal toxicity (increased mortality, clinical signs and body weight loss)	Developmental toxicity study in rabbits
	Acute RfD (general population) = 0.25 mg/kg/day		
Chronic Dietary	NOAEL=0.03 (UF=100)	Hepatocytic hypertrophy, chronic progressive nephropathy and tubular pigmentation	Chronic Toxicity -Rat
	Chronic RfD = 0.0003 mg/kg/day		
Short-term (Dermal)	Dermal NOAEL=50	Increased liver weight and clinical signs (piloerection and hunched posture) in males	28-Day Dermal Toxicity- Rats
Intermediate-Term (Dermal)			
Long-term (Dermal)	Not Applicable	Based on the current use pattern, no long-term dermal exposure is expected to occur.	
Short-term (Inhalation)	Oral NOAEL= 5 ^a	See acute dietary	Developmental toxicity in rats
Intermediate-Term (Inhalation)	Oral NOAEL=0.9 ^a	Increased liver weight and enzyme activity in males	Subchronic oral toxicity study in rats
Long-term (Inhalation)	Not Applicable	Based on the current use pattern, no long-term inhalation exposure is expected to occur.	

^a use route to route extrapolation