IMAGE

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

014504

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: March 14, 2001

MEMORANDUM

SUBJECT: ***THIAMETHOXAM*** - 2nd Report of the Hazard Identification Assessment Review Committee.

FROM: Pamela M. Hurley, Toxicologist Pamela M Hurley 3/15/01
Registration Action Branch 2
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair 3/15/01
and
Elizabeth Doyle, Co-Chair E. C. Doyle 3/15/01
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Pamela M. Hurley, Risk Assessor
Registration Action Branch 2
Health Effects Division (7509C)

PC Code: 060109

On March 23, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for THIAMETHOXAM with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for occupational/residential exposure risk assessments. On January 9, 2001, the HIARC re-evaluated the dermal absorption value in light of new data. The potential for increased susceptibility of infants and children from exposure to THIAMETHOXAM was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at these meetings are presented in this report.

1

Committee Members in Attendance

Members present were: Bill Burnam, Beth Doyle, Pamela Hurley, Elizabeth Mendez, David Nixon, Jess Rowland, Yung Yang, Jonathan Chen, Ayaad Assaad, Brenda Tarplee, Exec. Secretary

Member(s) in absentia:

Data evaluation prepared by: Robert P. Zendzian, Science Analysis Branch and Christine Norman, PMRA, Health Canada.

Also in attendance were: Bob Zendzian, Paula Deschamp, Nader Tadayon, Sheila Piper, Alberto Protzel, Mike Ioannou

Data Evaluation / Report Presentation

3/5/01
Robert P. Zendzian, Ph.D
Senior Pharmacologist

Pamela M Hurley
Pamela M. Hurley, Ph.D
Toxicologist

1. INTRODUCTION

On March 23, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for THIAMETHOXAM with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for occupational/residential exposure risk assessments. On January 9, 2001, the HIARC re-evaluated the dermal absorption value in light of new data. The potential for increased susceptibility of infants and children from exposure to THIAMETHOXAM was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996.

2. HAZARD IDENTIFICATION

2.1 Acute Reference Dose (RfD): General Population

Study Selected: Acute Neurotoxicity Study in the Rat **§ 870.6200**

MRID No.: 44703320

Executive Summary: In an acute neurotoxicity study, CGA 293343 technical (purity 98.7%), as a suspension in 0.5% aqueous carboxymethylcellulose, was administered by oral gavage to Sprague-Dawley Crl:CD BR rats, 10/sex/group, at dose levels of 0, 100, 500 or 1500 mg/kg bw. Functional Observational Battery (FOB) and locomotor activity (LMA) testing were performed before initiation of treatment, 2 to 3 hours post-dosing, and 1 and 2 weeks post-dosing. In addition, a detailed histopathological examination of perfuse central and peripheral nervous system tissues was conducted. Treatment-related mortality was noted for females in the 1500 mg/kg bw group, i.e., 3 females were found dead on study days 1 or 2. Body weight gain was decreased during the first week of the study for 1500 mg/kg bw males; however, there was a compensatory increase in body weight gain for these animals during study week 2 (i.e., total body weight gain and final body weights were comparable among all groups). Treatment-related neurobehavioural effects were observed in the FOB and LMA testing in the 500 and 1500 mg/kg bw groups at the 2-3 hour post-dosing examination. In the 500 mg/kg bw group, findings were limited to drooped palpebral closure, lower rectal temperature, increased forelimb grip strength (males only) and decreased locomotor activity. Additional findings in the 1500 mg/kg bw group included abnormal body tone, ptosis, impaired respiration, tremors, longer latency to first step in the open field, crouched-over posture, gait impairment, hypo-arousal, decreased number of rears, uncoordinated landing during the righting reflex test, slight lacrimation (females only) and higher mean average input stimulus value in the auditory startle response test (males only). These effects were no longer evident at the 1 week and 2 week post-dosing examinations. There were no treatment-related histopathological findings noted in the central or peripheral nervous system at any dose level tested. Based on the results of this study, **the NOAEL for acute neurotoxicity is 100 mg/kg bw, and the LOAEL is 500 mg/kg bw.**

Dose and Endpoint for Establishing RfD: 100 mg/kg based on treatment-related neurobehavioral effects observed in the FOB and LMA testing (drooped palpebral closure, lower rectal temperature, increased forelimb grip strength (males only) and decreased locomotor activity (at the 2-3 hours post-dosing examination) at 500 mg/kg.

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

Comments about Study/Endpoint/Uncertainty Factor: This study is appropriate because effects were observed after a single dose. This study will also be protective of any potential developmental effects.

$$\textbf{Acute RfD} = \frac{\text{100 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = \textbf{1 mg/kg}$$

2.2 Acute Reference Dose (RfD): Females 13-50

An endpoint could not be identified that would provide any more protection for Females 13-50 than the endpoint selected for the General Population. Developmental LOAELs were higher following *in utero* exposure to rats and rabbits.

2.3 Chronic Reference Dose (RfD)

Study Selected: 2-Generation Reproduction Study in the Rat § 870.3800

MRID No.: 44718707

Executive Summary: In a 2-generation reproduction study, CGA 293343, purity 98.6%, was administered to 30 Tif: RAI f (SPF) rats/sex/dose in the diet at concentrations of 0, 10, 30, 1000 and 2500 ppm (equal to 0, 0.61, 1.84, 61.25 and 158.32 mg/kg bw/day for males, and 0, 0.80, 2.37, 79.20 and 202.06 mg/kg bw/day for females). Each female in each generation was mated to produce two litters. For the parental animals, body weight gain was slightly lower in the 2500 ppm group during the first 6 weeks of the study, F_0 and F_1 generations, males only. However, the effect was marginal and was not considered to be toxicologically significant. Decreased testis weight was observed in the F_1 generation at 2500 ppm, and increased incidence and severity of tubular atrophy was observed in the testes in the F_1 generation at 30 ppm and above. Sperm motility was decreased in all treatment groups in both generations, however, there was no dose-response relationship, there was high variability among all groups and there were no treatment-related effects on sperm count or sperm morphology. A separate, complementary study was conducted to investigate this finding. On the basis of the special investigation, it was concluded that the initial findings were likely due to technical error and not related to treatment with CGA

293343. The supplemental information was limited to analysis of F_0 animals, hence no information relevant to the findings in F_1 animals is available. Increased incidence of hyaline changes was observed in the renal tubules for F_0 and F_1 males in the 1000 and 2500 ppm groups, and an increased incidence of renal tubular casts was noted for F_0 males in the 1000 ppm group, and F_0 and F_1 males in the 2500 ppm group. Hyaline change in renal tubules was also observed in one F_1 female at 2500 ppm. A slight increase in food consumption was observed in F_1 females during gestation with the F_{1a} and F_{1b} litters, but this was not considered to be toxicologically significant. For offspring, body weight gain was lower in the 2500 ppm group during the lactation period in the F_{1a}, F_{1b}, F_{2a} and F_{2b} litters, both sexes, resulting in lower body weights on days 7, 14 and/or 21 postpartum. Slightly lower body weight gain and body weights (days 7, 14 and/or 21 postpartum) were also noted in the 1000 ppm group for F_{2a} and F_{2b} females. However, the effect was marginal (≤8% lower than the control group values), F_{1a} and F_{1b} pups were not affected and males were not affected, and so this finding was not considered to be toxicologically significant. **In males, the reproductive toxicity LOAEL is 30 ppm (1.8 mg/kg bw/day) based on increased incidence and severity of tubular atrophy observed in testes of the F_1 generation; the NOAEL is 10 ppm (0.6 mg/kg bw/day).** There were no adverse, treatment-related effects on reproductive parameters (mating, gestation, fertility, viability) noted at any dose level tested, **therefore, the NOAEL for reproductive toxicity in females is 2500 ppm (202 mg/kg bw/day). For parental systemic toxicity, the LOAEL for males is 1000 ppm (61 mg/kg bw/day), based on increased incidence of hyaline change in renal tubules in F_0 and F_1 animals. The NOAEL is 30 ppm (1.8 mg/kg bw/day). The NOAEL for females is 2500 ppm (202 mg/kg bw/day, the highest dose tested) based on a slight increase in food consumption for F_1 females during gestation with the F_{1a} and F_{1b} litters which was not considered to be toxicologically significant. For offspring toxicity, the LOAEL is 2500 ppm (158 mg/kg bw/day for males, and 202 mg/kg bw/day for females) based on reduced body weight gain during the lactation period in all litters. The NOAEL is 1000 ppm (61 mg/kg bw/day in males and 79 mg/kg bw/day in females).**

Dose and Endpoint for Establishing RfD: 0.6 mg/kg/day based on increased incidence and severity of tubular atrophy in the testes of the F_1 generation males observed at 1.8 mg/kg/day.

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

Comments about Study/Endpoint/Uncertainty Factor: Although there are no indications of effects on other reproductive parameters (i.e. mating, gestation, fertility and viability) in the rat reproduction study, there are uncertainties regarding the testicular effects, especially since similar testicular effects are observed in a second species (dog). Rats are normally fecund. The lack of effects on other reproductive parameters in rats is not necessarily an indication that tubular atrophy in the testes would not be a problem in other species. Since no data are available to indicate how the testicular effects occur, whether or not they can be considered an endocrine effect (effects are observed in other endocrine organs in 3 species), or whether or not they can be considered adverse, the testicular effects were selected to provide a conservative approach for assessment of risk to humans.

5

Chronic RfD =	0.6 mg/kg/day(NOAEL) / 100 (UF) = **0.006 mg/kg/day**

2.4 Occupational/Residential Exposure

2.4.1 Incidental Oral Exposure (Short- and Intermediate-Term)

Study Selected: 2-Generation Reproduction Study in the Rat § 870.3800

MRID No.: 44718707

Executive Summary: See chronic dietary endpoint

Dose and Endpoint for Risk Assessment: 0.6 mg/kg/day based on increased incidence and severity of tubular atrophy in the testes on the F_1 generation males observed at 1.8 mg/kg/day.

Comments about Study/Endpoint:. Although there are no indications of effects on other reproductive parameters (i.e. mating, gestation, fertility and viability) in the rat reproduction study, there are uncertainties regarding the testicular effects, especially since similar testicular effects are observed in a second species (dog). Rats are normally fecund. The lack of effects on other reproductive parameters in rats is not necessarily an indication that tubular atrophy in the testes would not be a problem in other species. Since no data are available to indicate how the testicular effects occur, how much exposure will induce the effects, whether or not they can be considered an endocrine effect (effects are observed in other endocrine organs in 3 species), or whether or not they can be considered adverse, the testicular effects were selected to provide a conservative approach for assessment of risk to humans. In addition, the effects are considered to be appropriate for all exposure durations.

2.4.2 Dermal Absorption

Proposed Studies: In vivo dermal absorption of two formulated products containing Thiamethoxam and an In vivo dermal absorption study in the rat using technical thiamethoxam

MRID No.: 45200001 and 44703403

Executive Summaries:

Study Number 1: Potential dermal absorption of thiamethoxam in two end-use formulations was investigated in an in vivo rat study. The test material was applied as Helix 289 FS at two dose levels, a low dose (3.64 ug/cm^2) and a high dose (36.4 ug/cm^2). Adage 5FS was applied at a high dose only (36.4 ug/cm^2). Following a 10-hour exposure, the application site was washed and subgroups of 4 animals were sacrificed at various time points post-dosing. As a goal of the study was to characterize the fate of skin site

residues, groups of animals were sacrificed at 10 hr, 24 hr, 72 hr, 168 hr and 336 hrs post-dosing. Urine and feces were collected daily.

Following dermal application, the majority of the administered dose was recovered from the skin wash. The percent of applied dose accounted for by skin washes and rinse of the dose site appliance ranged from 63.16 to 75.7%. Significant quantities were also present at the application site after washing(i.e., 18.3 to 28.38%). Skin site residues did not decline significantly over the 336 hour postdosing period. The majority of the absorbed dose was present in the urine (0.60-3.36%), with smaller quantities present in the feces (0.01-0.36%), blood (0.0032 - 0.032%), cage wash (0.02-0.2%) and carcass (0.042-0.47%). For the Helix low dose group (3.4 ug/cm^2), percent dermal absorption (excluding residues retained at the skin site) increased with increasing time post-dosing. After 10 hr, dermal absorption was 1.27%. This value increased to 1.42% at 24 hr; 1.48% at 72 hr; 1.91% at 168 hr and 4.22% at 336 hr postponing. For the Helix high dose group (36.4 ug/cm^2), there was a general trend of increasing percent dermal absorption (excluding residues retained at the skin site), with increasing time post-dosing. After 10 hr, dermal absorption was 1.21%. This value was 1.03% at 24 hr; 1.24% at 72 hr; 2.47% at 168 hr and 2.14% at 336 hr postponing. For the Adage high dose group (36.4 ug/cm^2), percent dermal absorption (excluding residues retained at the skin site) increased with increasing time post-dosing. After 10 hr, dermal absorption was 0.83%. This value increased to 1.53% at 24 hr; 2.54% at 72 hr; 2.52% at 168 hr and 3.51% at 336 hr postponing. Although continued absorption of skin site residues may occur beyond 336 hr, this is expected to be limited due to the demonstrated slow loss of residues from the skin site and the extent of epidermal exfoliation which typically occurs over a 2-3 week period in mammals. As such, use of a dermal absorption value of 5% in cancer and noncancer occupational risk assessments is considered to adequately account for the small amount of continued absorption from the skin site. A study limitation was that numerous rats appeared to access the dose site, particularly in the latter part of the study, and this made interpretation of the results for these animals difficult. (These animals were therefore not included in calculations of percent dermal absorption.)

Study # 2: Groups of 12 rats (Tif:RAIf(SPF)) were administered thiamethoxam as a dispersible granular formulation at each of three dose levels: 2.5, 25.3, and 242 μg ai/cm^2. The application site was subject to a wash after 6 hr. Groups of 4 animals at each dose level were sacrificed after 6, 24, or 48 hours. Urine and feces were collected at 0-6 hr, 6-24 hr, and 24-48 hr intervals. Blood samples were taken at 0.5, 1, 2, 4, 6, 8, 24, and 48 hrs, and whole blood and plasma were collected from each animal after sacrifice. Skin wash, the application apparatus (0-ring + permeable tape), treated skin site, residual carcass, and untreated skin were also collected for analysis. Neither expired air or individual tissues were collected for analysis. Mean total recovery of radioactivity ranged from 95.11 to 99.74% of the applied dose. The majority of radioactivity was recovery from the skin wash. Mean radioactivity in the skin test site ranged from 3.76 to 24.33%; in urine from 0.13 to 2.61%; and in the feces from 'not detectable' to 0.14%. Mean radioactivity in whole blood did not exceed 0.02% and in the carcass did not exceed

7

0.72%. Estimates of dermal absorption were based on the sum of radioactivity in skin test site, urine, feces, blood, and carcass. After 6 hr, dermal absorption was 20.39%, 27.05 and 5.27% at the low, middle and high dose respectively. After 24 hr, dermal absorption was 21.28, 22.30 and 4.55% at the low, middle and high dose respectively. After 48 hr, dermal absorption was 19.62, 23.79 4.52% at the low, middle and high dose respectively.

Percentage (%) Dermal Absorption: 27.0 (rounded off from 27.05, highest mean dermal absorption value across all groups: the 6 hour time point at 25 $\mu g/cm^2$). This value is considered to represent the potential cumulative dermal absorption of test material that might occur after a 10 hour dermal exposure.

Comments about Dermal Absorption: As the study design (i.e., longest collection period was 48 hr) did not permit analysis of the fate of skin bound residues, residues at skin site were included in determination of dermal absorption. Given the uncertainty regarding actual deposition ($\mu g/cm^2$) of thiamethoxam under field conditions, and the differences in the test formulation and the proposed end-use formulation (i.e., formulation type, active ingredient composition, formulant composition differences) it was considered appropriate to use a conservative estimate of dermal absorption (i.e., 27%).

	Absorbed			Treated Skin		
	2.5	25	242 ug/cm^2	2.5	25	242 ug/cm^2
6hrs	0.44	2.72	0.71	19.95	24.33	4.56
24hrs*	1.52	1.63	0.59	19.76	20.67	3.96
48hrs*	1.31	2.87	0.76	18.31	20.92	3.76

*6 hour wash

Dermal Absorption Factor: 5%. This value represents the maximum amount absorbed for all dose groups for either formulation tested in the most recent study (MRID 45200001) rounded up from 4.22%, the value obtained at 336 hr postponing. This study supports the previously conducted dermal absorption study (MRID 44703403) which had to be repeated due to numerous deficiencies. A conservative dermal absorption value of 27% was estimated from the first study; however, this value included residues at the skin site, which could theoretically be further absorbed over a longer period of time than 48 hours, the longest time measurement for that study. Residues at the skin site in the repeat study were also in the 18-28% range; however, they did not need to be included in the estimated dermal absorption value because measurements were taken out to 336 hours postdosing. Thus, the amount that could potentially be absorbed over a longer period of time was actually measured in the repeat study. The percent residue remaining in the skin and the percent absorbed between the two studies are comparable. Given the more detailed presentation of the data in the new study, the Committee was able to determine that the percent absorbed was the more appropriate value for risk assessment for thiamethoxam, and that the body burden at any given time will not be increased due to residues remaining in the skin at the site of treatment.

8

2.4.3 Dermal Exposure (All Durations)

Study Selected: 2-Generation Reproduction Study in the Rat § 870.3800

MRID No.: 44718707

Executive Summary: See chronic dietary endpoint

Dose and Endpoint for Risk Assessment: 0.6 mg/kg/day based on increased incidence and severity of tubular atrophy in the testes on the F_1 generation males observed at 1.8 mg/kg/day.

Comments about Study/Endpoint: A 21-day dermal toxicity study in rats is available. The Committee, however, selected a reproductive NOAEL because: 1) although there are no indications of effects on other reproductive parameters (i.e. mating, gestation, fertility and viability) in the rat reproduction study, there are uncertainties regarding the testicular effects, especially since similar testicular effects are observed in a second species (dog). Rats are normally fecund. The lack of effects on other reproductive parameters in rats is not necessarily an indication that tubular atrophy in the testes would not be a problem in other species. Since no data are available to indicate how the testicular effects occur, how much exposure will induce the effects, whether or not they can be considered an endocrine effect (effects are observed in other endocrine organs in 3 species), or whether or not they can be considered adverse, the testicular effects were selected to provide a conservative approach for assessment of risk to humans. For these reasons, the effects are considered to be appropriate for all exposure durations; 2) the reproductive parameters are not evaluated in the dermal toxicity study and thus the consequences of these effects cannot be ascertained for the dermal route of exposure.

Since an oral NOAEL was selected a dermal absorption factor of 5% should be used for this dermal risk assessment.

2.4.4 Inhalation Exposure (All Durations)

Study Selected: 2-Generation Reproduction Study in the Rat § 870.3800

MRID No.: 44718707

Executive Summary: See chronic dietary endpoint

Dose/Endpoint for Risk Assessment: 0.6 mg/kg/day based on increased incidence and severity of tubular atrophy in the testes on the F_1 generation males observed at 1.8 mg/kg/day.

9

Comments about Study/Endpoint: Other than acute toxicity, no inhalation studies are available. Therefore, the reproductive endpoint is selected for inhalation exposure. Although there are no indications of effects on other reproductive parameters (i.e. mating, gestation, fertility and viability) in the rat reproduction study, there are uncertainties regarding the testicular effects, especially since similar testicular effects are observed in a second species (dog). Rats are normally fecund. The lack of effects on other reproductive parameters in rats is not necessarily an indication that tubular atrophy in the testes would not be a problem in other species. Since no data are available to indicate how the testicular effects occur, how much exposure will induce the effects, whether or not they can be considered an endocrine effect (effects are observed in other endocrine organs in 3 species), or whether or not they can be considered adverse, the testicular effects were selected to provide a conservative approach for assessment of risk to humans. In addition, the effects are considered to be appropriate for all exposure durations.

Since an oral NOAEL was selected an inhalation absorption factor of 100% should be used for this inhalation risk assessment.

2.4.5 Margins of Exposure for Occupational/Residential Risk Assessments

A Margin of Exposure (MOE) of 100 is adequate for dermal and inhalation occupational exposure risk assessments. The MOEs for residential exposure risk assessment will be determined by the FQPA Safety Factor Committee.

2.5 Recommendation for Aggregate Exposure Risk Assessments

The dermal and inhalation exposures are converted to an oral equivalent dose by adjusting for percent dermal and inhalation absorption. The dietary oral exposures from food and water are then added to the oral equivalent doses for dermal and inhalation exposure, and compared to the oral NOAEL to calculate aggregate risk.

3 CLASSIFICATION OF CARCINOGENIC POTENTIAL

3.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No.: 44718707

Executive Summary: In a combined chronic toxicity and oncogenicity study, CGA 293343, 98.6% a.i. was administered to 80 Tif: RAIf (SPF) Sprague-Dawley rats/sex/dose in the diet at dose levels of 0, 10, 30, 500 or 1500 ppm (0, 0.41, 1.29, 21.0 or 63.0 mg/kg bw/day) in males and 0, 10, 30, 1000 or 3000 ppm (0, 0.48, 1.56, 50.3 or 155 mg/kg bw/day) in females for 24 months. The animals were divided into 4 groups per dose level, with 50/sex/group used in the main chronic toxicity and oncogenicity study, 10/sex/group for hematology, clinical chemistry and urinalysis, 10/sex/group for hematology and 10/sex/group for interim sacrifice at 12 months. Treatment with CGA 293343 had no

10

effect on appearance and behaviour, mortality, food consumption, ophthalmology, hematology, clinical chemistry and urinalysis. Body weight gain was reduced in high-dose females during the first half of the study and water consumption was slightly increased in high-dose males. At the interim sacrifice, there were no differences observed in organ weights and gross pathology between control and treated animals. Microscopic kidney lesions were observed in males treated at 500 ppm and above. Increased incidence of lymphocytic infiltration of the renal pelvis was observed in high-dose males and a slight increase in the severity of hemosiderosis of the spleen was observed in high-dose females. At terminal sacrifice, there were no toxicologically significant changes in organ weights or gross pathology. Microscopic examination revealed increased incidence of foci of cellular alteration in the livers and chronic tubular lesions in the kidneys of high-dose females, and lymphocytic infiltration in the kidneys and chronic nephropathy in high-dose males. There was no evidence of treatment-related neoplasia in male or female rats. Dosing was considered adequate based on the observed reduction in body weight gain among high-dose females. **The LOAEL for systemic toxicity was 1500 ppm in males, equal to 63 mg/kg bw/day**, based on histopathologic changes in the kidneys. **The NOAEL in males was 500 ppm, equal to 21 mg/kg bw/day**, based on the presence of regenerative kidney lesions at interim sacrifice that were not observed at terminal sacrifice. **The LOAEL for systemic toxicity was 3000 ppm in females, equal to 155 mg/kg bw/day**, based on the observed reduction in body weight gain and the incidence of foci of cellular alteration in the livers and chronic tubular lesions in the kidneys. **The NOAEL in females was 1000 ppm, equal to 50 mg/kg bw/day.**

Discussion of Tumor Data: There was no evidence of treatment-related neoplasia in male or female rats; however, foci of alteration were seen in high-dose females. If these animals had been tested at higher dose levels, tumors may have been induced.

Adequacy of the Dose Levels Tested: Dosing was considered adequate in the context of the review, based on the observed reduction in body weight gain among high-dose females and the increase in incidence of chronic nephropathy in males. However, when considered in comparison with the mouse study, the dose levels selected for this study may not be adequate. The Registrant states that the tumor response in the mouse is species specific. Among the data provided to support this position was a statistical correlation of parameters most closely associated with development of hepatocellular adenoma and/or carcinoma in the mouse. This statistical analysis identifies the following parameters as most significantly correlated to liver tumor development:

- treatment level
- pigmented cells
- foci of cellular alteration
- hypertrophy
- inflammatory cell infilatration
- necrosis
- adenoma (as determinant for carcinoma).

The chronic rat study was not dosed as high as the mouse study. Evidence from the short-term studies in the rat indicate hepatocellular hypertrophy at higher dose levels. The chronic study was not tested in that range either. When rats were exposed to higher doses of thiamethoxam, as used in short-term studies, liver toxicity was observed in both sexes. The observations included clinical pathology (increased AST, AlkP, GGT, cholesterol, triglyceride), increased absolute and relative liver weights, hepatocellular hypertrophy, inflammatory cell infiltration, hepatocellular degeneration and Kupffer cell pigmentation. These observations seem to indicate that if higher doses were used in the rat chronic toxicity and oncogenicity study, liver pathology would occur. This is apparent from the liver histopathology among high-dose females, in which an increase in the incidence of foci of cellular alteration was observed in females receiving 155 mg/kg bw/day. The assertion that the oncogenic response is species-specific is not supported by the data. The most important consideration in this context is the dose level selection in the rat chronic toxicity and oncogenicity study. High-dose males were treated at daily doses that were lower than the LOAEL's for liver toxicity in the short-term studies, and proliferative, pre-neoplastic lesions were observed in high-dose females.

3.2 Carcinogenicity Study in Mice

MRID No. 44703326

Executive Summary: In a carcinogenicity study, CGA 293343 technical, 98.6% was administered to 60 mice/sex/dose in the diet, at dose levels of 0, 5, 20, 500, 1250 or 2500 ppm (0, 0.65/0.89, 2.63/3.68, 63.8/87.6, 162/215 or 354/479 mg/kg bw/day in males/females, respectively) for 78 weeks. An additional 10 mice/sex in the control and high dose were used for interim sacrifice after 9 months of treatment. Treatment with CGA 293343 had no effect on survival or appearance and behaviour, with the exception of a slight increase in the incidence of distended abdomen in the top two dose groups. This was usually associated with adverse liver pathology. Decreased body weight gain was observed in high-dose males and females with no effect on food consumption. There was no effect on hematological parameters. Increased absolute and relative liver weights were observed in males and females of the top two dose groups. In females, relative liver weight was also increased at 500 ppm. Changes in the morphology and histology of the liver of treated animals were observed at doses of 500 ppm and above, and included hepatocyte hypertrophy, single cell necrosis, inflammatory cell infiltration, pigment deposition, foci of cellular alteration, hyperplasia of Kupffer cells and increased mitotic activity. The incidence of hepatocellular adenoma was increased in males and females at 500 ppm and above, and the incidence of hepatocellular adenocarcinoma was increased in both sexes at 2500 ppm. There was no difference in latency of tumour formation nor in the lethality of observed tumours between control and treated groups, however there was an increase in the number of animals with multiple tumours. **The systemic LOAEL is 500 ppm, equal to 63.8 and 87.6 mg/kg bw/day in males and females, respectively**, based on increased incidence of microscopic pathology observations in the liver at 500 ppm and

above in both sexes. **The systemic NOAEL is 20 ppm, equal to 2.63 and 3.68 mg/kg bw/day in males and females, respectively**. Dosing was considered adequate based on the observed reduction in body weight gain in high-dose males and females.

Discussion of Tumor Data: There was an increase in the incidence of hepatocellular adenoma in both sexes at 500 ppm and above and an increase in the incidence of hepatocellular adenocarcinoma in females at 1250 ppm and in both sexes at 2500 ppm, the highest dose tested. There was neither a difference in latency of tumour formation nor a difference in the lethality of observed tumours between control and treated groups; however, there was an increase in the number of animals with multiple tumours. It is noted that there was no departure point between the nonneoplastic effects in the liver and the neoplastic lesions. They were both increased at the same dose.

Adequacy of the Dose Levels Tested: Dosing was considered adequate based on the observed reduction in body weight gain in high-dose males and females.

3.3 **Classification of Carcinogenic Potential**: The HIARC recommended that the carcinogenic potential of THIAMETHOXAM be assessed by the Cancer Assessment Review Committee. This recommendation is based on the increase in hepatocellular adenoma and adenocarcinoma in male and female mice.

4 MUTAGENICITY

In a reverse gene mutation assay in bacteria, strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 of *S. typhimurium* and *E. coli* WP2 uvrA were exposed to thiamethoxam (98.6%) at concentrations of 312.5, 625, 1250, 2500 or 5000 μg/plate in the presence and absence of mammalian metabolic activation (rat-liver post mitochondrial supernatant (S9)). CGA 293343 tech. was tested up to a limit concentration of 5000 μg/plate. There was no increase in the number of revertants at any of the concentrations tested, in the presence and absence of exogenous metabolic activation. Normal background growth was observed in all strains and at all concentrations. There was no evidence of cytotoxicity. The positive controls induced the appropriate responses in the corresponding strains. **There was no evidence of induced mutant colonies over background.**

In a reverse gene mutation assay in bacteria, strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 of *S. typhimurium* were exposed to thiamethoxam (98.6%) at concentrations of 312.5, 625, 1250, 2500 or 5000 μg/plate in the presence of mammalian metabolic activation (mouse-liver post mitochondrial supernatant (S9)). A series of six experiments were conducted, using different induction systems to generate the S9 fraction: non-induced mouse liver, Aroclor 1254 induced mouse liver, or thiamethoxam induced mouse liver, following dietary administration of thiamethoxam for 14 days at concentrations of 50, 500 or 2500 ppm. A range-finding cytotoxicity assay was not conducted. In the mutagenicity assays, CGA 293343 tech. was tested

up to a limit concentration of 5000 μg/plate. There was no increase in the number of revertants at any of the concentrations tested, in the presence of any of the exogenous metabolic activation systems. Normal background growth was observed in all strains, at all concentrations, and using all of the different activation systems. The positive controls induced the appropriate responses in the corresponding strains. **There was no evidence of induced mutant colonies over background.**

In a mammalian cell gene mutation assay at the HGPRT locus, Chinese Hamster V79 cells cultured *in vitro* were exposed to CGA 293343 tech., (98.6% a.i.), in dimethylsulfoxide at concentrations of 123.3, 370, 1110 or 3330 μg/ml in the presence of mammalian metabolic activation (post mitochondrial S9, derived from Aroclor 1254 induced rat liver) and 61.7, 185, 555 or 1665 μg/ml in the absence of mammalian metabolic activation. CGA 293343 was tested up to the solubility limit concentrations of 3333.30 μg/ml. In the presence and absence of metabolic activation, no significant increase in mutant frequency was observed at any concentration of CGA 293343 in either the original or the confirmatory mutagenicity assay. The positive controls induced the appropriate response. **There was no evidence of induced mutant colonies over background.**

In a mammalian cell cytogenetics assay, CHO cell cultures were exposed to CGA 293343 tech. in dimethylsulfoxide at concentrations of 0, 283.75, 567.5 and 1135 μg/ml (original experiment) or 0, 1135, 1702.5 and 2270 μg/ml (confirmatory experiment) for a 21 hour treatment time and 0, 851.25, 1135 and 1702.5 μg/ml for a 45 hour treatment time in the absence of metabolic activation and at concentrations of 0, 1135, 2270 and 4540 μg/ml (original experiment) or 0, 2270, 3405 and 4540 μg/ml (confirmatory experiment) for a 3 hour treatment time with 18 hour recovery and 0, 2270, 3405 and 4540 μg/ml for a 3 hour treatment with 42 hour recovery in the presence of metabolic activation. CGA 293343 tech. was tested up to cytotoxic or solubility limit concentrations. Positive controls induced the appropriate response, demonstrating that the test system is capable of detecting substances known to induce chromosomal aberrations. **There was no evidence of chromosome aberrations induced over background.**

In an *in vivo* mouse bone marrow micronucleus assay, groups of Tif: MAGf[SPF] mice, 5/sex/dose/sacrifice time were treated by oral gavage with CGA 293343 (98.6% a.i.) at doses of 0, 312.5, 625, 1000 (all males and 16-hour females) and 1250 (24- and 48-hour females) mg/kg bw. An additional 3 rats per sex were assigned to the high-dose group as reserve animals. Bone marrow cells were harvested at 16, 24 and 48 hours post-treatment. The vehicle was bidistilled water. A positive control group of 5 males and 5 females received a single oral dose (64 mg/kg bw) of cyclophosphamide and were sacrificed 24 hours later. Slides were prepared from harvested bone marrow, and were evaluated for the presence of micronucleated polychromatic erythrocytes (MPCEs) as well as for possible target cell cytotoxicity (a significant decrease in the ratio of PCEs to total erythrocytes). In the 1250 mg/kg bw group, 7/13 females were found dead within 5 hours post-treatment. All remaining animals survived the study period. Reduced locomotor activity was noted for 3/5 males and 1/5 females in the 625 mg/kg bw group, and for 10/18 males and 1/5 females in the 1000 mg/kg bw group. The only other clinical finding was ataxia, noted in 2/18

males and 1/5 females in the 1000 mg/kg bw group. There was no evidence of target cell cytotoxicity. The positive control induced significant increases in MPCEs, in the absence of target cell cytotoxicity. **There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow for males or females after any CGA 293343 treatment time, and so is therefore not considered to be a clastogenic agent.**

In an unscheduled DNA synthesis assay, primary rat hepatocyte cultures were exposed to CGA 293343 tech., (98.6% a.i.), in dimethylsulfoxide at concentrations of 0, 13.01, 52.04, 208.13, 416.25, 832.5 or 1665 μg/ml for 16-18 hours. CGA 293343 tech. was tested up to precipitating concentrations. The positive controls induced the appropriate response. **There was no evidence that unscheduled DNA synthesis was induced, as determined by radioactive tracer procedures (nuclear silver grain counts).**

5 FQPA CONSIDERATIONS

5.1 **Adequacy of the Data Base**: The database is adequate for FQPA considerations. The following acceptable studies are available:

-- Acute mammalian neurotoxicity study
-- Developmental toxicity studies in rats & rabbits
-- Two-generation reproduction study

The subchronic mammalian neurotoxicity study was not tested at sufficiently high dose levels for an adequate negative study. A new study is not required at this time because no neuropathology was observed at the dose levels tested and the weight of the evidence from the other toxicity studies indicates that there is no reason for concern.

5.2 **Neurotoxicity**: Two mammalian neurotoxicity studies are available, an acute neurotoxicity study and a 90-day neurotoxicity study, both conducted with the rat. In the acute neurotoxicity study, thiamethoxam was administered by oral gavage at dose levels of 0, 100, 500 or 1500 mg/kg bw. No treatment-related effects were observed in the 100 mg/kg bw group. In the 500 mg/kg bw group, drooped palpebral closure, lower rectal temperature, increased forelimb grip strength (males only) and decreased locomotor activity were observed 2-3 hours after dosing. In the 1500 mg/kg bw group, additional findings at this time period included abnormal body tone, ptosis, impaired respiration, tremors, longer latency to first step in the open field, crouched-over posture, gait impairment, hypo-arousal, decreased number of rears, uncoordinated landing during the righting reflex test, slight lacrimation (females only) and higher mean average input stimulus value in the auditory startle response test (males only). These effects were no longer evident at the 1 week and 2 week post-dosing examinations. In addition to these findings, 3 females were found dead within the first 2 days after treatment. There were no treatment-related histopathological findings noted in the central or peripheral nervous

system at any dose level tested. Based on the results of this study, **the NOAEL for acute neurotoxicity is 100 mg/kg bw, and the LOAEL is 500 mg/kg bw.**

In a 90-day neurotoxicity study, thiamethoxam was administered in the diet at dose levels of 0, 0.7, 1.9, 31.8 or 95.4 mg/kg bw/day for males and 0, 0.7, 2.1, 73.2 or 216.4 mg/kg bw/day for females. There were no treatment-related systemic or neurotoxicological effects observed at any dose level tested. In addition, no treatment-related histopathological findings were noted in the central or peripheral nervous system. **A LOAEL for neurotoxicological and systemic effects was not established. The NOAEL for males is 95.4 mg/kg bw/day and for females is 216.4 mg/kg bw/day.**

Evidence of neurotoxicity from other oral studies: In the 28-day dog study (2/sex/dose) there was a decrease in absolute but not relative brain weight in females at 43 mg/kg/day. This does not appear in either the 90-day study (up to 50 mg/kg/day) or the chronic dog study (up to 45 mg/kg/day). In the mouse oncogenicity study there was an increase in relative brain weight in high dose males which was attributed to reduction in body weight gain. In the rat chronic/oncogenicity study, there was a slight increase in incidence of brain deformation in high dose males. Microscopically, this was associated with hydrocephalus and pressure atrophy which was secondary to pituitary adenoma. Malignant astrocytomas were present in the top two doses in males; however, the frequencies were similar to historical controls. In the range-finding developmental rabbit study, tonic spasms, hunched posture, hypoactivity were observed prior to death at 500 mg/kg/day (all had died on test). In the rat developmental study, hypoactivity, piloerection were observed at the highest dose tested (750 mg/kg/day). **It is noted that the observed clinical signs occurred at very high dose levels, in most cases prior to death; the brain deformations were due to the pituitary adenomas squeezing the brain; and the astrocytomas were within the historical control range.**

5.3 Developmental Toxicity

In a developmental toxicity study CGA 293343, purity 98.6%, was administered to 24 pregnant Tif: RAI f (SPF) rats/dose by oral gavage at dose levels of 0, 5, 30, 200 and 750 mg/kg bw/day from days 6 through 15 of gestation. Maternal body weight gain was lower in the 200 mg/kg bw/day group, and there was a net loss in body weight in the 750 mg/kg bw/day group during the first half of the dosing period, and final body weight was lower in the 750 mg/kg bw/day group. In addition, slightly lower corrected final body weight, lower corrected body weight gain, and decreased food consumption during the dosing period were noted in the 200 and 750 mg/kg bw/day groups. The only other treatment-related maternal findings were general clinical signs of toxicity observed in the 750 mg/kg bw/day group during the dosing period, i.e., hypoactivity, piloerection and regurgitation of test material. **The maternal LOAEL is 200 mg/kg bw/day, based on lower body weight, lower body weight gain and decreased food consumption. The maternal NOAEL is 30 mg/kg bw/day.** Developmental effects were characterized as lower fetal

body weight and an increased incidence of skeletal anomalies in the 750 mg/kg bw/day group. In addition, an increased incidence of skeletal variations was noted in the 200 and 750 mg/kg bw/day groups. However, these transient, reversible delays in ossification were not considered adverse effects, but were regarded to be secondary to the maternal toxicity observed at the affected dose levels. There was no evidence of any teratogenic effects related to treatment with CGA 293343 at any dose level tested. **The developmental LOAEL is 750 mg/kg bw/day, based on an increased incidence of skeletal anomalies. The developmental NOAEL is 200 mg/kg bw/day.**

In a developmental toxicity study CGA 293343, purity 98.6%, was administered to pregnant Russian, Chbb:HM rabbits 19 per dose by oral gavage at dose levels of 0, 5, 15, 50 and 150 mg/kg bw/day from days 7 through 19 of gestation. Treatment-related maternal findings in the 150 mg/kg bw/day group were a net loss in body weight and lower food intake during the dosing period, slightly lower final body weight, 3 unscheduled deaths, hemorrhagic uterine contents and hemorrhagic discharge in the perineal area. In the 50 mg/kg bw/day group, the only treatment-related finding was slightly lower food consumption during the dosing period, which was not considered to be toxicologically significant. **The maternal LOAEL is 150 mg/kg bw/day, based on maternal deaths, hemorrhagic uterine contents and hemorrhagic discharge, decreased body weight and food intake during the dosing period. The maternal NOAEL is 50 mg/kg bw/day.** Developmental effects were characterized as lower fetal body weight and an increased incidence of post-implantation loss (due to an increased incidence of total litter resorptions) in the 150 mg/kg bw/day group. A slight increase in the fetal or litter incidence of a few skeletal anomalies/variations were considered to possibly reflect a marginal, treatment-related effect, but were not considered adverse findings. There was no evidence of any teratogenic effects related to treatment with CGA 293343. **The developmental LOAEL is 150 mg/kg bw/day, based on decreased fetal body weights, increased incidence of post-implantation loss and a slight increase in the incidence of a few skeletal anomalies/variations. The developmental NOAEL is 50 mg/kg bw/day.**

5.4 Reproductive Toxicity

In a 2-generation reproduction study, CGA 293343, purity 98.6%, was administered to 30 Tif: RAI f (SPF) rats/sex/dose in the diet at concentrations of 0, 10, 30, 1000 and 2500 ppm (equal to 0, 0.61, 1.84, 61.25 and 158.32 mg/kg bw/day for males, and 0, 0.80, 2.37, 79.20 and 202.06 mg/kg bw/day for females). Each female in each generation was mated to produce two litters. For the parental animals, body weight gain was slightly lower in the 2500 ppm group during the first 6 weeks of the study, F_0 and F_1 generations, males only. However, the effect was marginal and was not considered to be toxicologically significant. Decreased testis weight was observed in the F_1 generation at 2500 ppm, and increased incidence and severity of tubular atrophy was observed in the testes in the F_1 generation at 30 ppm and above. Sperm motility was decreased in all treatment groups in both generations, however, there was no dose-response relationship, there was high variability among all groups and there were no treatment-related effects on sperm count or

sperm morphology. A separate, complementary study was conducted to investigate this finding. On the basis of the special investigation, it was concluded that the initial findings were likely due to technical error and not related to treatment with CGA 293343. The supplemental information was limited to analysis of F_0 animals, hence no information relevant to the findings in F_1 animals is available. Increased incidence of hyaline changes was observed in the renal tubules for F_0 and F_1 males in the 1000 and 2500 ppm groups, and an increased incidence of renal tubular casts was noted for F_0 males in the 1000 ppm group, and F_0 and F_1 males in the 2500 ppm group. Hyaline change in renal tubules was also observed in one F_1 female at 2500 ppm. A slight increase in food consumption was observed in F_1 females during gestation with the F_{1a} and F_{1b} litters, but this was not considered to be toxicologically significant. For offspring, body weight gain was lower in the 2500 ppm group during the lactation period in the F_{1a}, F_{1b}, F_{2a} and F_{2b} litters, both sexes, resulting in lower body weights on days 7, 14 and/or 21 postpartum. Slightly lower body weight gain and body weights (days 7, 14 and/or 21 postpartum) were also noted in the 1000 ppm group for F_{2a} and F_{2b} females. However, the effect was marginal (≤8% lower than the control group values), F_{1a} and F_{1b} pups were not affected and males were not affected, and so this finding was not considered to be toxicologically significant. **In males, the reproductive toxicity LOAEL is 30 ppm (1.8 mg/kg bw/day) based on increased incidence and severity of tubular atrophy observed in testes of the F_1 generation; the NOAEL is 10 ppm (0.6 mg/kg bw/day).** There were no adverse, treatment-related effects on reproductive parameters (mating, gestation, fertility, viability) noted at any dose level tested, **therefore, the NOAEL for reproductive toxicity in females is 2500 ppm (202 mg/kg bw/day). For parental systemic toxicity, the LOAEL for males is 1000 ppm (61 mg/kg bw/day), based on increased incidence of hyaline change in renal tubules in F_0 and F_1 animals. The NOAEL is 30 ppm (1.8 mg/kg bw/day). The NOAEL for females is 2500 ppm (202 mg/kg bw/day, the highest dose tested) based on a slight increase in food consumption for F_1 females during gestation with the F_{1a} and F_{1b} litters which was not considered to be toxicologically significant. For offspring toxicity, the LOAEL is 2500 ppm (158 mg/kg bw/day for males, and 202 mg/kg bw/day for females) based on reduced body weight gain during the lactation period in all litters. The NOAEL is 1000 ppm (61 mg/kg bw/day in males and 79 mg/kg bw/day in females).**

5.5 Additional Information from Literature Sources (*if available*)

No additional information is available from the literature.

5.6 Determination of Susceptibility

There is no quantitative or qualitative evidence of increased susceptibility of rats or rabbit fetuses to in utero exposure to thiamethoxam in the developmental toxicity studies. The developmental NOAELs are either higher than or equal to the maternal NOAELs. The toxicological effects in fetuses do not appear to be any more severe than those in the dams or does.

In the rat reproduction study there are no toxicological effects in the dams, whereas for the pups, reduced bodyweights are observed at the highest dose level, starting on day 14 of lactation. This translates to an overall decrease in bodyweight gain during the entire lactation period. Prior to day 14, pups are beginning to eat as well as continuing to nurse. Therefore, their exposure to thiamethoxam is much higher than usual. Since this is the case, although the NOAEL for this effect (61/79 mg/kg/day for ♂/♀) is lower than the NOAEL for the dams (202 mg/kg/day), the decrease in bodyweight gain for pups during the lactation period is not considered to be a susceptibility issue. On the other hand, reproductive effects in males appear in the F_1 generation in the form of increased incidence and severity of testicular tubular atrophy. The increase in severity is based on an increased incidence of grade 2 minute focal tubular changes (grade 1 is defined as minimal and grade 2 is defined as slight). The incidences of minute focal tubular changes were as follows: 12/30, 13/30, 17/30, 19/30 and 18/30 in the control, 0.6, 1.8, 61, and 158 mg/kg/day dose groups, respectively. These animals were exposed to the test material in utero whereas the F_0 males, which did not have these effects, were not exposed to the test material in utero. Therefore, since no data are available to indicate how the testicular effects occur, whether or not they can be considered an endocrine effect (effects are observed in other endocrine organs in 3 species), or whether or not they can be considered adverse, **the HIARC has determined that there is suggestive evidence of increased quantitative susceptibility for male pups (NOAEL: 0.6 mg/kg/day for increased incidence of testicular tubular atrophy at 1.8 mg/kg/day) when compared to the parents (NOAEL: 1.8 mg/kg/day for hyaline changes in renal tubules at 61 mg/kg/day).**

5.7 Recommendation for a Developmental Neurotoxicity Study

Based on the following weight-of-the-evidence considerations, the HIARC **recommended** a developmental neurotoxicity study in rats for THIAMETHOXAM.

5.7.1 Evidence that suggest requiring a Developmental Neurotoxicity study:

- Effects on endocrine organs were observed across species. These include fatty change of the adrenal cortex, hypertrophy of thyroid follicular epithelium, hepatocellular hypertrophy, and atrophy of seminiferous tubules in rats; ovarian atrophy and a slight, transient increase in adrenal weight in mice; and evidence of delayed maturation in the ovaries, reduced spermatogenesis with minimal to moderate occurrence of spermatic giant cells in the testes, and atrophy of the seminiferous tubules in dogs.

- There was a significant decrease in alanine amino transferase levels in the companion animal studies and in the dog studies. These are suggestive of either depression of the co-factor, pyridoxal phosphate that is necessary for ALT activity or that there is, by some undisclosed mechanism, a suppression of ALT synthesis. Since pyridoxal phosphate is an active form of pyridoxine (Vitamin B6), any effects that decrease its function or cell concentrations may result in serious adverse developmental effects.

- Thiamethoxam interferes with the nicotinic acetyl choline receptors of the insect's nervous system. Since the mode of action of this insecticide on insects is through a neurologic mechanism, there is concern for developmental neurotoxicity in humans. Therefore, a developmental neurotoxicity study is needed to characterize any potential neuro- and/or developmental neurotoxicity.

- There were transient clinical signs of neurotoxicity in the acute oral, the acute mammalian neurotoxicity study, the rat developmental study (dams), and the range-finding developmental toxicity study in the rabbit (does, only prior to death), all at dose levels of 500 mg/kg or greater.

- There is suggestive evidence of increased quantitative susceptibility in the rat reproduction study along with a concern for the testicular effects observed in this study.

5.7.2 Evidence that **do not** support a need for a Developmental Neurotoxicity study:

- Under the conditions of the toxicological studies conducted on this chemical, including the acute and subchronic mammalian neurotoxicity studies, there are no indications of treatment-related histopathological findings in either the central or peripheral nervous system.

- The reproductive effects observed in rats and dogs are already characterized in existing studies. These particular effects do not indicate that this chemical is likely to be a developmental neurotoxicant.

- No malformations of the central nervous system were observed in the developmental and reproduction studies.

- No clinical signs of neurotoxicity were observed in the pups in the 2-generation reproduction study.

6 HAZARD CHARACTERIZATION

The toxicology database for thiamethoxam is complete and there are no data gaps. The scientific quality is relatively high and the toxicity profile of thiamethoxam can be characterized for all effects, including potential developmental, reproductive and neurotoxic effects. The data indicate increased quantitative susceptibility following postnatal exposure for both male and female pups and following prenatal exposure for male pups when compared to the parents in the rat reproduction study. Reduced bodyweight gains were observed in male and female pups during the lactation period at dose levels in which there was no toxicity in dams; and testicular tubular atrophy was observed in F_1 males which had been exposed in utero, but not in the F_0 males (the parents of the F_1 males) which had not been exposed in utero. The F_0 males had kidney changes at a higher dose level.

Technical thiamethoxam is slightly acutely toxic to rats and moderately toxic to mice via the oral route and of low toxicity to rats via the dermal and inhalation routes of exposure. It is classified as Toxicity Category III in the acute oral and dermal studies and Category IV in the acute inhalation study. It is not irritating to the skin and minimally irritating to the eye. It is not a dermal sensitizer by the method of Magnusson and Kligman.

The database on thiamethoxam indicates 4 primary targets for this chemical: the liver, kidney, hematopoietic system, and testes. In addition, effects on the thyroid (rats and dogs) and the adrenal gland (rats) are seen in the short-term studies as well as significant decreases in alanine aminotransferase (ALT) in the dog and companion animal studies. The **liver** effects occur across species, sexes and routes of administration. In the rat, inflammatory cell infiltration and necrosis of single hepatocytes are observed in the 28-day dermal study and hepatocellular hypertrophy and lymphohistiocytic infiltration of the liver are observed in the subchronic oral studies. Chronic oral exposure induces an increase in the incidence of foci of cellular alteration in females. In the mouse, hepatocellular hypertrophy, necrosis of single hepatocytes, and lymphocytic infiltration (subchronic and chronic); apoptosis, induction of microsomal enzymes, and Kupffer cell pigmentation (subchronic); and Kupffer cell hyperplasia, increased incidence of foci of cellular alteration and increased mitotic activity (chronic) are observed. Males are more sensitive to the liver pathology than females. Chronic dosing also results in the development of benign and malignant liver tumours in both sexes. An increase in the number of animals with multiple tumours is also observed; however, treatment does not affect the latency to tumour formation nor lethality of the observed tumours. The incidence of non-neoplastic and neoplastic pathology is increased at the same dose level, i.e., there is no clear departure point between doses that induce tumours and other systemic toxic effects. In both rats and mice, there appears to be increasing severity of effects with increasing dose. In rats, the lowest dose in which an effect is observed in the liver does not appear to significantly decrease with increasing length of exposure to the test material. Due to dose spacing, one cannot tell whether or not this is the case in mice. Mice appear to be the most sensitive species, with induction of hepatocellular hypertrophy at dose levels as low as 14 mg/kg/day in the subchronic feeding study.

The **kidney** effects occur in both sexes of the rat but are found primarily in the male rat. They are observed following either oral or dermal exposure. The majority of the kidney effects (hyaline

2 /

changes in the renal tubules)are attributed to accumulation of α-2-u globulin, a protein which is unique to male rats, in the proximal convoluted tubules. While the observed pathology is consistent with α-2-u globulin mediated kidney toxicity, no data were provided to confirm that thiamethoxam or its metabolite(s) bind to α-2-u globulin, nor was the protein identified in the lesions of the affected animals. In addition, the same lesion (eosinophilic droplets within the cytoplasm of the proximal convoluted tubules) is observed in one high-dose female in the F1 generation of the 2-generation rat reproductive toxicity study. In the short-term studies, the following treatment-related kidney effects are observed in males: dilated renal pelvis, focal calcification of the renal cortex, pelvic dilatation with epithelial hyperplasia, renal cyst, lymphohistiocytic infiltration, acute tubular lesions, cast formation, and tubular basophilic proliferation. In addition, an increase in the incidence and severity of chronic tubular lesions are found in both sexes and increase in severity of nephrocalcinosis is observed in females. In the chronic feeding study, lymphocytic infiltration of the renal pelvis, chronic tubular lesions, and basophilic proliferation of renal tubules are observed in males at the interim sacrifice. At the terminal sacrifice, the incidences lymphocytic infiltration in the kidneys of males, chronic nephropathy in males, and chronic tubular lesions in the kidneys of females appear to be treatment-related. The kidney effects are observed at lower doses in the oral studies when compared to the dermal study. The dermal study revealed systemic effects that were consistent with those observed in dietary studies; however, females are more sensitive than males. The hyaline change in renal tubules is only observed in high-dose males, and liver and kidney toxicity are observed in both mid- and high-dose females. Based on the available data, it appears that the hyaline changes occur only in the subchronic and reproduction studies and the incidence and severity are dose-related. The incidences and severity of the other kidney effects are also generally dose-related, however, in a few cases, the dose-response is variable. In the short-term studies the incidence of hyaline change dropped at the highest dose levels. It was proposed that this is due to excessive liver toxicity preventing the production of α-2-u globulin.

Hematological effects are observed in the rat, dog and mouse with the dog being the most sensitive species. Both sexes appear to be affected; although the male appears to be more affected in the rodent and the female more affected in the dog. In the rat, increased spleen weights, increases in the incidence and severity of hemosiderosis and/or extramedullary hematopoiesis are observed in both the subchronic and chronic studies. In the mouse, a slight reduction in erythrocytes, hemoglobin and hematocrit, accompanied by increased mean corpuscular volume mean corpuscular hemoglobin are observed in the subchronic feeding study at very high dose levels. In the dog, leukopenia and slight microcytic anemia are observed in the subchronic oral study.

Testicular effects are observed in the rat and dog. They consist of decreased testes weights and increased incidence and severity of seminiferous tubular atrophy at low dose levels in the rat; decreased testes weights associated with microscopic evidence of reduction in spermatogenesis and occurrence of spermatic giant cells in the testes at toxic dose levels in the subchronic dog study; and atrophy of the seminiferous tubules at minimally to moderately toxic dose levels in the chronic dog study. The effects in the rat are only observed in the F_1 males in the two-generation reproduction study and are not observed at any other time. Although the dose-response for both the incidence and severity of total "minute focal tubular change" (12/30, 13/30, 17/30, 19/30,

18/30 for incidences and 1.3, 1.2, 1.5, 1.6, 1.6 for severity) and the incidence of grade 2 minute focal change (4/30 ,3/30, 9/30, 11/30, 11/30) are somewhat flat for the 3 dose levels which are elevated, the incidences of the grade 2 lesions are well above both the concurrent and historical controls. In addition, although there is no dose-response for the incidence of "diffuse tubular atrophy" at the middle2 and high dose levels (7/30 and 3/30, respectively, versus 0/30 in the control group), there is somewhat of a dose-response for mean severity (0.0, 3.0, 2.0, 3.6, 3.7). The incidence in the middle2 dose group is above the historical control range and the incidence in the high dose group is at the upper limit of the historical control range. These are the effects that are driving the toxicological endpoint selection for risk assessment because they are observed at very low dose levels. It is anticipated that they may be observed after either intermediate-term or chronic exposure, particularly when exposure occurs in utero. Based on the observations in the dog studies, it is possible that in utero may not be a prerequisite; however, it is likely that the level of exposure would have to be higher.

Thyroid effects in the rat (thyroid follicular cell hypertrophy) and dog (increase in thyroid weight) may be due to induction of microsomal enzymes in the liver, which in turn affect the hypothalmus-pituitary-thyroid-liver homeostatic process for regulation of thyroid hormones. Evidence of this is the presence of hepatocellular hypertrophy in several species. The **adrenal** effects observed in the subchronic rat studies generally consist of fatty change and inflammatory cell infiltration of the adrenal cortex.

ALTlevels are significantly decreased in the dog and companion animal studies. Although there is no proven toxicological significance to this effect, there is concern because these decreases are suggestive of either depression of the co-factor, pyridoxal phosphate that is necessary for ALT activity or there is suppression of ALT synthesis.

Carcinogenicity: Thiamethoxam induces hepatocellular adenomas and carcinomas in male and female Tif:MAGf (SPF) mice. It has been referred to the HED Cancer Peer Review SARC. Supplementary studies investigating the effects of treatment on hepatic cell proliferation in rats and mice and biochemical parameters in mouse liver provide some evidence that the carcinogenic mode of action may be via a non-genotoxic, threshold mechanism, however information gaps exist. There is no information on the reversibility of the observed findings upon cessation of treatment. Under the conditions of the assays, thiamethoxam does not induce gene mutations or in vivo or in vitro chromosomal aberrations, and it does not induce unscheduled DNA synthesis.

Potential Endocrine Effects: A number of parameters are affected in various species following treatment with thiamethoxam for varying durations, that raise the question of possible interaction with endocrine systems. The specific findings in rats include increased plasma cholesterol, hepatocellular hypertrophy, increased adrenal weights, fatty change of the adrenal cortex and hypertrophy of thyroid follicular epithelium. In the 2-generation reproductive toxicity study, decreased testis weights and increased incidence of atrophy of seminiferous tubules are observed in the F_1 generation. Equivocal results in sperm motility were subsequently investigated in a separate, complementary study which was restricted to assessment of sperm parameters in F_0 animals, hence no information is available regarding this observation in F_1 animals. In mice, high doses cause decreased ovary weight and ovarian atrophy in the 90-day study and a slight,

transient increase in adrenal weight in females at interim sacrifice in the oncogenicity study. In dogs, decreased mean testis and ovary weight are observed in the 90-day study, at a dose that results in significant body weight loss, necessitating cessation of treatment for 7 days and resumption at a lower dose. These organ weight changes are accompanied by histopathological evidence of delayed maturation in the ovaries and reduced spermatogenesis with minimal to moderate occurrence of spermatic giant cells in the testes. Atrophy of the seminiferous tubules is the key observation in the establishment of the NOAEL in the 1-year dog study.

7 DATA GAPS

There are no toxicological data gaps for thiamethoxam.

8 ACUTE TOXICITY

Acute Toxicity Profile of Thiamethoxam

GDLN	Study Type	MRID	Results	Tox Category
870.11	Acute Oral - rat	44703314	LD_{50}: 1563 mg/kg (♂+♀)	III
870.12	Acute Dermal	44703316	LD_{50} > 2000 mg/kg (♂+♀)	III
870.13	Acute Inhalation	44703317	LC_{50} > 3.72 mg/L (♂+♀)	IV
870.24	Primary Eye Irritation	44703318	PIS = 10 at 1 hr PIS = 0 at 24 hr Minimally irritating	IV
870.25	Primary Skin Irritation	44703319	PIS = 0	IV
870.26	Dermal Sensitization	44710401	Is not a sensitizer using method of Magnusson and Kligman	N/A

9 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (General Population including Infants & Children)	NOAEL= 100 UF = 100	Drooped palpebral closure, lower rectal temperature, increased forelimb grip strength, decreased locomotor activity at 500 mg/kg	Acute neurotoxicity - rat
	Acute RfD = 1 mg/kg		
Chronic Dietary	NOAEL = 0.6 UF = 100	Increased incidence and severity of tubular atrophy in testes	2-Generation reproduction study - rat
		Chronic RfD = 0.006 mg/kg/day	
Oral Nondietary (All Durations)	NOAEL = 0.6	Increased incidence and severity of tubular atrophy in testes	2-Generation reproduction study - rat
Dermal (All Durations)[a]	NOAEL = 0.6	Increased incidence and severity of tubular atrophy in testes	2-Generation reproduction study - rat
Inhalation (All Durations)[a]	NOAEL = 0.6	Increased incidence and severity of tubular atrophy in testes	2-Generation reproduction study - rat

[a]Appropriate route-to-route extrapolation should be performed for these risk assessments. Exposure values using absorption factors of (5%) for dermal and 100% for inhalation (default value) should be converted to equivalent oral doses and compared to the oral NOAEL.