



Risk Assessment Process of Amitraz on Environment and Human Health

Corresponding Author:

Ms. Mohammadali Ziaei Madbuni,
PhD Student of Entomology, Vali-e-Asr University Of Rafsanjan - Iran (Islamic Republic of)

Submitting Author:

Ms. Mohammadali Ziaei Madbuni,
PhD Student of Entomology, Vali-e-Asr University Of Rafsanjan - Iran (Islamic Republic of)

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Author(s): Ziaei Madbuni M, Amini M

Abstract

Amitraz is the common name for N'-(2,4-dimethylphenyl)-N-[[[(2,4-dimethylphenyl) imino] methyl]-N-methylmethanimidamide. Amitraz is a triazapentadiene compound, a member of the amidine chemical family. It is an insecticide and acaricide used to control red spider mites, leaf miners, scale insects, and aphids. On cotton it is used to control bollworms, white fly, and leaf worms. On animals it is used to control ticks, mites, lice and other animal pests. The EPA classifies Amitraz as Class III - slightly toxic. Amitraz is slightly toxic to mammals if ingested orally. The dose of Amitraz that is lethal to half of the test animals that ingest it is called the median lethal dose, or the LD₅₀. The oral LD₅₀ is 523- 800 mg/kg for amitraz in rats. The oral LD₅₀ is greater than 1,600 mg/kg for mice. Dermal exposure results in an LD₅₀ of greater than 1,600 mg/kg for rats and greater than 200 mg/kg for rabbits. The Lethal Concentration 50 or LC₅₀ is the concentration of the chemical in air or water that kills half of the experimental animals exposed to it. The inhalation LC₅₀ (6 hours) of amitraz for rats is 65 mg/l of air. Amitraz is not a skin irritant and does not sensitize skin. At high doses, amitraz can reduce the function of the hypothalamus, which helps regulate the metabolism by controlling hormone release in the body. A daily dose of 200 mg of amitraz per kilogram of body weight for ten weeks causes decreased growth and food consumption.

Introduction

Hundreds of chemicals are capable of inducing cancer in humans or animals after prolonged or excessive exposure. There are many well-known examples of chemicals that can cause cancer in humans. Chemically-induced cancer generally develops many years after exposure to a toxic agent (1). Developmental toxicants are agents that cause adverse effects on the developing child. Effects can include birth defects, low birth weight, biological dysfunctions, or psychological or behavioral deficits that become manifest as the child grows (2). Amitraz is registered for use on pears, cattle, hogs, and cotton (3). It is not permitted on apples to prevent its residues

in processed apples or meat producing animals which consume apple processing waste (4). Amitraz was a restricted use pesticide in 1985 because some studies showed it causes cancer in mice. But re-evaluation of the evidence has led to the current classification of Amitraz as an unrestricted or General Use Pesticide (GUP) (5). Amitraz is available in an emulsifiable concentrate, wettable powder, or a pour-on powder (6). The highest dose of amitraz which has no observable effect on the death of unborn rats (fetotoxic NOEL) is 3 mg/kg/day. The highest dose of amitraz that does not cause an observable effect in the death of rat embryos (Embryotoxic NOEL) is 5 mg/kg/day (7). However, an EPA study indicates that the highest dose at which amitraz has no observable effect on test rats' offspring (teratogenic NOEL) is 12 mg/kg/day (7). The teratogenic NOEL of rabbits is 25 mg/kg/day (8). These studies indicate that high doses of amitraz exposure during pregnancy produced adverse effects in laboratory animals. Likely human exposures are very much less than those which produced effects, and these effects are unlikely in humans under normal circumstances. A variety of tests indicate that amitraz is not mutagenic and does not cause damage to DNA (9). Amitraz is broken down rapidly in soil containing oxygen. The half- life in soil, the amount of time needed for the chemical to degrade to half its original concentration, is less than one day. Degradation occurs more rapidly in acidic soils than in alkaline or neutral soils (10).

This document characterizes the risk associated with dietary and occupational exposure to amitraz, a formamidine compound with insecticidal and acaricidal activity. Amitraz is presently registered by the U.S. EPA (U.S. Environmental Protection Agency) and DPR (Department of Pesticide Regulation) for the control of ticks and lice on cattle and swine, ticks on dogs, and to control pear psylla and mites on pears. Amitraz is also registered by the U.S. EPA for the control of bollworm, tobacco budworm, pink boll worm, whitefly, and mites on cotton. In addition, amitraz has been registered by the U.S. EPA for the control of mites that infect honey bees. While this registration has been voluntarily canceled, existing stocks can still be used.

Review

Risk assessment process

The risk assessment process incorporates four aspects: hazard identification, dose response evaluation, exposure assessment, and risk characterization. Hazard identification entails review and evaluation of the toxicological properties of each pesticide. The dose-response assessment then considers the toxicological properties and estimates the amount that could potentially cause an adverse effect (11). The amount that will not result in an observable or measurable effect is the No-Observed-Effect Level (NOEL). A basic premise of toxicology is that at a high enough dose, virtually all substances will cause toxic manifestations (12). Chemicals are often referred to as "dangerous" or "safe", as though these concepts were absolutes. In reality, these terms describe chemicals that require low or high dosages, respectively, to cause toxic effects (13). Toxicological activity is determined in a battery of experimental studies that define the types of toxic effects that can be caused, and the exposure levels (doses) at which effects may be seen. State and federal testing requirements mandate that substances be tested in laboratory animals at doses high enough to produce toxic effects, even if such testing involves chemical levels many times higher than those to which people might be exposed (14). In addition to the intrinsic toxicological activity of the pesticide, the other parameters critical to determining risk potentials are the level, frequency and duration of exposure. The purpose of the exposure evaluation is to determine the potential amount of the pesticide likely to be delivered through occupational, or dietary routes on an acute or chronic basis. The risk characterization then integrates the toxic effects observed in the laboratory studies, conducted with high dosages of pesticide, to potential human exposures to low dosages of pesticides in the diet or work place (15). The potential for possible nononcogenic adverse health effects in human populations is generally expressed as the margin of safety, which is the ratio of the dosage that produced no effects in laboratory studies to the estimated dietary and work related dosage. For oncogenic effects, the probability of risk is calculated as the product of the cancer potency of the pesticide and the estimated human dosage (16).

Toxicology

Central nervous system (CNS) effects in humans have been detected within hours of amitraz exposure. The effects seen in humans included paleness, dry mouth,

drowsiness, disorientation, light headed feeling, slurred speech, and loss of consciousness. The acute no observed effect level (NOEL) used in this risk assessment was 0.125 mg/kg and was based on the indicated CNS response in humans. Toxic effects associated with sub-chronic exposure were indicated in a variety of studies. The most prevalent effects included decreased body weight changes and CNS depression. The toxic effects of chronic exposure to amitraz included CNS depression (specific signs not reported), depressed growth rate, a reduction in food intake, hyperplastic nodules, and hyperkeratosis of the forestomach. The "CNS" effects were considered a response to acute exposure as they were observed 3 hours after dosing (17). On the basis of hyperplastic nodules in females and hyperkeratosis of the forestomach in males (in B6C3F1 mice), a LOEL of 2.3 mg/kg/day was established for chronic toxicity. An estimated NOEL of 0.23 mg/kg/day for non-oncogenic effects was calculated using a default procedure of dividing the LOEL by an uncertainty factor of 10 (18). Chronic exposure to amitraz has also been associated with oncogenicity. An increase in lymphoreticular, liver, and lung tumors in CFLP mice has been reported. Hepatocellular tumors have also been associated with exposure to amitraz in B6C3F1 mice (19). Animal studies have indicated that amitraz is a potential reproductive toxicant while developmental effects were considered minor. Genotoxic potential was indicated for 2,4-dimethylaniline (an amitraz metabolite) in bacteria (Ames test) and mammalian cells grown *in vitro* (L5178Y mouse lymphoma assay) while amitraz exhibited mutagenic potential only in the mouse lymphoma assay. In the mouse dominant lethal assay, one study produced positive results while the other resulted in negative data. For all other tests, amitraz was considered negative for genotoxic potential (20).

1. Acute toxicity

Clinical signs associated with acute exposure of laboratory animals to amitraz included: central nervous system depression, ataxia, ptosis, emesis, labored respiration, muscular weakness, tremors, hypothermia and bradycardia. Clinical signs or symptoms reported in humans treated with amitraz included: paleness, dry mouth, drowsiness, slurred speech, disorientation, and loss of consciousness. These effects were observed following a single oral dose of 0.25 mg/kg. An acute NOEL of 0.125 mg/kg was established from human data (21).

a) Animal Studies

The LD50's (the dose required to cause death in 50% of the exposed population) ranged from 100 to greater than 1,600 mg/kg. On the basis of lethality after oral

exposure, the most sensitive animals were dogs and baboons. These animals were at least 4 times more sensitive than rats, mice, and guinea pigs (22).

b) Human Studies

The acute toxicologic effects of amitraz in humans have been reported in a urinary excretion study by Campbell and Needham (1984) (also see pharmacokinetics). A single oral dose (0.25 mg/kg) of ¹⁴C-amitraz was given to two male human volunteers. Approximately 90 minutes after dosing, one subject was pale and complained of a dry mouth, drowsiness, and disorientation. Ten minutes later the subject lost consciousness. The subject was "rousable" but was not fully conscious for 6 hours. Approximately 160 minutes after dosing, the second subject complained of a dry mouth, and a light headed feeling. He also exhibited slurred speech (23). The NOEL established by this study was 0.125 mg/kg. The acute NOEL used for this risk assessment was obtained from the two human metabolism studies (see Hazard ID Section for additional discussion of the studies). On the basis of the observed clinical signs (i.e., paleness, dry mouth, drowsiness, slurred speech, disorientation, and loss of consciousness), the NOEL for acute exposure to amitraz was assumed to be 0.125 mg/kg (highest non effective dose tested) (24).

2. Sub – chronic toxicity

At high doses (e.g., 200 mg/kg/day), effects included, dermal erythema, dermal desquamation, subcutaneous hemorrhage, diarrhea, lethargy, emaciation, weight loss, squealing, and death. At low doses (e.g., at or near 3 mg/kg/day) the most prevalent clinical effect was a decrease in body weight gain. On the basis of CNS depression and catarrhal conjunctivitis reported in an oral study in dogs, a NOEL of 0.25 mg/kg/day was established for sub-chronic exposure to amitraz (20).

3. Chronic toxicity and oncogenicity

Reported toxic effects included central nervous system depression, depressed growth rate, and reduction in food intake. On the basis of the time of onset, the central nervous system effects were considered acute. For chronic toxicity, a LOEL of 2.3 mg/kg/day was established based on liver hyperplastic nodules in females, and hyperkeratosis of the forestomach of male mice. An estimated NOEL of 0.23 mg/kg/day was calculated using a default procedure of dividing the LOEL of 2.3 mg/kg/day by an uncertainty factor of 10 (18). No significant induction of tumors was reported in rats. In CFLP mice, an increase in lymphoreticular and lung tumors was detected in females, while liver tumors were detected in both males and females. Only

the lymphoreticular tumors, however, were significant at the 0.05 level. In B6C3F1 mice, a significant increase in liver tumors was detected in females, while a significant increase in lung tumors was detected in males (25).

4. Genotoxicity

a) Gene Mutation

Bacteria

Amitraz was tested for mutagenic potential in the *Salmonella typhimurium* gene mutation assay (Ames test) with tester strains TA98, TA100, TA1535, TA1537 and TA1538. The test was conducted both in the presence and absence of metabolic activation (mouse liver). The test was conducted with half log concentrations ranging from 33.3 µg/plate to 10 mg/plate amitraz in acetone. Concentrations at or exceeding 333 µg/plate resulted in precipitation. An increase in the number of revertants (when compared to concurrent acetone controls) was indicated in tester strain TA1538, both in the presence and absence of metabolic activation. An increase was also detected in tester strain TA100 in the presence of metabolic activation. These increases in mutagenicity were not, however, reproducible in subsequent tests. DPR considered the study acceptable as a FIFRA guideline study (26). Additional studies were conducted to evaluate the mutagenic potential of amitraz in *Salmonella* and *E. Coli* (27-29). No mutagenic potential was indicated for amitraz in any of these studies, however, due to inadequate documentation and or supporting data, DPR did not consider any of the studies acceptable under FIFRA guidelines. In the Zimmer, et al. study, 2,4- dimethylaniline (an amitraz metabolite), was considered positive for mutation induction. Amitraz was reported to be negative for mutation induction in the Host Mediated Assay (30-31). Both of these reports had insufficient documentation to support findings. DPR did not consider these studies acceptable under FIFRA guidelines.

Mammalian Cells

Authors reported an increase in mutation when 2,4- dimethylaniline, a metabolite of amitraz, was tested in the mouse lymphoma L5178Y (thymidine kinase) assay. Test article concentrations included 1, 3.3, 10, 33.3, 100, 200, 300, 333.3, 400, 500 and 600 µg/ml. A dose related increase in mutation frequency was detected in the presence of S-9 (mouse liver metabolic activation mixture). DPR considered this study acceptable under FIFRA guidelines (32). Other investigation also tested amitraz in the L5178Y mammalian cell mutation assay. The test was

performed 4 times in the presence and absence of metabolic activation (Aroclor 1254 induced mouse liver S-9). Test concentrations ranged from 0.06 to 33 μ g/ml (33). The study authors concluded that amitraz was not positive for mutation induction in the mouse lymphoma assay. After close evaluation of the data, however, a negative (non-mutagenic) conclusion could not be supported. In assay number 1, no evidence of mutagenic activity was noted. In assay numbers 2 and 3, mutagenic activity was indicated (i.e., in the presence and absence of metabolic activation, both an increase in mutation frequency (greater than 2-fold) and a corresponding increase in absolute mutant number were observed). In assay number 4, in the presence of metabolic activation, an increase in mutation frequency was noted, however, a corresponding increase in absolute mutant number was not detected. DPR considered the study acceptable under FIFRA guidelines (32-33). On the basis of the reported findings, the mutagenic potential of amitraz in the mouse lymphoma assay can not be discounted. This is supported by the mutagenic potential indicated by the amitraz metabolite, 2,4-dimethylaniline in the mouse lymphoma assay in the presence of metabolic activation (34).

b) Structural Chromosomal Aberration

In Vivo cytogenetics

An amitraz metabolite (2,4-dimethylaniline) was tested for genotoxic activity in the mouse micronucleus test. The test article was administered, by gavage, to groups of male CD-1 mice at 0, 56.3, 112.5 or 225 mg/kg. No increases in micronuclei were reported; however, the study had a number of deficiencies that inhibited interpretation. These deficiencies included a lack of female data, no dose justification, a lack of appropriate sampling times, and the lack of scoring criteria. DPR did not consider the study acceptable under FIFRA guidelines (35).

In Vitro cytogenetics

Thongsinthusak, et al., (1991) reported on the ability of amitraz to induce chromosomal aberrations in cultured human lymphocytes. For this test, cultured human lymphocytes, stimulated to divide by the addition of phytohemagglutinin, were exposed to amitraz both in the presence and absence of a rat S-9 metabolic activation mixture. Dosages included 0, 5, 10, and 20 μ g/ml in the absence of metabolic activation, and 0, 3, 15, and 30 μ g/ml in the presence of activation. Twenty-two hours after treatment with the test article, mitotic activity was arrested by the addition of colchicine. Cells were processed for scoring and examined for chromosomal damage. No evidence of

an increase in chromosomal aberrations was reported. DPR considered the study acceptable under FIFRA guidelines (34).

c) Other Genotoxic Effects

DNA Damage

Mehler et al. (1990) tested amitraz for potential to induce unscheduled DNA synthesis (UDS). Amitraz was tested in human embryonic lung fibroblasts for UDS induction at dosages that ranged from 0 to 300 μ g/ml. The initial DPR review of this study concluded that the study was acceptable as a FIFRA guideline study. Net nuclear grain counts, however, were not reported (i.e., nuclear grain counts were not corrected for cytoplasmic grain counts) (36). Oshita et. al, (1988) used the alkaline elution assay to test amitraz and several of its metabolites for DNA damage potential. The metabolites tested included: N-(2,4-dimethylphenyl)-N'-methylformamidine (U-40,481); 2,4-dimethylformanilide (U-36,893); 2,4-dimethylaniline (U-54,915A); and 4-amino-3-methylbenoxic acid (U-54,914). Under the conditions of this study, no significant increase in single strand breaks was reported following exposure to amitraz or the examined metabolites (37). Due to a number of deficiencies, however, the study was considered unacceptable. The deficiencies included incomplete documentation of procedures and no indication of test article purity. DPR considered the study unacceptable under FIFRA guidelines.

Morphological Cell Transformation

The amitraz metabolite 2,4-dimethylaniline was tested for its ability to induce morphological transformation in C3H/10T $\frac{1}{2}$ mouse embryo fibroblasts (38). The assay was performed both in the presence and absence of a mouse liver metabolic activation mixture (S-9). Concentrations tested included 0, 5, 10, and 20 μ g/ml in of presence of S-9, and 0, 100, 200, and 400 μ g/ml in the absence of S-9. From this study, it was concluded that 2,4-dimethylaniline does not induce morphological cell transformation in C3H/10T $\frac{1}{2}$ cells. DPR considered the study acceptable under FIFRA guidelines. Amitraz was tested for its ability to induce morphological transformation in C3H/10T $\frac{1}{2}$ mouse embryo fibroblasts (39). The assay was performed both in the presence and absence of a mouse liver metabolic activation mixture (S-9). Concentrations tested included 0, 12.5, 25, and 37.5 μ g/ml in of presence of S-9, and 0, 5, 10, and 15 μ g/ml in the absence of S-9. Amitraz did not induce morphological transformation in this test. DPR considered the study acceptable under FIFRA guidelines.

Exposure

Exposure scenarios considered in this risk assessment included dietary and occupational exposures (both separately and combined). Absorbed dosage estimates were made for acute, seasonal, annual, and lifetime exposures. For occupational exposure, the absorbed daily dosage (ADD) estimates for amitraz exposure ranged from 0.5 to 46.7 mg/kg/day (40). For seasonal exposure (60 days for pears, 120 days for cotton, and 365 days for livestock), the average daily dosage (SADD) estimates for amitraz exposure ranged from 0.3 to 22.1 mg/kg/day (41). The annual average daily dosage (AADD) estimates for amitraz exposure ranged from 0.01 to 3.64 mg/kg/day (42). On the basis of the 95th percentile of user-day exposures for the population subgroups examined, the potential acute dietary exposure of amitraz, from pears, meat, milk, cotton seed, eggs, poultry and honey ranged from 0.4 to 2.3 µg/kg/day (42-43). The population sub-group with the largest potential dosage (2.3 µg/kg/day) was "non-nursing infants less than 1 year of age". The potential acute dietary exposure of amitraz, from only pears ranged from 1.4 to 15.3 µg/kg/day. The absorbed daily dosage (ADD) estimates for amitraz exposure ranged from 5.5 to 51.7 mg/kg/day (44). For seasonal exposure, the combined seasonal average daily dosage (SADD) estimates for amitraz exposure ranged from 0.2 to 22.3 mg/kg/day. The combined annual average daily dosage (AADD) estimates for amitraz exposure ranged from 0.23 to 3.86 mg/kg/day (45). The combined life-time average daily dosage (LADD) estimates for amitraz exposure ranged from 0.23 to 2.16 mg/kg/day. The job classification with the highest potential exposure each time period was pear harvesters (43).

Risk characterization

On the basis of the indicated effects and estimated dosages, margins of safety, defined as the ratio of NOEL to the absorbed dose, were calculated for both occupational and dietary exposures to amitraz. In general, a margin of safety equal to or greater than 10 is considered adequate for the protection of human health when it is based on NOELs from human studies. When exposure is based on NOELs from non-human mammalian studies, an additional factor of 10 is generally used (i.e., MOS of 100). For amitraz, margins of safety for acute exposure were based on human data. Margins of safety for seasonal, annual, and lifetime exposures, however, were based on NOELs from non-human mammalian data (i.e., a dog study for seasonal and a mouse study for annual and life-time exposures). For occupational exposure, margins of safety for acute exposures to amitraz

ranged from 3 to 7 for mixer/loader/applicators in pear orchards (5), pear harvesters (3), mixer/loaders involved with the aerial treatment of cotton (4), pilots (7) and flaggers (4). For all other job classifications evaluated, margins of safety for acute exposure to amitraz were greater than 10 (17). For seasonal exposures, the calculated margin of safety for pear harvesters was 11. For all other job classifications evaluated, margins of safety for seasonal exposure to amitraz were at least 100. For chronic (annual) exposures, the calculated margin of safety for pear harvesters was 63. For all other job classifications evaluated, margins of safety for annual exposure to amitraz were greater than 100. For chronic (life-time) exposures, non-oncogenic margins of safety were all greater than 100 (17-18). For dietary exposure, the margin of safety for acute exposure to amitraz was 8 for children ages 1 to 6. For all other population subgroups, margins of safety were greater than 10. For combined (occupational and dietary) exposure, margins of safety for acute exposures to amitraz were ranged from 2 to 8 for mixer/loader/applicators in pear orchards (4), pear harvesters (2), mixer/loader/applicators involved with the ground treatment of cotton (8) mixer/loaders involved with the aerial treatment of cotton (3), pilots (6) and flaggers (4) (17).

Environmental fate

The environmental fate studies evaluated in this risk assessment indicate that amitraz is unstable under both light and dark conditions. Hydrolysis appears to be more of a degradation factor than photolysis, and breakdown of the parent compound is pH sensitive. Microbial and chemical degradation is rapid with a half-life of approximately 8 minutes. Other studies have shown that amitraz is rapidly metabolized in plants and does have the potential to leach in various soil types (46).

1. Hydrolysis/Photolysis

Amitraz is unstable in aqueous solutions under both light and dark conditions. Chemical degradation has been attributed primarily to hydrolysis rather than photolysis (47). Additionally, the rate of hydrolysis and the resulting degradation products were greatly affected by the pH. In basic solutions (pH 9.2) the primary hydrolysis product was 2,4-dimethylphenyl formamide (BTS 27-919) with smaller amounts of N'-(2,4-dimethylphenyl)-Nmethyl formamidine (BTS 27-271). As the pH decreased, the proportion of BTS 27-271 to BTS 27-919 increased and the rate of hydrolysis increased (46-47).

2. Microbial Degradation

Amitraz degradation was studied in several sandy-loam and loam soils under aerobic, anaerobic, and sterile conditions (48). Only small quantities of amitraz and its metabolites were extractable after the first study day. Extractable metabolites from soils exposed to aerobic and anaerobic conditions were primarily composed of BTS 27-271 with smaller quantities of BTS 27-919, and trace amounts of 2,4-dimethylaniline (BTS 24-868) and the parent compound. Under sterile conditions the major degradation products were BTS 27-919 and BTS 27-271. The half-life for amitraz on soil under simulated sunlight was 7.7 minutes. Study results suggested that both chemical (hydrolysis) and microbial degradation occurred (48).

3. Mobility (soil, air, water, plants)

Data submitted to the federal and California regulatory agencies indicate that leaching of amitraz may occur in some soil types (49-50). Amitraz was found to be moderately mobile in sandy loam, silt loam, and clay soils, and very mobile in sandy soil.

4. Plant Residues/Metabolism

The metabolism of radio-labeled (¹⁴C) amitraz has been investigated in pears (51). Amitraz was applied to pears at an application rate of 0.06% ai at two test sites. At harvest (either 29 or 61 days after treatment), approximately 48% of the applied radioactivity remained in the fruit (45% in the 29 day samples and 52% in the 61 day samples). The distribution of the recovered radioactivity between the organic soluble, aqueous soluble and fiber bound fractions was 34.8, 22.3, and 42.9% respectively for the 29 day samples. For the 61 day samples the fractions were 33.7, 30.9, and 35.5% for the organic soluble, aqueous soluble and fiber bound fractions, respectively. In the 29 day samples, the primary metabolites were BTS 27-271 (N-(2,4-dimethylphenyl)-N'-methyl-formamidine) and BTS 27-919 (2,4-dimethylformanilide), accounting for 16.4 and 4.7%, respectively for the recovered radioactivity. BTS 24-868 (2,4-dimethylaniline), BTS 28-037 (N,N'-bis-2,4-dimethylphenyl formamidine), and amitraz were present in smaller quantities, accounting for 1.3, 1.2, and 0.5%, respectively of the recovered radioactivity. In the 61 day samples, the primary metabolites were also BTS 27-271 and BTS 27-919, accounting for 11.6 and 5.9%, respectively for the recovered radioactivity. BTS 24-868, BTS 28-037, and amitraz were present in smaller quantities, accounting for 1.1, 1.1, and 1.3%, respectively of the recovered radioactivity. One metabolite, 2,4-dimethylaniline (BTS 24-868) has been associated with pulmonary tumors in female HAM/ICR mice (52) discussed by Rech (1989) (53). Furthermore,

2,4-dimethylaniline was found to express genotoxic potential in the L5178Y mouse lymphoma gene mutation assay (54). Other potential plant metabolites may include compounds, such as dimethylamine, that have been shown to cause liver tumors in mice (55).

Conclusion(s)

The toxicology data base for amitraz has indicated potential adverse effects in human and laboratory animal studies. Effects reported after acute exposure to the pesticide have generally been associated with the central nervous system. Studies have indicated that amitraz is a potential reproductive toxicant while developmental effects were considered minor. Chronic exposure to amitraz has been associated with an increased incidence of oncogenicity in mice. The genotoxicity data base indicates that amitraz and 2-4-dimethylaniline (a primary plant metabolite and an intermediate mammalian metabolite of amitraz) have mutagenic potential. Several occupational activities associated with the agricultural use of amitraz, and one population sub-group potentially exposed to amitraz through the diet, have margins of safety less than the values conventionally considered to be protective of human health. In these cases, mitigation should be considered to reduce potential exposure. Cancer risk estimates for occupational exposures (including dietary) to amitraz through the use on pears, cotton, or livestock, and non-occupational exposures via consumption of commodities treated with amitraz, were between 1 and 12 in 100,000. For dietary exposure only, cancer risk estimates were between 7 and 12 in 1,000,000. An additional assessment of acute risk potential based on U.S. EPA tolerances indicates that margins of safety based on current U.S. EPA set tolerance levels are less than the values conventionally considered to be protective of human health.

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