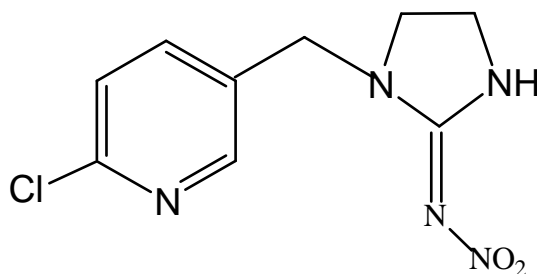


# IMIDACLOPRID

## RISK CHARACTERIZATION DOCUMENT DIETARY AND DRINKING WATER EXPOSURE



 California Environmental Protection Agency  
Department of Pesticide Regulation

February 9, 2006

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**Health Assessment Section  
Medical Toxicology Branch  
Department of Pesticide Regulation  
California Environmental Protection Agency**

**February 9, 2006**

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## LIST OF ABBREVIATIONS

ACh	Acetylcholine
AChE	Acetylcholinesterase
AChR	Acetylcholine receptor
AP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
BEAD	Biological and Economical Analysis Division
BMD	Benchmark Dose
BMR	Benchmark Response
BR	Breathing Rates
CEC	Critical Exposure Commodity Analysis
CK	Creatin Kinase
CNS	Central Nervous System
CSFII	Continuing Survey of Food Intake by Individuals
CYP	Cytochrome P450
DEEM <sup>TM</sup>	Dietary Exposure Evaluation Model
DNT	Developmental Neurotoxicity
DPR	Department of Pesticide Regulation
ED	Effective Dose
ENEL	Estimated No Effect Level
ERK	Extracellular Signal-Regulated Kinase
FDA	Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FOB	Functional Observational Battery
FQPA	Food Quality Protection Act
GD	Gestation Day
GLDH	Glutamate Dehydrogenase
GWSS	Glassy-Winged Sharpshooter
LD <sub>50</sub>	Median Lethal Dose
LC <sub>50</sub>	Median Lethal Concentration
LD	Lactation Day
LED	95% Confidence Limit of the Effective Dose
LOD	Limit of Detection
LOEL	Lowest Observed Effect Level
MAPK	Mitogen-Activated Protein Kinase
MFO	Mixed Function Oxidases
MMAD	Aerodynamic Droplet Size
MOE	Margin of Exposure
MRLs	Maximum Residue Levels
MTD	Maximum Tolerated Dose
nAChR	Nicotinic Acetylcholine Receptor
NCBI	National Center for Biotechnology Information



ND..... Non-Detected Residues, Non-Detects  
NOEL.....No Observed Effect Level  
PCT..... Percent of the Crop Treated  
PDP..... Pesticide Data Program  
PCPA ..... Pesticide Contamination and Prevention Act of 1985  
PND..... Postnatal Day  
ppm..... Part per Million  
ppb ..... Part per Billion  
RAC.....Raw Agricultural Commodity  
RCD.....Risk Characterization Document  
RfD .....Reference Dose  
RPF .....Relative Potency Factor  
SB950.....Birth Defect Prevention Act of 1984  
SCE..... Sister Chromatid Exchange  
SNV.....Specific Numerical Values  
TOPE .....Time to Peak Effect  
USDA.....United States Department of Agriculture  
USEPA..... U.S. Environmental Protection Agency  
WHO ..... World Health Organization

## I. SUMMARY

### I.A. INTRODUCTION

Imidacloprid is a neurotoxic insecticide, which belongs to the class of the neonicotinoid pesticides. Imidacloprid is registered to control insect pests on agricultural and nursery crops, structural pests and parasites on companion animals. This risk assessment addresses the potential human health effects arising from exposure to imidacloprid in the food and drinking water. The exposures from ambient air, occupational activities and residential uses, as well as aggregate exposures from various combined scenarios, will be subsequently addressed in an addendum to this document.

Imidacloprid is an agonist of the nicotinic acetylcholine receptor (nAChR) at the neuronal and neuromuscular junctions in insects and vertebrates. It is structurally and functionally related to nicotine. The toxicity of imidacloprid is largely due to interference of the neurotransmission in the nicotinic cholinergic nervous system. Prolonged activation of the nAChR by imidacloprid causes desensitization and blocking of the receptor, and leads to incoordination, tremors, decreased activity, reduced body temperature and death. Presently, there is no specific antidote, which acts as an antagonist to the effects imidacloprid.

Imidacloprid represents the new generation of neurotoxic insecticides, which exhibit more selective toxicity for insects relative to mammals. Since being introduced in the insecticide market in 1992, the use of imidacloprid has increased yearly. It ranked as one of the top selling pesticides in the world in 2001-2002. For the most part, it is replacing the acetylcholinesterase inhibitors, the organophosphorus compounds and methylcarbamates. Imidacloprid is a Category II acute toxicant, and thus, is classified as a General Use Pesticide. The U.S. Environmental Protection Agency (USEPA) developed for imidacloprid an oral chronic reference dose (RfD) of 0.057 mg/kg/day.

In the environment, the principal routes of dissipation for imidacloprid are aqueous photolysis, microbial degradation and uptake by plants. Imidacloprid is currently listed by the DPR as a potential ground water contaminant, based on its high solubility in water, mobility and persistence in soil. The major degradation product of imidacloprid in the environment is desnitro-imidacloprid.

### I.B. TOXICOLOGICAL PROFILE

**Pharmacokinetics-** Imidacloprid is quickly absorbed by the oral route and rapidly distributed in nearly all organs and tissues. In rats, the oral absorption was estimated as 92-99%. Imidacloprid degrades to a large number of metabolites formed by multiple pathways. The same, or similar metabolites are found in rats, goats and hens. Based on structural considerations, the following metabolites may be of toxicological significance: 6-chloronicotinic acid, imidazolidine 4- and 5-hydroxy compounds, olefinic imidacloprid, desnitro-imidacloprid and the nitrosoimine compound. Metabolites were excreted primarily in the urine as glutathione and glycine conjugates of mercaptotonicotinic acid and hippuric acid. Imidacloprid or its metabolites penetrated the blood-brain barrier. The parent compound and some of its metabolites have been detected in milk, meat of goats and hens, and eggs. Pharmacokinetic studies were not available for a direct determination of the rate of absorption from dermal and inhalation routes.

**Acute Toxicity-** Acute toxicity of imidacloprid was examined via the oral route in rats and mice, and via the inhalation and dermal routes in rats. Mice appeared to be more sensitive to the acute oral toxicity of imidacloprid than rats. In mice, the median oral lethal doses (LD<sub>50</sub>) ranged between 131-168 mg/kg (Category II oral toxicant). Imidacloprid was classified as Category III dermal toxicant, Category IV inhalation toxicant and Category IV eye and skin irritant. An acute (single dose) oral exposure of rats and mice to imidacloprid caused clinical signs characteristic for nicotine intoxication, such as incoordination, tremors, spasms and respiratory difficulties. Other symptoms included decreased motility and lethargy. The same clinical signs were observed in rats following a 4-hour exposure to imidacloprid via the inhalation route.

**Subchronic Toxicity-** Reduction in body weight was the most common toxic effect observed in the subchronic oral and inhalation studies in rats, and in oral studies in mice and dogs. The liver was the principal target organ as demonstrated by the hepatic necrosis or hypertrophy in rats and dogs, elevated activities of serum enzymes, and alteration of clinical chemistry parameters such as triglycerides, cholesterol and the blood clotting time. Additional morphological effects included testicular degeneration in rats and dogs; atrophy of thyroid gland and bone marrow, and advanced involution of the thymus in dogs. Imidacloprid was a potent inducer of the hepatic mixed-function oxidases. Subchronic exposure of dogs to imidacloprid resulted in severe tremors.

**Chronic Toxicity-** Reduction in body weight was the most common toxic effect in the chronic oral studies in rats and mice. The principal morphologic effect was thyroid lesions in rats. Mice developed hypersensitivity to anesthesia after chronic treatment with imidacloprid, suggesting that imidacloprid may reduce the ability of the animals to respond to an additional challenge with xenobiotics.

**Genotoxicity-** Imidacloprid was negative in a battery of genotoxicity tests, including *in vitro* gene mutation tests, *in vivo* chromosomal aberration tests and tests for DNA damage and repair capabilities. In mammalian tests *in vitro*, imidacloprid caused sister chromatid exchange and, at cytotoxic doses, chromosomal aberrations.

**Oncogenicity-** In the chronic toxicity/oncogenicity studies there was not sufficient evidence to indicate that imidacloprid was oncogenic to rats and mice.

**Reproductive Toxicity-** The reported effects of imidacloprid on reproduction included disproportionately high number of male fetuses in rats, lower fetal body weight in rabbits and testicular degeneration in rats and dogs.

**Developmental Toxicity-** The reported imidacloprid-induced developmental effects in rats and rabbits included lower fetal body weight, increased resorptions and skeletal alterations.

**Developmental Neurotoxicity-** Developmental neurotoxicity study (DNT) revealed decreased body weights, reduced motor activity level and changes in dimensions of brain structures (reduction in the thickness of corpus callosum and a decreased width of caudate putamen).

## **I.C. RISK ASSESSMENT**

### **Hazard Identification-**

Acute Toxicity: Two acute oral NOELs (No-Observed-Effect Level) were used to address the acute dietary exposure to imidacloprid. The acute NOEL of 9 mg/kg/day was based on decreases

in motor activity in adult rats. This NOEL was calculated with the Benchmark Dose (BMD) approach. It represented the threshold dose LED<sub>05</sub>, which caused a 5% reduction in the motor activity of rats. The NOEL of 9 mg/kg/day was utilized in estimating the risk for acute dietary exposure to imidacloprid to the general population.

The estimated NOEL for developmental neurotoxicity in rats was 5.5 mg/kg/day, based on significant decreases in the dimensions of brain structures in postnatal day (PND) 11 pups. This NOEL was estimated from the LOEL by applying a 10-fold default factor. The ENEL of 5.5 mg/kg/day was pertinent to acute exposures to imidacloprid in women of childbearing age to protect against fetal exposure

Subchronic Toxicity: The subchronic oral NOEL of 7.3 mg/kg/day was selected to characterize the risk of subchronic oral exposure of humans to imidacloprid. This NOEL was based on morphological changes of the liver and the thyroid gland, and tremors in dogs.

Chronic Toxicity: The chronic NOEL of 5.7 mg/kg/day was based on an increase in incidence and severity of mineralized particles in thyroid gland in rats. This NOEL was employed in estimating the human risk for chronic dietary exposure to imidacloprid.

**Exposure Assessment-** This document pertains only to the assessment of the dietary exposure to imidacloprid. The exposure from ambient air, the occupational exposure and the exposure from residential uses will be addressed subsequently in an addendum to this document.

Dietary and Drinking Water Exposure: The dietary exposure to imidacloprid residues in food and in the drinking water was calculated using the deterministic approach (Point Estimate, Tier 2). The dietary exposure estimates were based primarily on the maximum allowed residue level (tolerance). The DPR presents the acute Point Estimate exposures at the 95<sup>th</sup> and 99<sup>th</sup> percentiles. At the 95<sup>th</sup> exposure percentile, the estimated acute exposures to imidacloprid ranged from 15 µg/kg/day to 51 µg/kg/day. At the 99<sup>th</sup> percentile, the exposures ranged from 23 µg/kg/day to 78 µg/kg/day. At both, the 95<sup>th</sup> and 99<sup>th</sup> percentiles, the population subgroups “Children 1-2 years” and “All Infants” were identified to receive the highest dietary exposure from imidacloprid. The high-end exposure mostly reflected residues at the tolerance. Drinking water did not emerge as a major contributor to the total dietary exposure. The chronic dietary exposures ranged from 1.75 µg/kg/day for Females 13-49 yrs. to 7.41 µg/kg/day for Children 1-2 yrs.

## **I.D. RISK CHARACTERIZATION AND RISK APPRAISAL**

The critical NOELs for characterizing the risk from exposure to imidacloprid were derived from studies with laboratory animals. The potential risk from exposure to imidacloprid was evaluated by comparing the MOE (a quotient of the NOEL and the exposure level) to benchmarks. The benchmark MOE of 100 was generally considered prudent for protection of humans against imidacloprid toxicity.

Dietary Exposure: The acute dietary MOEs ranged from 175 to 614 at the 95<sup>th</sup> percentile, and from 115 to 394 at the 99<sup>th</sup> percentile. The high-end exposure mostly reflected residues at the tolerance. Children 1-2 yrs were identified as the most highly exposed population. The chronic MOEs to imidacloprid were greater than 770 for all of the evaluated population subgroups.

**Risk Appraisal-** The main uncertainties with the toxicity of imidacloprid were associated with (i) the use of animal data to evaluate the toxic effects in humans and (ii) the estimation of the NOEL, when a NOEL could not be established from a study. In this respect, evidence from the DNT study in rats, suggested that imidacloprid may affect the neural development. Significant decreases in the dimensions of brain structures were observed at the dose of 54.7 mg/kg/day at PND 11. However, the NOEL for developmental neurotoxicity could not be determined, because pups from intermediate doses (8–19 mg/kg/day) were not included in the evaluation. Assuming that the LOEL for DNT is 54.7 mg/kg/day, the NOEL could be estimated (ENEL) as low as 5.5 mg/kg/day by applying a 10-fold default factor. The ENEL of 5.5 mg/kg/day might be applicable to repeated exposures to imidacloprid to all population subgroups. Because decreases in brain structures could theoretically result from a single exposure *in utero*, the ENEL of 5.5 mg/kg/day could be used to estimate the risk of acute exposure to imidacloprid in women of childbearing age.

The uncertainties in the dietary exposure assessment were introduced with the use of the tolerance as surrogate for residue concentration. The uncertainties in the risk characterization were associated with the default assumptions for the 10-fold interspecies sensitivity and the 10-fold variation in the sensitivity within the human population. One specific area of uncertainty is the use of toxicity thresholds to calculate the acute and chronic MOEs. The chronic dietary MOEs were estimated based on the chronic NOEL of 5.7 mg/kg/day for thyroid effects in rats. This chronic NOEL is sufficiently close to the ENEL of 5.5 mg/kg/day for decreases in thickness of brain structures, and therefore, would be adequate for protection against the potential effects of imidacloprid on the developing nervous system. The acute MOEs were estimated based on the acute NOEL of 9 mg/kg/day for decreases in motor activity in rats. Using the ENEL of 5.5 mg/kg/day for women of childbearing age to protect against fetal exposure would result in acute MOEs of 366 and 239 at the 95<sup>th</sup> and 99<sup>th</sup> percentiles, respectively.

## **I.E. TOLERANCE ASSESSMENT**

The tolerance assessment was conducted to estimate the point estimate exposure and risk to a single label-approved commodity with imidacloprid residues at the tolerance. The DPR estimates the acute tolerance exposure as the sum of the 95<sup>th</sup> percentile exposure for the commodity of concern at the tolerance and a background exposure for all other commodities. The chronic exposure from total dietary exposures was added as a surrogate for background exposure.

Because of the large number of registered commodities (>270), tolerance assessment was carried out only for foods with (i) significant impact on the dietary exposure (ii) very high USEPA tolerances (i.e., >5 ppm), (iii) major uses in California and (iv) high consumption foods for infants and children. The MOEs were at or above the benchmark of 100 for all of the evaluated population subgroups for all of the analyzed foods. The lowest MOEs were 170, 175 and 196 for Children 1-2 yrs and Infants, who consumed tomato paste, spinach and broccoli with tolerance levels of imidacloprid.

## **I.F. CONCLUSIONS**

This health risk assessment for imidacloprid evaluated the risk to 16 population subgroups from potential residues in food and drinking water. Dietary exposures were estimated under acute and chronic scenarios. The exposure estimates were based primarily on the maximum allowed residue level (tolerance) as surrogate for residue concentration. The critical NOELs were derived from studies with laboratory animals; therefore, a MOE of 100 was used as the benchmark to determine the level of human health protection.

The acute point estimate MOEs ranged from 115 to 614 at the DPR high-end percentiles (95<sup>th</sup> and 99<sup>th</sup>), and thus, were greater than the benchmark MOE of 100. Children 1-2 yrs. and Infants were identified as the most highly exposed population subgroups, with MOEs of 175 and 195 at the 95<sup>th</sup> percentile, and 115 and 128 at the 99<sup>th</sup> percentile. The acute MOEs were estimated based on the acute NOEL of 9 mg/kg/day for decreases in motor activity in rats.

The risk from acute dietary exposure to imidacloprid in women of childbearing age requires further consideration. Evidence from the developmental neurotoxicity study in rats, suggested that imidacloprid may affect the neural development. The estimated NOEL for decreases in dimensions of brain structures was 5.5 mg/kg/day. This ENEL might be pertinent to acute exposures of women of childbearing age to protect for fetal exposure. Based on the ENEL of 5.5 mg/kg/day, the acute dietary MOEs for females 13-49 yrs. would be 366 at the 95<sup>th</sup> and 239 at 99<sup>th</sup> percentiles, which exceed the general health protective benchmark MOE of 100.

The MOEs for all of the evaluated population subgroups from chronic dietary exposure were greater than 770, based on the chronic NOEL of 5.7 mg/kg/day for thyroid effects in rats. This NOEL is sufficiently similar to the estimated NOEL for developmental neurotoxicity (5.5 mg/kg/day), and thus, would be adequate for protection against potential developmental effects of imidacloprid.

The acute tolerance exposure was calculated as the sum of the 95<sup>th</sup> percentile exposure for the commodity of concern at the tolerance and a background exposure. The MOEs for exposure to tolerance level imidacloprid were at or above the benchmark of 100. The lowest MOEs were 170-196 for Children 1-2 yrs. and Infants, who consumed tomato paste, spinach and broccoli.

The MOEs in this RCD reflect only the risk from the dietary exposure. The potential human exposures from ambient air, occupational activities and residential uses of imidacloprid will be subsequently evaluated in an addendum to this RCD. Aggregate exposures to specific population subgroups from various combined scenarios will also be determined. These additional exposures will lead to reductions in the MOEs estimated in this assessment. Dietary exposure may have to be reevaluated using refinements such as measured residue levels from monitoring studies, when data become available.

## II. INTRODUCTION

Imidacloprid [N-(6-chloropyridin-3-ylmethyl)-2-nitroiminoimidazolidine] is a member of a new class of pesticides, the neonicotinoid insecticides. It is effective against sucking insects on plants and companion animals, against turf insects and some beetles. Due to its systemic activity, imidacloprid is extensively used for soil application, seed and foliar treatment. Like the other neonicotinoids, imidacloprid shares structural similarity and a common mode of action with the tobacco toxin, nicotine. The toxicity of imidacloprid is based on interference of the neurotransmission in the nicotinic cholinergic nervous system. Imidacloprid binds to the nicotinic acetylcholine receptor (nAChR) at the neuronal and neuromuscular junctions in insects and vertebrates. The nAChR is an ion channel, which endogenous agonist is the excitatory neurotransmitter acetylcholine (ACh). The receptor normally exists in a closed state, however, upon ACh binding, the complex opens a pore and becomes permeable for cations. The channel openings occur in short bursts, which represent the lifetime of the receptor-ligand complex. ACh is then rapidly degraded by the enzyme acetylcholinesterase (AChE). In contrast, imidacloprid bound to the nAChR is inactivated very slowly. Prolonged activation of the nAChR by imidacloprid causes desensitization and blocking of the receptor and leads to paralysis and death.

Imidacloprid was the first neonicotinoid registered by the United States Environmental Protection Agency (USEPA) for use as a pesticide. It possesses selective toxicity for insects relative to mammals and displays a broad spectrum of useful properties. These properties include high insecticidal potency, control of insects resistant to the major pesticides (e.g. organophosphates, carbamates and pyrethroids) and efficacy in soil application due to its mobility from the roots to the upper parts of plants (Kagabu, 2004). Since being introduced in the insecticide market in 1992, the use of imidacloprid has increased yearly. It ranked as one of the top selling pesticides in the world in 2001-2002. For the most part, it is replacing the acetylcholinesterase inhibitors, the organophosphorus compounds and methylcarbamates, which display higher mammalian toxicity and decreased effectiveness due to pest resistance.

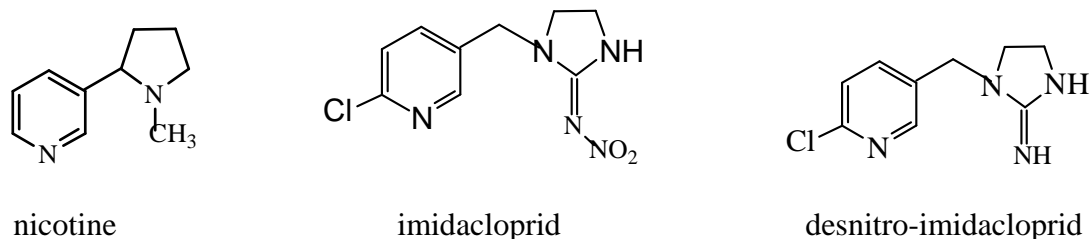
This human health risk assessment for imidacloprid was conducted because adverse effects on the liver and the thyroid gland were observed following subchronic and chronic exposures. This Risk Characterization Document (RCD) evaluated the potential health hazard from exposure to imidacloprid residues in the food and drinking water. The exposures from ambient air, occupational activities and residential uses of imidacloprid, as well as aggregate exposures from various combined scenarios, will be subsequently evaluated in an addendum to this RCD. The toxicological profile was based on studies on file at the DPR, which were submitted for fulfilling the pesticide registration data requirements under the California Birth Defect Prevention Act of 1984 (SB 950). Published experimental data were also used to characterize the imidacloprid toxicity. Relevant publications were searched from the electronic databases at the National Center for Biotechnology Information (NCBI, <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>; <http://toxnet.nlm.nih.gov/>). The most recent database search was conducted in November 2004, and the document was updated accordingly.

## II.A. MECHANISM OF ACTION

### II.A.1. Imidacloprid and the Neonicotinoids

Imidacloprid was discovered in 1984 at Nihon Bayer Agrochem in Japan by screening novel synthetic compounds for a high affinity to the insect nicotinic AChRs receptors, but with low toxicity to vertebrate species (Kagabu, 1997). Its molecule includes the insecticidal N-(3-pyridinyl)methyl group of nicotine and a nitroimine moiety (Fig.1). Because of their structural similarity to nicotine, imidacloprid and related insecticides (acetamiprid, thiacloprid, thiamethoxam and nitenpyram) were termed neonicotinoids (Tomizawa and Yamamoto, 1993). Nicotine possesses only modest insecticidal activity and is not stable for use in the field for crop protection. Imidacloprid has greater insecticidal activity than nicotine, and its stability is suitable for field use. Both the neonicotinoids and nicotinoids act as agonists at the nAChR. The principal differences between the two classes of compounds are that the nicotinoids are ionized at physiological pH and selective for the mammalian nAChR; whereas the neonicotinoids are not ionized and more selective for the insect nAChR. The selectivity of the neonicotinoids toward insects relative to mammals reflects the fundamental differences in the subunit combination and pharmacological profiles between the nAChR in insects and mammals (for review see Tomizawa and Casida, 2003).

**Figure 1.** Chemical Structures of Nicotinoid and Neonicotinoid Compounds.



### II.A.2. Nicotinic ACh Receptors (nAChRs) as Target for Imidacloprid

The nAChRs are cation selective ligand-gated ion channels, which are involved in the physiological responses to acetylcholine. All nAChRs are transmembrane oligomers. They are made up of homologous subunits, which are encoded by a large multigene family. Most have significant calcium permeabilities, enabling them to regulate Ca<sup>2+</sup>-dependent processes. The functions and pharmacological properties of the nAChRs depend on the subunit composition and cellular and subcellular distribution.

**Vertebrate nAChRs.** The vertebrates nAChRs are assembled from five identical or different subunits. In mammals, the nAChRs are expressed at the neuromuscular junction (muscle nAChRs), within the central and peripheral nervous system (neuronal nAChRs); and also on some non-neuronal cells. Subunit composition of these pentameric channels varied between muscle and brain. In neurons, most nAChRs contain two  $\alpha$  and three  $\beta$  subunits. The  $\alpha$ 1,  $\beta$ 1,  $\gamma$ ,  $\delta$  and  $\epsilon$  subunits make up heteropentamers in muscle cells (Le Novere and Changeux, 1995; Le Novere et al, 2002). Nicotine is the typical agonist of nAChRs; bungarotoxin, tubocurarine, pancuronium and hexamethonium are antagonists for the ganglionic and neuromuscular transmission. Residues contributing to ACh binding site in vertebrates have been identified and



referred to as loops. Loop F, designated as a negative subsite, is considered to interact with the quaternary nitrogen atom of ACh and nicotine (Corringer et al., 2000). Imidacloprid has no such nitrogen (Fig.1). Structural studies predicted that the electron deficient nitrogen atom of the imidazolidine group of imidacloprid corresponds to the positively charged, protonated form of nicotine and is likely to interact with the mammalian nicotinic receptors (Matsuda et al., 2000).

At the vertebrate neuromuscular junction and autonomic ganglia, each postsynaptic nAChR binds two molecules of ACh to form a ligand-receptor complex. This complex then undergoes a conformational change to open an ion channel, which is permeable to extracellular  $\text{Na}^+$  and  $\text{Ca}^{2+}$  and promotes efflux of intracellular  $\text{K}^+$ . At the cellular level, the immediate impact on nAChRs activation is a cation influx and membrane depolarization (Berg and Conroy, 2002). The most important long-term consequence of the synaptic signaling is transcriptional regulation. The nAChR-mediated transcription requires calcium influx and calcium release from internal stores to initially activate  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinases (CaMKII/IV) and then mitogen-activated protein kinases (MAPK; Liu and Berg, 1999). These enzymes, in turn, activate transcription factor CREB, which alter expression of genes involved in transmitter synthesis (Chang and Berg, 2001; Gueorguiev et al., 2000).

Although nAChRs are expressed in the mammalian CNS, it relies on glutamatergic transmission as its primary form of excitatory signaling. Current evidence suggests that the physiological role for nAChRs in the CNS is not as mediators of rapid chemical transmission, but rather as modulators of synaptic signaling (Sharma and Vijayaraghavan, 2002). In the CNS, the neuronal nAChRs appear to be involved in complex central functions, including control of voluntary motion, memory and attention, sleep and wakefulness, reward and pain, and anxiety (Cordero-Erausquin et al., 2000). In mammals, the acute neurotoxicity of imidacloprid is largely due to action at the  $\alpha 4\beta 2$  and the homomeric  $\alpha 7$  receptors in the brain (Tomizawa et al., 2001; Shimomura et al., 2002). The CNS effects cause excessive stimulation, convulsions, seizures then depression and coma. The action of imidacloprid in the brain is very complex due to its biotransformation to a large number of metabolites with varying stability and toxicity. One of these metabolites, desnitro-imidacloprid (Fig. 1), is of particular interest, because it has a nicotinic-type action that prefers mammalian versus insect nAChRs (Tomizawa and Casida, 1999; Tomizawa and Casida, 2000).

Neuronal-type nAChRs are now being discovered in many non-neuronal cells such as keratinocytes, bronchial epithelial cells, lymphocytes, chondrocytes, glial cells and astrocytes (for review see Sharma and Vijayaraghavan, 2002). In some of these cell systems additional components of the cholinergic signaling have been found, including AChE, ACh and choline acetyltransferase; but synapses have not yet been identified (Grando, 2001). Calcium appears to be the major mediator of the nAChR activation and the consequences of receptor activation are likely to be cell-type specific. Recent findings suggest that nAChRs on non-excitabile cells might regulate cellular functions like cell death and cell migration, in addition to the modulation of cellular signaling. The presence of nAChRs in non-excitabile cells implies a broader scope for imidacloprid actions, which needs to be considered when assessing its toxicity to humans.

Several human neuropathologies have been linked to genetic alterations of nAChRs genes or autoimmune disruption of the receptor proteins, including congenital myasthenia, autosomal dominant frontal lobe nocturnal epilepsy and possibly a schizophrenic syndrome (for review see Lindstrom, 2002). These receptors are also involved at various degrees in several neuropathologies such as Parkinson and Alzheimer's diseases, and Gilles de la Tourette's

syndrome. Autoimmune responses to specific neuronal nAChR subunits have been found in the skin disease pemphigus, in which cells of the epidermis lose adherence. However, the most widespread human pathology associated with neuronal nAChRs is the addiction to nicotine (Mansvelder and McGehee, 2002).

The physiological role of nAChRs has been investigated *in vivo* by gene inactivation or overexpression. Knockout mice of  $\alpha 3$  or both  $\beta 2$  and  $\beta 4$  subunits developed a perinatal-lethal dysautonomia (Xu et al., 1999a,b). Knockin mice with high levels of expression of  $\alpha 4$  subunits died near birth; but at lower levels of expression displayed increased anxiety and poor motor activity. These phenotypes resulted from hyperactivity of nAChRs in some neurons and death of other neurons and resembled toxic signs seen after chronic exposures to nicotine and imidacloprid.

**Insect nAChRs.** Invertebrates possess a variable number of genes encoding nAChR subunits (Gundelfinger and Schulz, 2000; Marshall et al., 1990; Eastham et al., 1998). Putative nAChR subunits have been purified from *Drosophila*, *Musca*, *Schistocerca* and *Periplaneta* (Tomizawa et al., 1996; Hanke and Breer, 1986). All known nAChR sequences are of neuronal type, but differ significantly from the vertebrate neuronal receptors. Novel insect nAChR subunits have been predicted from the *Drosophila* genome data (Littleton and Ganetzky, 2000). It is presently unknown which subunits of the insect nAChR bind imidacloprid.

High affinity [<sup>3</sup>H]-imidacloprid binding sites were detected in a broad range of insects, including green peach aphid, cowpea aphid, glassy-winged sharpshooter, whitefly, cockroach, migratory locust, tobacco hornworm, fruit fly and housefly (Zhang et al., 2000; Tomizawa and Casida, 2003). Both in insects and mammals, imidacloprid appears to act on multiple nAChRs subtypes with differential sensitivity. The prolonged activation of these receptors by imidacloprid results in toxicity, typical for cholinergic hyperactivity, e.g. uncoordinated abdominal quivering, wing flexing, tremor and violent whole body shaking, followed by prostration and death (Schroeder and Flattum, 1984).

### II.A.3. Imidacloprid Binding Affinity, Agonist Potency and Intracellular Signaling

The potency of imidacloprid for insect brain nAChRs is substantially higher than for mammalian brain channels. For example, the binding affinity of imidacloprid to *Drosophila* nAChRs is over 550-fold greater than the affinity to the mammalian  $\alpha 4\beta 2$ ; and imidacloprid is about 900-fold more toxic to houseflies than to mice (see LD<sub>50</sub> values in Table 1; Tomizawa et al., 2000; 2001). The current model postulates that, unlike the anionic ACh-binding subsite in vertebrates, the subsite in the insect nAChRs consists of cationic amino acids, which interact with the negatively tipped nitro group of imidacloprid (Tomizawa et al., 2003). Consistent with this model, minor structural changes in imidacloprid molecule, such as replacing the =NNO<sub>2</sub> group with =NH (desnitro-imidacloprid, Fig. 1), drastically increases the specificity for the mammalian nAChR subtypes (Tomizawa and Casida, 1999). The imino group of desnitro-imidacloprid is readily protonated and the resulting positive charge may improve the fit into the mammalian negative ACh subsite (Matsuda et al., 2000).

The binding affinity and agonist potency of imidacloprid have been reported for several vertebrate species. Imidacloprid inhibited [<sup>3</sup>H]- $\alpha$ -Bgt binding and displayed weak agonist effects in muscle type nAChR from *Torpedo* electric organ (Tomizawa et al., 1995; Tomizawa and Casida, 1999). It was an agonist of the nAChRs in mouse N1E-115 neuroblastoma and BC3H1 muscle cells (Zwart et al., 1992; 1994). Imidacloprid activated the rat  $\alpha 4\beta 2$  and  $\alpha 7$  ion channels

expressed in *Xenopus* oocytes, albeit with much lower potency than ACh (Yamamoto et al., 1998); and displayed a partial agonistic activity with the recombinant chick  $\alpha 4\beta 2$  and  $\alpha 7$  receptors (Matsuda et al., 1998; 2000). Imidacloprid bound with lower affinity to  $\alpha 1$ ,  $\alpha 3$ ,  $\alpha 4$  and  $\alpha 7$  nicotinic AChR subtypes compared to its desnitro metabolite (Chao and Casida, 1997; Tomizawa and Casida, 1999). The reported safety of imidacloprid as an insecticide was attributed to its high potency on insect AChRs, but poor interaction with vertebrate neuronal receptors. Clearly, this observation is based on only the toxicity of the parent compound.

Chronic nicotine treatment *in vivo* is known to cause an increase in the number (up-regulation) of nicotinic AChRs in mammalian brain, based on radioligand binding. It has been proposed that the up-regulation is related to receptor desensitization (Marks et al., 1992; Pauly et al., 1996). Imidacloprid and its metabolite desnitro-imidacloprid also up-regulated the  $\alpha 4\beta 2$  nicotinic AChR subtype, which represent more than 90% of the high affinity [ $^3\text{H}$ ]nicotine binding sites in mammalian brain. Exposure of  $\alpha 4\beta 2$ -expressing mouse fibroblast M10 cells for 3 days to imidacloprid and desnitro-imidacloprid caused up to 8 fold increase of [ $^3\text{H}$ ]nicotine binding (Tomizawa and Casida, 2000). The potency of desnitro-imidacloprid was similar to nicotine, whereas a 300-fold higher concentration of imidacloprid was required to induce this level of up-regulation. The active concentrations of nicotine, desnitro-imidacloprid and imidacloprid, which caused a half-maximal increase in [ $^3\text{H}$ ]nicotine binding sites in M10 cells, were 760 nM, 870 nM and 70,000 nM. The potency order for receptor up-regulation correlated with the *in vitro* binding affinities ( $\text{IC}_{50}$  of 7 nM, 8.2 nM and 2600 nM for nicotine, desnitro-imidacloprid and imidacloprid, respectively). The correlation between the up-regulation and binding potencies of the agonists indicated that binding to the  $\alpha 4\beta 2$  channels initiated the increase in the receptor number. Experimental data support the hypothesis that the increased number of receptors is due to prevention of AChR degradation, rather than an adaptive mechanism to compensate for the loss of channel function. The biological consequences of the imidacloprid and desnitro-imidacloprid-induced up-regulation of neuronal AChRs are not known. However, it has been shown that mice chronically treated with nicotine became tolerant to its acute effects on locomotor activity and body temperature (Marks et al., 1992; Salminen and Ahtee, 2000).

Electrophysiological studies revealed that imidacloprid induced multiple conductance states of single channel currents in rat phaeochromocytoma PC12 cells (Nagata et al., 1996; 1998). The main conductance and subconductance of these currents were similar to those caused by ACh. Unlike ACh, which evoked currents mainly in the main conductance state, imidacloprid induced predominantly currents in the subconductance state. Furthermore, imidacloprid acted as a partial agonist of the nAChRs in these cells. An interesting model was proposed to explain these findings. Imidacloprid may bind to two different sites on the neuronal nAChRs. One is the agonist-binding site and the other is the blocking site, which may be located at or near the channel pore. Imidacloprid may bind to the agonist site and compete with other agonists, including ACh and nicotine. The binding of imidacloprid to the agonist site generates the main conductance current. The binding of imidacloprid to the blocking site interferes with ion permeation, resulting in a partial suppression of the ACh-induced currents. The possible dual action of imidacloprid as an agonist and antagonist of the mammalian nAChRs needs further experimental verification.

Neuronal nAChRs activate complex downstream signaling pathways, which are initiated with an increase in the level of intracellular calcium (Berg and Conroy, 2002). One of the key components participating in the nAChR signaling is the extracellular signal-regulated kinase

(ERK), also known as mitogen-activated protein kinase (MAPK; Schaeffer and Webber, 1999). ERK pathway is a necessary intermediate in the signaling from the nAChR toward gene expression (Chang and Berg, 2001). In neurons, ERK/MAPK cascades regulate important physiological processes such as cell differentiation, growth and survival, memory processing and synaptic plasticity (Grewal et al., 1999). The current model for ERK activation is that the nicotinic cholinergic stimulation triggers an initial cytosolic influx of sodium, creating membrane depolarization and a subsequent increase in the intracellular calcium concentrations. Depending on the cell type, calcium serves as a second messenger to activate protein kinase C (PKC) or protein kinase A (PKA), which in turn trigger the ERK/MAPK cascade to activate the transcription factor CREB and expression of specific genes (Cox and Parsons, 1997; Dajas-Bailador et al., 2002). In mouse neuroblastoma N1E cells, imidacloprid, desnitro-imidacloprid and nicotine activated the ERK cascade. The stimulation of  $\alpha 4\beta 2$  receptor was coupled to the phosphorylation of ERK in a  $Ca^{2+}$  and PKC-dependent manner (Tomizawa and Casida, 2003). Both, desnitro-imidacloprid and nicotine induced phosphorylation of ERK at 1  $\mu M$ , whereas 100 fold higher concentration was required for imidacloprid to activate the kinase. The potencies of the three nicotinic agonists in inducing ERK phosphorylation were consistent with their binding affinities and toxicity. The principal finding of this study was that low concentrations of imidacloprid and its metabolite affected neuronal functions. The importance of the insecticide-induced changes in the nAChR signal transduction at the organismal level remains to be evaluated.

Imidacloprid binding to neuronal nAChRs may be dependent on the phosphorylated state of the receptors. According to a proposed model for cockroach neurons, the nAChRs can exist either in a phosphorylated or dephosphorylated form (Courjaret and Lapied, 2001). Increased cAMP via a calcium/calmodulin (CaM)-sensitive adenylyl cyclase activates PKA, which in turn phosphorylates and maintains the nAChR in a functional form. In contrast, dephosphorylation, which is catalyzed by a CaM kinase-regulated protein phosphatase, renders the receptor nonfunctional. Imidacloprid preferentially bound and activated the phosphorylated form of the channel. These results indicated that conditions, which alter the nAChR phosphorylation/dephosphorylation mechanisms, may significantly affect the toxicity of imidacloprid.

## **II.B. REGULATORY HISTORY**

Imidacloprid was first registered in the United States by the USEPA in 1994 as Merit® insecticide for use on turf and ornamentals (USEPA 1994). Subsequently, it was registered with the USEPA for use on various food and feed crops, tobacco, ornamentals, buildings for termite control and on cats and dogs for flea control. Currently, as a Category II acute toxicant, it is classified as a General Use Pesticide. USEPA has developed for imidacloprid an oral chronic reference dose (RfD) of 0.057 mg/kg/day. Imidacloprid is classified as a “Group E” carcinogen, indicating “no evidence of carcinogenicity in humans” (USEPA 1999a,b; 2003).

USEPA has evaluated the human risk from aggregate exposure to imidacloprid (USEPA, 2003). The aggregate exposures included dietary exposure to establish tolerances on food commodities, exposure from drinking water and in residential settings. An occupational exposure assessment has not been conducted. The USEPA utilized imidacloprid residue levels at the tolerance for its acute and chronic dietary exposure assessments. The main conclusion from these assessments was that the aggregate exposure to imidacloprid of the US population, infants and children would

not result in harm. Consequently, tolerances for the combined residues of imidacloprid and its metabolites containing the 6-chloropyridinyl moiety were established on a large number of raw agricultural commodities, meat, milk, poultry and eggs (CFR 2003a). There are no CODEX Maximum Residue Levels (MRLs) for residues of imidacloprid. There are currently Canadian and Mexican MRLs for imidacloprid on potato, but these MRLs are not equivalent to the US-recommended tolerance level.

In California, the Department of Pesticide Regulation (DPR) completed a health risk assessment for imidacloprid in 1993, which evaluated imidacloprid for emergency use on cotton under the Section 18 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA; Lewis et al., 1993). Based on this risk assessment, the emergency registration of imidacloprid for use on cotton was approved. Subsequently, in 1997 imidacloprid was registered to control aphids and whiteflies on cotton.

Imidacloprid has played a significant role in reducing the populations of the glassy-winged sharpshooter (GWSS, *Homalodisca coagulata*) in California. GWSS can feed and reproduce on over 70 species of crop and ornamental plants. This insect is a new pest for California and poses a serious threat to the vineyards, due to its ability to spread *Xylella fastidiosa*, the bacterium that causes the Pierce's disease in grapes. Vines develop Pierce's disease when *X. fastidiosa* overgrows the water conducting system of the plants (xylem) and blocks the flow of water to the affected leaves (Bentley et al., 2004). Because of its systemic properties, imidacloprid is currently one of the few effective insecticides, which is registered to control GWSS in vineyards, citrus orchards and stone fruit in California.

### **II.C. TECHNICAL AND PRODUCT FORMULATIONS**

Imidacloprid is effective against piercing-sucking and some chewing insect pests of agricultural crops and pets. It is available as granular and wettable powders, liquid forms and flowable formulations. It is more efficient as a systemic pesticide (e.g. within the plant) via soil application or seed treatment, however it is also used as a foliar spray. In the US, Bayer Agricultural Products is the main producer of the trade name imidacloprid.

As of March 2004, the following products containing imidacloprid were registered in California for use on food and feed crops: Admire™ 2 Flowable (21.4% a.i.); Merit® Concentrate Insecticide (75% a.i.), Merit® 0.5 Insecticide (0.5% a.i.), Merit® 1G Greenhouse and Nursery Insecticide (75% a.i.), Merit® 2 Insecticide (21.4% a.i.), Merit® 75 Wettable Powder and Merit® 75 Solupack Wettable Powder (75% a.i.); Gaucho® 480 Flowable (40.7% a.i.), Gaucho® 600 Flowable (48.7% a.i.), Gaucho® 75 St Insecticide and Gaucho® 75 ST FS Insecticide (75% a.i.); Provado® 1.6 Flowable (17.4% a.i.), Provado® 75 Solupack Wettable Powder (75% a.i.); Leverage™ 2.7 (17% a.i.); Marathon® 1% Granular, Marathon® 60 Wettable Powder (60% a.i.) and Marathon II Greenhouse and Nursery Insecticide 21.4% a.i.).

The food commodities on which imidacloprid formulations can be applied are presented in Tables 17 and 18. In addition, a special local need registration (SLN) of Admire™ 2 Flowable (21.4% a.i.) was obtained for the use on grape. The product Gaucho TOPS-MZ Potato Seed-Piece Treatment contains imidacloprid (1.25%) in combination with the fungicide pesticide mancozeb (6%).

Imidacloprid is currently registered for use on the following residential non-dietary sites: Granular products for application to lawns and ornamental plants; Ready-to-use spray for

application to flowers, shrubs and house plants; Plant spikes for application to indoor and outdoor residential potted plants; Ready-to-use potting medium for indoor and outdoor plant containers; Liquid concentrate for application to lawns, trees, shrubs and flowers; Ready-to-use liquid for directed spot application to cats and dogs (Advantage® 9.1% a.i.). The formulation K9 Advantix™ is used to control ticks, mosquitoes and fleas on pets and contains imidacloprid (8.8% a.i.) in combination with permethrin (44 % a.i.).

In addition, there are numerous registered products intended for use by commercial applicators to residential sites. These include: gel baits for cockroach control (Pre-Empt® cockroach gel bait, 2.5% a.i.), products for commercial ornamental, lawn and turf pest control (Pointer™ Insecticide, 5% a.i.); products for ant and fly control (Pre-Empt liquid ant bait, 0.005 a.i.; Quickbayt Fly Bait 0.5% a.i.); and products used as preservatives for wood products, building materials, textiles and plastics (Premise® 2 Insecticide 21.4% a.i.; Premise® 75 Insecticide, Premise® 75% a.i.; Premise® 0.5 SC, 5.6% a.i., and Preventol™ Preservative Insecticide, 21.4 % a.i.).

#### **II.D. USAGE**

From 1996 to 2001, over 510,000 pounds of imidacloprid were used in California. The amounts applied in 1996, 1997, 1998, 1999 and 2000 were 70,685; 80,036; 62,882; 102,323; 101,409 and 98,000 pounds, respectively. The major usages of imidacloprid include: lettuce (53 %), structural pest control (16.9%), cotton (17%), grapes (11%), melons (9.7%), broccoli (5%), landscape maintenance (5.3%), cauliflower (4%), tomato (2.3%) and peppers (1.8%). Other uses accounted for less than 1% (DPR 2002d; <http://www.cdpr.ca.gov/docs/pur/pur01rep/chmrpt01.pdf>).

#### **II.E. ILLNESS REPORTS**

In California, 118 cases of illnesses were linked to imidacloprid from 1995 to 2001 (DPR, 2001b). The health effects attributed to exposure to imidacloprid alone, or in combination with other pesticides, were rated as definite (3 cases), probable (65 cases) or possible (50 cases). Two of the illnesses identified as “definite”, were caused by imidacloprid applications to grapes and broccoli. The clinical signs of the workers included eye irritation, blurred vision, tearing and pain in both eyes. The third “definite “ case was reported for a kennel worker who had imidacloprid splashed into the eyes. The clinical signs were burning and corneal abrasion in the eye. The majority of the illnesses “probably” caused by imidacloprid were reported for agricultural workers, which applied a pesticide mixture of imidacloprid, methamidophos and oxydemeton-methyl on broccoli. The most common clinical signs included: rash, breathing difficulty, headache, tearing eyes, nausea, itching, dizziness, increased salivation, vomiting, numbness and dry mouth.

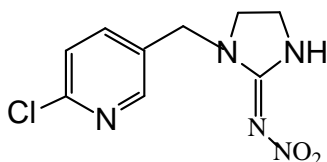
#### **II.F. PHYSICAL AND CHEMICAL PROPERTIES**

Chemical name:	1-(6-chloro-3-pyridin-3-ylmethyl)-N-nitroimidazolidin-2-ylidenamine
CAS Registry number:	13826-41-3
Common name(s):	Imidacloprid
Trade names:	Admire, Acidor (Agro Chemical Industries), Gaucho, Genesis, Prescribe (Gustafson LLC); Marathon (Olympic Horticultural

Products); Confidate, Imadate (The Arab Pesticides & Veterinary Drugs Mfg. Co.); ( Farm Chem. Handbook, 2002)

Molecular formula:  $C_9H_{10}ClN_5O_2$

Molecular weight: 255.66



Structural Formula

Physical appearance: light yellow powder

Solubility: 0.58 g/l water at 20°C. Soluble in acetone, acetonitrile, methylene chloride and dimethylformamide, DMSO

Melting point: 120-134°C

Vapor pressure:  $1.5 \times 10^{-9}$  mmHg at 20°C

Density: 1.54 g/cm<sup>3</sup> at 23°C

Henry's Constant  $9.9 \times 10^{-13}$  atm m<sup>3</sup>.mol<sup>-1</sup> at 20°C

## **II.G. ENVIRONMENTAL FATE**

**Summary:** In the environment, the principal routes of dissipation for imidacloprid are aqueous photolysis, microbial degradation and uptake by plants. Imidacloprid photodegraded rapidly (half-life of 4 hours) in water, compared to soil (half-life of 171 days). It was hydrolytically stable at pH 5 and 7, but hydrolyzed slowly in sterile alkaline solutions (half-life of 355 days). The half-life of the imidacloprid degradation in anaerobic soil was 27 days. Imidacloprid was persistent in aerobic soil under laboratory conditions (half-life of 188 to > 365 days). The presence of vegetation substantially increased the rate of imidacloprid degradation in the soil (half-life of 48 days). Studies on the imidacloprid mobility in soil revealed that imidacloprid residues leached into the 6-12 inch soil depth under field conditions.

Imidacloprid is currently listed by the DPR as a potential ground water contaminant, based on its high solubility in water, mobility and persistence in soil. The low vapor pressure of imidacloprid indicates that its volatilization from soil and leaf surfaces may not be a major route of dissipation. Presently, information on imidacloprid residues in ground and surface water or in air samples in California is not available.

The major degradation product of imidacloprid in the environment is desnitro-imidacloprid. Other products, which have been found in laboratory studies, included 5-hydroxy-imidacloprid, imidacloprid-urea, 6-chloronicotinic acid and carbon dioxide. Additional discussion on the fate of imidacloprid in the environment is presented in Volume II, Environmental Fate (Bacey 2001, <http://www.cdpr.ca.gov/docs/emppm/pubs/fatememo/imid.pdf>).

### **II.G.1. Hydrolysis**

The hydrolysis of imidacloprid was investigated in sterile aqueous buffered solutions at 25°C for 30 days (Yoshida, 1989). Pyridine-labeled <sup>14</sup>C-imidacloprid (5 ppm) was hydrolytically stable at

pH 5 and 7. It hydrolyzed very slowly at pH 9 with an estimated half-life of 355 days. In alkaline solutions the major metabolite (7% of the total radioactivity) could not be identified. The other hydrolysis product was imidacloprid urea (1.7% of the total radioactivity).

### **II.G.2. Photolysis or Photodegradation**

The photodegradation of [pyridinyl-<sup>14</sup>C-methyl]imidacloprid was studied in sterile water, under the conditions of maximum hydrolytic stability (pH 7 at 23°C). Imidacloprid (5.4 mg/l) was continuously irradiated with a sunlight-simulating xenon lamp. The half-life of the photodegradation was 57 min. Based on this half-life, the environmental half-life was estimated at about 4.2 hours. Similarly, imidacloprid was degraded quickly (~ 4h) under natural sunlight in the greenhouse. The major photodegradation products were desnitro-imidacloprid (17.2%) and imidacloprid urea (10 % of the applied radioactivity, Anderson 1991).

The photodegradation of [pyridinyl-<sup>14</sup>C]imidacloprid was investigated on sandy loam soil. [Pyridinyl-<sup>14</sup>C] imidacloprid was applied at a concentration of 48.5 mg/kg onto the soil layer. It was continuously irradiated with a sunlight-simulating xenon lamp for 15 days at 25°C. Imidacloprid degraded with a half-life of 38.9 days under the experimental conditions. The calculated environmental half-life was 171 days. The major photodegrade was 5-hydroxy imidacloprid (Yoshida 1990).

### **II.G.3. Microbial Degradation**

The anaerobic metabolism of imidacloprid was investigated in microbially active water and the accompanying sediment, which were obtained from a pond. Imidacloprid was applied to the water at an application rate of 0.6 mg/l and incubated for 358 days. This dose rate was about 1.5 fold higher than the actual field use rate (0.5 lb a.i./acre). Under these conditions, [pyridinyl-<sup>14</sup>C-methyl]-imidacloprid degraded with a half-life of 27 days. Desnitro-imidacloprid was identified as the only major metabolite. After 60 days, large amounts of this metabolite were bound to the sediment. At the end of the incubation period, imidacloprid degraded to less than 0.1 % in both, water and sediment. The final degradation product was carbon dioxide (Fritz and Hellpointer, 1991).

The aerobic metabolism of imidacloprid was studied on microbially active, sandy loam soil in the dark, at 20°C. [Pyridinyl-<sup>14</sup>C-methyl]-imidacloprid was applied to the soil at a dose rate of 0.33 mg/kg soil. After 366 days of incubation, imidacloprid accounted for more than 60% of the applied radioactivity. The extrapolated half-life of its degradation was greater than 1 year. Seven metabolites were observed at the end of the incubation period, but they represented less than 2% of the applied parent compound. The degradation of imidacloprid in soil was proposed to be via denitrification, oxidation and cleavage of the dihydro-imidazole ring to yield 6-chloronicotinic acid and ultimately carbon dioxide (Anderson et al., 1991).

Additional aerobic metabolism studies of imidacloprid were conducted on microbially active, flooded sandy loam soil BBA 2.2, Hoefchen silt and Monheim 1 sandy loam in the dark at 20°C. The application rates were 0.33 mg/kg (BBA 2.2 and Monheim 1 soils) and 0.36 mg/kg (Hoefchen silt) and the incubation period was 100 days. Under the experimental conditions, the radiolabeled imidacloprid degraded with estimated half-lives of approximately 188, 248 and 100 days, respectively. (Anderson et al., 1990; Anderson and Fritz, 1990; Anderson and Fritz, 1991).

The effect of growing vegetation on the degradation of imidacloprid in soils was investigated in BBA 2.2 loamy soil. The soil was fertilized to maintain a nutrient supply for the plants. [Pyridinyl-<sup>14</sup>C-methyl]-imidacloprid was applied at 0.23 mg a.i./kg soil and grass was then



planted as vegetation. The samples were incubated in the greenhouse at 17-20°C for 274 days. The half-life of imidacloprid degradation in samples with vegetation was 48 days, whereas in samples without vegetation the degradation was significantly slower (half-life 190 days). Under vegetation, the main metabolite was desnitro-imidacloprid, whereas 5-hydroxy-imidacloprid was the major degradate in the soil without growing vegetation. The grass absorbed about 10% of the applied radioactivity. Therefore, the accelerated degradation of imidacloprid could not be attributed solely to the uptake by the vegetation (Scholz, 1992).

#### **II.G.4. Mobility and Field Dissipation**

##### **II.G.4.a. Soil**

A soil adsorption/desorption study was carried out to characterize the mobility of imidacloprid in soil (Fritz, 1988). Aqueous solutions of [pyridinyl-<sup>14</sup>C-methyl]-imidacloprid were equilibrated for 48 h at 25°C with four different soil types – sandy loam, slit loam, low-humus sandy soil and silty clay. The highest tested concentration of imidacloprid was approximately 290 mg/l. The soil to water ratio was 1:4. Based on the soil-carbon sorption constant ( $K_{oc}$ ), the mobility of imidacloprid could be classified as high in silt ( $K_{oc}$  of 132) and medium in low-humus sandy soil, silty clay and sandy loam ( $K_{oc}$  of 157, 212 and 256, respectively).

In a subsequent study, aqueous solutions of [pyridinyl-<sup>14</sup>C-methyl]-imidacloprid were incubated at 25°C with four different soil types – sand, loamy sand, slit loam and loam. The mobility of imidacloprid was classified as medium ( $K_{oc}$  of 277-411; Williams et al, 1992).

A soil adsorption/desorption study was carried out to characterize the sorption properties of the major metabolite of imidacloprid, desnitro-imidacloprid. Aqueous solutions of [<sup>14</sup>C]-desnitro-imidacloprid were equilibrated at 25°C with four different soil types – sand, loamy sand, slit loam and loam. The highest tested concentration of desnitro-imidacloprid was approximately 250 ppm. The soil to water ratio was 1:3 for sand, loamy sand and 1:5 for slit loam. Desnitro-imidacloprid had a stronger sorption affinity for soil than the parent compound. Based on the  $K_{oc}$  values, it can be classified as a medium mobility compound in sand ( $K_{oc}$  327) and low mobility compound in loamy sand, slit loam and loam ( $K_{oc}$  of 833, 942 and 866, respectively). Therefore, desnitro-imidacloprid is less likely to leach through the soil than the parent chemical (Dyer et al., 1992).

##### **II.G.4.b. Ambient Air**

Preliminary ambient air monitoring studies were conducted in Santa Clara, Imperial and Butte Counties, California (DPR 2001a; 2002 a,b,c). Ground applications of imidacloprid foliar spray were used in residential properties, businesses, commercial parking lots, curbsides and public parks in Cupertino (Santa Clara county), Imperial Spa (Imperial County) and Chico (Butte County), which were infested with GWSS. A total of 8 air samples from the treated areas were analyzed at the time of application, 24 and 48 h post application. Information on the geographic relationship between the location of the monitoring and the application site was not provided. There were no imidacloprid detections in the air. The detection limit was 0.5 µg/sample.

##### **II.G.4.c. Ground Water**

The California Pesticide Contamination and Prevention Act (PCPA) of 1985 established a set of data requirements for identifying potential ground water contaminants. Pesticides with parameters exceeding Specific Numerical Values (SNVs) established by DPR, are considered to pose a risk to ground water (Kollman and Guo, 2000). The SNVs include: Solubility (SNV>3

ppm),  $K_{oc}$  ( $SNV < 1900 \text{ cm}^3/\text{g}$ ), Hydrolysis ( $SNV > 14$  days), Aerobic Metabolism ( $SNV > 610$  days) and Anaerobic Metabolism ( $SNV > 9$  days). DPR identified imidacloprid as a potential ground water contaminant based on its high water solubility (514 ppm), low  $K_{oc}$  ( $262 \text{ cm}^3/\text{g}$ ), long hydrolysis half-life ( $t_{1/2} = 30$  days), long aerobic soil metabolism ( $t_{1/2} = 997$  days) and long anaerobic soil metabolism ( $t_{1/2} = 27$  days). Recently, DPR developed analytical methods for detection of imidacloprid residues to perform actual screening for imidacloprid and its metabolites in the water of the California wells.

#### **II.G.4.d. Surface Water**

Preliminary surface water monitoring studies were conducted in Santa Clara, Imperial and Butte Counties, California. Imidacloprid was applied via soil injection or foliar spray in areas infested with GWSS (DPR 2001a; 2002 a,b,c). A total of 11 surface water samples were collected at five creeks and at a fishpond. The location of the monitoring sites was generally indicated as upstream or downstream of the application area, however, more specific information was not provided. Imidacloprid residues were not detected in any of these samples. The detection limit was 0.05 ppb.

#### **II.G.5. Field Dissipation**

A series of field dissipation studies were performed at different sites (Georgia, Minnesota and California) with various soil types to evaluate the degradation and mobility of imidacloprid under actual field conditions. Imidacloprid formulation 240FS (23.3% a.i. liquid suspension) was applied to the soil at the highest recommended rate of 0.5 lb a.i./acre. Soil core samples were analyzed for imidacloprid immediately post-application through 18 months. Each core was sectioned into 6-inch segments.

The half-life for imidacloprid dissipation in loamy sand and sandy loam was 12 days. Imidacloprid applied to a field planted with corn had a half-life of 7 days. Residues at or above the detection limit (10 ppb) were not detected below 0-6-inch soil depth (Rice et al., 1991a,b). Imidacloprid applied to a tomato plot dissipated with a half-life of 53 days. Residues above the detection limit (10 ppb) were detected below the 6-inch soil depth, indicating that the pesticide had leached into the 6-12 inch soil dept (Rice et al., 1991c). The half-life for imidacloprid dissipation in the turf grass was 61-107 days with no leaching below the 0-6 inch soil depth (Rice et al., 1992a,b).

The field dissipation studies revealed that imidacloprid had a shorter half-life under field conditions (7 to 146 days), when compared to the half-life observed under aerobic laboratory conditions (greater than 1 year, Anderson et al., 1991). This difference in the imidacloprid stability was attributed to the combined effect of various dissipation pathways under field conditions, including photolysis, hydrolysis, chemical and microbial degradation and plant uptake.

#### **II.G.6. Plant /Metabolism**

Accumulation Studies on Rotational crops: [Pyridinyl]- $^{14}\text{C}$ -methyl]-imidacloprid was applied to sandy loam at an application rate of 454 g a.i./ha (Vogeler et al., 1992). The rotational crops red beet, Swiss chard and wheat were planted after 30 days (first rotation), 120 days (second rotation) and after 271 days (third rotation) after application of the pesticide. The plant parts, which were analyzed for radioactivity included: wheat forage, wheat straw, wheat grain, Swiss chard foliage, red beet leaves and red beet roots. The samples were analyzed from 0 to 412 days post-application. The concentration of imidacloprid in the soil decreased from 0.36 mg/kg at day

0 to 0.13 mg/kg at day 412. The half-life for imidacloprid dissipation in soil was 179 days. The major metabolite in the soil was 5-hydroxy imidacloprid (4.7% of the total applied radioactivity). The residual radioactivity in plants and plant parts ranged from 0.07 mg/kg to 0.5 mg/kg in crop I. The residual radioactivity in straw was higher (2.5 mg/kg in crop I), due to the process of dehydration of green wheat. The decrease in radioactivity was the most in the wheat straw 2.5 mg/kg (crop I) to 0.9 mg/kg (crop III). Imidacloprid, taken up by the crops, was further metabolized to several major products including desnitro-imidacloprid, 5-hydroxy imidacloprid and 6-chloronicotinic acid. The rotational studies revealed that the plant uptake of imidacloprid is one of its major dissipation pathways in the soil (Vogeler et al., 1992).

Rotational crop studies with imidacloprid were conducted in Massachusetts, Kansas and California, after a single soil application of imidacloprid (2.5% granular formulation) at a rate of 0.29-0.32 lb/acre (Minor, 1994). Cereal grain crops (wheat and sorghum), root crops (turnips) and leafy vegetable crops (spinach and mustard green) were planted at 1, 4, 8 and 11- month rotational intervals, which are typically used in the normal practice. Imidacloprid residues were measured as 6-chloronicotinic acid. The highest residue level (1.81 ppm) was detected in cereal forage and straw in California at the 1-month interval, which declined to 0.12 ppm at the 8-month plant-back interval. Based on the rate of residue decline, the concentration of imidacloprid in all rotational crops was calculated to be lower than 0.05 ppm at the 11-month interval after the application of the pesticide.

### III. TOXICOLOGY PROFILE

#### III.A. PHARMACOKINETICS

**Summary:** Five pharmacokinetic studies with [<sup>14</sup>C]-imidacloprid in Wistar rats (strain BOR:WISW SPF Cpb) were submitted to the DPR (Klein 1987, 1990a and 1990b; Klein and Karl 1990; and Klein and Brauner 1991a). There were two pharmacokinetic studies in laying hens and two studies in lactating goats (Klein and Brauner 1990, 1991b; Klein, 1992 and Karl et al., 1991). All studies were performed at the Bayer AG Laboratory in Germany.

In the rat, imidacloprid was quickly and well absorbed from the gastrointestinal tract, rapidly distributed in nearly all organs and tissues, and quickly passed through the body. The oral absorption was estimated as 92-99%, based on the urinary recovery after oral and intravenous dosing. Imidacloprid underwent degradation to a large number of metabolites formed by multiple pathways, both alternative and sequential. The same, or similar metabolites were found in rats, goats and hens. Based on structural considerations or potency relative to the parent compound, the following metabolites may be of toxicological significance: 6-chloronicotinic acid, imidazolidine 4- and 5- hydroxy compounds, olefinic imidacloprid, desnitro-imidacloprid and the nitrosoimine compound. Metabolites were excreted primarily in the urine as glutathione and glycine conjugates of mercaptonicotinic acid and hippuric acid. Pharmacokinetic studies were not available for a direct determination of the rate of absorption from dermal and inhalation routes.

#### III.A.1. Absorption

##### III.A.1.a. Oral Absorption

To investigate the oral absorption of imidacloprid, Wistar rats (5/sex/dose) received a single intravenous (i.v.) dose of 1 mg/kg or single oral doses of 1 and 20 mg/kg of <sup>14</sup>C-imidacloprid (methylene-labeled, 150.7 μCi/mg; Klein, 1987; Klein and Karl, 1990). These doses corresponded to 0.2% and 5% of the rat oral LD<sub>50</sub> (424 mg/kg, Table 1) and did not cause toxic signs. In parallel experiments, rats were pre-loaded for 14 days with non-radiolabeled imidacloprid (1 mg/kg) and then received single oral doses of 1 mg/kg or 20 mg/kg <sup>14</sup>C-imidacloprid. Additional tests were carried out to measure the radioactivity in the expired CO<sub>2</sub> in 5 male rats, which received a single oral dose of 20 mg/kg <sup>14</sup>C-imidacloprid. To characterize the bile excretion, five more rats were bile-fistulated, prior to receiving intraduodenally a single dose of 1 mg/kg <sup>14</sup>C-imidacloprid (Klein, 1987).

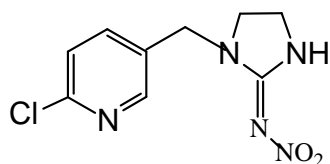
In the above studies, imidacloprid was labeled with <sup>14</sup>C in the methylene moiety. Because nearly half of the identified metabolites did not contain the imidazolidine moiety, a comparative study was conducted, using imidacloprid labeled with <sup>14</sup>C in the 4- and 5- position of the imidazolidine moiety (Klein and Brauner, 1991a). In the later experiments, radiolabeled imidacloprid was given as a single oral dose to 5 male and female rats at 1 mg/kg; or to 5 male rats at 150 mg/kg. There were no major differences in the behavior of the total radioactivity between the methylene- and imidazolidine-radiolabeled imidacloprid.

The absorption of orally administered <sup>14</sup>C-imidacloprid was rapid as evidenced by the calculated lag-time of less than 2.5 min. The average half-life of absorption was estimated as about 35 min (for both sexes and all dose-groups). After oral administration of 1 mg/kg or 20 mg/kg [<sup>14</sup>C]-imidacloprid, the plasma concentrations reached maximum between 1.1 h and 2.5 h at; and at 4 h

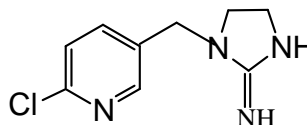
after 150 mg/kg (Klein, 1987; Klein and Brauner, 1991a). Approximately 90-98% of the administered radioactivity was recovered within 24 h. Adjusted for 100% mass balance, the average radioactivity recovered in the urine within 48 h was 78% (males) and 74% (females) at 1 mg/kg imidacloprid. At 20 mg/kg imidacloprid, these values were 77% and 82% for males and females, respectively. The urinary recovery after 14 day-preloading was in the same range (74% for the males and 75% for the females (Klein and Karl, 1990). Adjusted for 100% recovery, the 48-hour radioactivity in the feces was 18-26% of the administered activity.

The major urinary metabolites were 6-chloronicotinic acid and its glycine conjugate (WAK 3583), which represented about 30% of the recovered radioactivity (Klein and Karl, 1990; Fig. 2). Additional urinary metabolites included 5-OH-imidacloprid (WAK 4103, 15-18%), the parent compound (9-15%) and olefinic imidacloprid (NTN 35884, 8-13%). Metabolites identified in the feces included a glycine conjugate of 6-methylmercaptopyridonic acid, imidacloprid, olefinic imidacloprid and desnitro-imidacloprid (all at 2-3%).

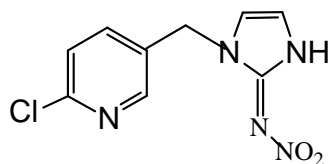
**Figure 2.** Chemical Structure of Imidacloprid Metabolites Containing the 6-Chloropyridinyl moiety.



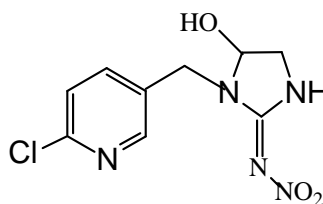
Imidacloprid (NTN 33893)



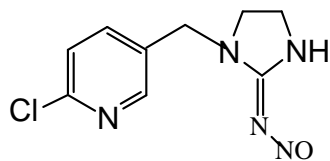
Desnitro-imidacloprid (Guanidine, NTN 33823)



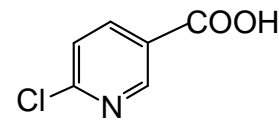
Olefinic-imidacloprid (NTN 35884)



5-OH-imidacloprid (WAK 4103)



Nitrosoimine-imidacloprid (WAK 3839)



6-Cl-nicotinic acid (WAK 3583)

Experiments with bile-fistulated rats confirmed that the absorption of imidacloprid was nearly complete (Klein, 1987). After intraduodenal dose of 1 mg/kg, the total radioactivity recovered in the urine and in the bile was about 95%. Less than 1% of the radioactivity was left in the carcass after 48 h. Very little radioactivity (< 0.2%) was recovered in the expired air in males, which received 1 mg/kg imidacloprid. The oral absorption can also be estimated by comparing the urinary recovery from oral and from i.v. dosing. In rats, which received 1mg/kg <sup>14</sup>C-imidacloprid, the estimated oral absorption was 92-99%. Together, these results demonstrated that imidacloprid was completely (100%) absorbed via the oral route in rats.

The absorption of imidacloprid was studied in Caco-2 cell line, derived from a human colon adenocarcinoma (Brunet et al., 2004). Caco-2 cells are commonly used as an *in vitro* model to predict the intestinal absorption of drugs and chemicals in humans, because they have properties similar to the intestinal mucosa (Yamashita et al., 2000). The apical and basolateral sides of Caco-2 cells represent the luminal and blood sides, respectively, of the gastrointestinal tract *in vivo*. For a large number of model compounds a correlation has been established between permeability in the Caco-2 system and the fraction absorbed in humans (Artursson et al., 2001). In the Caco-2 system, imidacloprid crossed the trans-epithelial layer very quickly at 37°C. Based on the apparent permeability coefficient ( $22 \times 10^{-6}$  cm/s) imidacloprid could be classified as a highly absorbed compound, presenting 100% efficiency of *in vivo* absorption in humans. Both, the uptake and the efflux of imidacloprid were energy-dependent and sensitive to pretreatment of the cell surface with trypsin. These results suggested that imidacloprid may be absorbed *in vivo* by inward and outward active transport systems.

#### **III.A.1.b. Dermal and Inhalation Absorption**

There were no pharmacokinetic studies to determine the rate and extent of imidacloprid absorption upon inhalation exposure or via the dermal route. In the absence of data for inhalation uptake, both the DPR and the USEPA assume a default of 100%. The dermal absorption could be estimated by comparing the oral and dermal LD<sub>50</sub>. The ratio between the oral and dermal LD<sub>50</sub> for rats was 8.5% (see Table 1 and studies by Bomann, 1989b and Krotlinger, 1989). An oral developmental toxicity study and a 28-Day subchronic dermal toxicity study in rabbits were the only available studies to compare the oral and dermal thresholds. The developmental toxicity study established a maternal LOEL of 72 mg/kg/day (Becker and Biedermann, 1992; Section III.G.2. under DEVELOPMENTAL TOXICITY). A LOEL could not be determined from the 28-day dermal study in rabbits, because no toxicity was observed at the only tested dose of 1000 mg/kg/day (Flucke, 1990, Section III.C.4 under SUBCHRONIC TOXICITY). A dermal absorption of 7.3% could be calculated from the oral LOEL of 72 mg/kg/day and from a dermal NOEL of 1000. However, this dataset may not provide a reliable estimate of the dermal absorption, because a dermal toxicity threshold was not clearly defined in the 28-day dermal study.

#### **III.A.2. Distribution**

##### **III.A.2.a. Tissues and Organs**

Analysis of the basic pharmacokinetic parameters revealed that imidacloprid was widely and rapidly distributed in the rat body. This was evidenced by (i) the large apparent distribution volume (V<sub>c</sub>), which accounted for about 84% of the total body volume distribution volume and (ii) by the short half-life for distribution of the radioactivity after an i.v. administration (3 h). The same half-lives for distribution of the radioactivity (2.6-3.6 h) were calculated after single oral

doses of 1 and 20 mg/kg or after multiple doses of 1 mg/kg. To quantify the radioactivity in the body, male rats were sacrificed at 1-48 h (5 animals/ time point) after oral administration of 20 mg/kg <sup>14</sup>C-imidacloprid. Imidacloprid had a high ability to permeate tissues, as radioactivity was detected in all of the 13 tested tissues and organs. All tested organs contained the highest radioactivity at 40 min to 1.5 h after dosing. The highest concentrations were measured in the gastrointestinal tract, liver, kidney, lung and heart. The respective concentrations (P)<sup>1</sup> of the radioactivity in these tissues normalized to dose were 4 (GI), 1.3-1.7 (liver and kidney), 0.9 (lung) and 0.74 (heart). The brain, which is a presumed target for imidacloprid, was not among the tissues and organs analyzed for radioactivity. Overall, the results from the distribution studies indicated that there was no dependence on dose, sex or pretreatment.

The whole body autoradiography confirmed the findings from the quantitative pharmacokinetic studies. In these experiments, one male rat was injected intravenously with 20 mg/kg methylene-labeled <sup>14</sup>C-imidacloprid and sacrificed 5 min later (Klein, 1987). Six more male rats received the same dose orally and were sacrificed in a period of 1-to 48 h. Sections from the fixed rats were then prepared for autoradiography. Five min after an i.v. injection, the concentration of the radioactivity in the blood was lower than in many of the organs such as liver, kidney, muscle and thyroid, thus indicating a fast turnover of imidacloprid. One hour after an oral administration, imidacloprid was readily absorbed from the gastrointestinal tract, as the radioactivity was found in nearly all organs and tissues. The high labeling of the liver and over the entire kidney was indicative of an ongoing biotransformation and renal excretion. Other tissues with increased radioactivity included the glandular organs (adrenal, thyroid and salivary glands) and connective tissues associated with the skin, walls of aorta and spinal cord. The intensive labeling over the kidney at 4 and 8 h was consistent with the high rate of renal excretion estimated in the quantitative pharmacokinetic study (about 60% at 8 h). Radioactivity was also found in the CNS, thus indicating that imidacloprid and its metabolites penetrated the blood-brain barrier. However, of all analyzed organs and tissues, the fatty tissues and the CNS had the lowest labeling.

### **III.A.2.b. Milk, Meat and Eggs**

The USEPA has established tolerances for imidacloprid and its metabolites containing the 6-chloropyridinyl moiety on milk (0.1 ppm), meat (0.3 ppm) and eggs (0.02 ppm; CFR 2003a). Tolerances are the highest level of residues permitted in agricultural commodities. Four residue studies with methylene-labeled-<sup>14</sup>C-imidacloprid in hens and goats were available on file in the DPR.

**Goat:** [<sup>14</sup>C-methylene]Imidacloprid was administered to one 41 kg lactating goat by intubation in three consecutive daily doses of 10 mg/kg. The goat was sacrificed 2 h after the last dose (Karl et al, 1991; Klein, 1992). The highest plasma concentration of 3.98 mg/ml was measured after 2 h of last dosing. The highest radioactivity of 3.16-3.65 µg/g in the milk was determined 8 h after the first dose and 2 hours after the third dose; the concentration in the milk prior to second dosing was 2.77 µg/g. Assuming a daily milk production of about 2 liters, the radioactivity in the milk was about 0.4% of the total administered radioactivity. The total residue in the edible tissues and organs measured two hours after the third dose was about 5% of the administered radioactivity. The respective residual radioactivity in the edible tissues was 1.3% (liver), (0.1%)

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<sup>1</sup> P, Relative concentration defined as:

P=Radioactivity (grams) of tissue/radioactivity administered (grams) of body weight

kidney, (3%) muscles and 0.4% (fat). The main compounds in the milk and the edible tissues were imidacloprid, olefinic imidacloprid (NTN 35884) and 4- and 5-OH-imidacloprid.

**Hens:** Five laying hens were intubated with 10 mg/kg methylene-labeled-  $^{14}\text{C}$ -imidacloprid for 3 days (Klein and Brauner 1990, 1991b). The highest radioactivity of 0.34  $\mu\text{g/ml}$  in the plasma was measured at 0.5 h after the third dosing. At that time, the total residue in the edible tissues and organs was about 3% of the total dose. The highest radioactivity of 1.347  $\mu\text{g/g}$  in eggs was found 2 h after the last dose. This level was less than 0.2% of the total administered radioactivity. The main metabolite in the eggs was the olefine-imidacloprid. Olefine- and desnitro-imidacloprid were detected in muscle and kidney tissues.

### **III.A.3. Metabolism**

Based on the profile of the metabolites, two major routes were proposed for the imidacloprid metabolism in the rat (Fig. 3, Klein and Karl, 1990; Thyssen and Machmer, 1999). In the first route, imidacloprid undergoes oxidative cleavage to imidazolidine and 6-chloronicotinic acid. The imidazolidine is directly excreted via the urine. The nicotinic moiety is detoxified via glutathione conjugation to a derivative of mercapturic acid and then to mercaptonicotinic acid. The mercaptonicotinic acid is, in turn, conjugated with glycine to hippuric acid-conjugate for excretion. The second route involves hydroxylation in the imidazolidine ring, followed by elimination of water and formation of an unsaturated metabolite (olefinic imidacloprid NTN 35884). The metabolism in hens and goats was similar to that in rats (Klein and Brauner, 1991a,b; Karl et al., 1991; Klein 1992).

Studies with recombinant human isozymes of CYP450 have suggested that a single isozyme, CYP3A4, both oxidizes and reduces imidacloprid at the imidazolidine and nitroimine moieties (Schulz-Jander and Casida, 2002). A major metabolite upon incubation of imidacloprid with the human microsome-NADPH system was tentatively identified as a derivative of hydrazone (the  $=\text{N-NO}_2$  moiety becomes  $=\text{N-NH}_2$  or desnitro-imidacloprid). Based on these results, a yet unidentified microsomal NADPH-nitro reductase was implicated to bioactivate imidacloprid in humans into the more toxic metabolite desnitro-imidacloprid (Schulz-Jander et al., 2002).

In rats, there were no sex differences in the metabolic profile at the lower dose (1 mg/kg imidacloprid (Klein and Karl, 1990). However, male rats showed an increased ability to metabolize higher doses of imidacloprid (20 mg/kg), resulting in significantly lower amount of the parent compound and an increased level of the metabolite olefinic imidacloprid. The formation of other biotransformation products was similar in males and females.

From a toxicological point of view, the formation of the metabolite desnitro-imidacloprid (NTN 33823) in rats is of particular interest, because of the following considerations: (i) this metabolite displayed a nicotinic-type action with a markedly higher toxicity to mammals than imidacloprid, (ii) desnitro-imidacloprid was identified as the major degradation product of imidacloprid in the environment (i.e. the major photodegradate and the major product of microbial and plant metabolism) and (iii) desnitro-imidacloprid was a major metabolite produced *in vitro* with human liver microsomes. In rats, desnitro-imidacloprid was identified only in the feces and represented a relatively small amount of the total recovered radioactivity (about 2-3%, Klein, 1987). In hens, desnitro-imidacloprid was detected in eggs, muscle and fat tissues (5-12%, Klein and Brauner 1990, 1991b).

An additional biotransformation product of imidacloprid, the nitrosoimine metabolite WAK 3839, was identified in the urine of chronically fed rats and mice (1 year, 1800 ppm, Klein,



1990b). WAK 3839 represented about 9% of total urinary radioactivity. Since this metabolite was not found after a single dosage of up to 150 mg/kg, it was proposed that the reduction of the NO<sub>2</sub>-moiety of imidacloprid takes place only if the enzymes catalyzing other biotransformation reactions (e.g. oxidative cleavage to 6-chloronicotinic acid) are saturated by chronic “flooding” of the liver with imidacloprid. In rats, the acute toxicity of WAK 3839 was about 5-fold lower than that of imidacloprid (Kaoru, 1991).

The toxicity of the major metabolites of imidacloprid in rats, (6-chloronicotinic acid 4- or 5-OH-imidacloprid and olefinic imidacloprid) has not been evaluated in mammals. Studies in invertebrates showed that the olefinic- and hydroxy- compounds had similar acute toxicity to the parent compound, whereas the 6-chloronicotinic acid did not act as a nicotinic agonist (Nauen, et al., 2001a,b). All of these compounds contain the 6-chloropyridinyl moiety and are included in the tolerances established for the imidacloprid residues (Fig. 2).

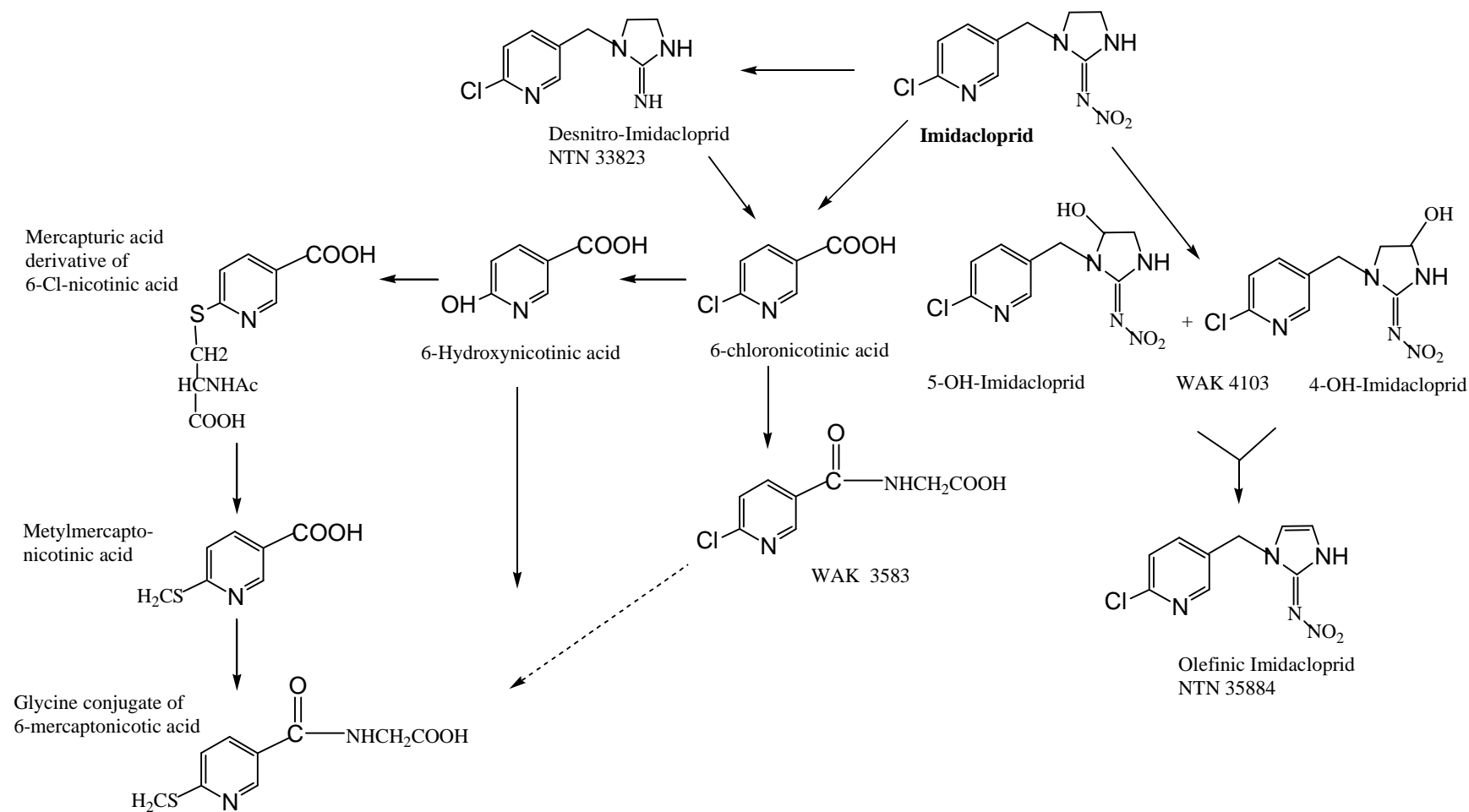
#### **III.A.4. Excretion**

The half-lives for excretion of the radiolabeled imidacloprid were calculated in rats after a single i.v. dose of 1 mg/kg, after single oral doses of 1 and 20 mg/kg or after multiple doses of 1 mg/kg (Klein, 1987). The excretion half-life values varied greatly (from 26 h to 118 h), but the variation was not dose-, sex-, or route-dependent. In all dose groups, less than 1% of the radioactivity was left in the body after 48 h of dosing. The results from the whole body autoradiography confirmed that within 24-48 h the radioactivity was nearly eliminated from the body, with skin, nasal mucosa, liver, kidney and the thyroid being the only tissues with residual radioactivity. Altogether, these data indicated that imidacloprid did not significantly accumulate in the rat body.

#### **III.A.5. Chemical Interactions and Toxicity Variation**

Metabolic modifiers and other pharmaceutical drugs have been shown to modify the toxicity of imidacloprid. The CYP450-inhibiting piperonyl butoxide synergized the toxicity of imidacloprid (Liu et al., 1993). In subchronic and chronic feeding studies, mice developed hypersensitivity to ether, which was used as anesthesia during procedures such as blood withdrawal and tattooing (Eiben, 1988b, Watta-Gebert, 1991). These animals exhibited dyspnea, respiratory failure and spasms and died shortly after administration of ether. The specific mechanism of the imidacloprid-induced hypersensitivity to ether is presently unknown. This effect needs to be considered when assessing the toxicity of imidacloprid to humans, since it may reduce the ability of the body to respond to an additional challenge with xenobiotics.

**Figure 3. Biotransformation Pathways of Imidacloprid**



(From Thyssen and Machmer, 1999)

## **III.B. ACUTE TOXICITY**

**Summary:** Acute toxicological studies are conducted to establish the median lethal dose (LD<sub>50</sub>) or concentration (LC<sub>50</sub>), which in turn are used to determine the toxicity category of the technical grade and the formulations. Depending on the dose range used in the test, it may be possible to establish an acute NOEL (No-Observed-Effect Level) from these limited studies. In risk assessment, the NOEL is commonly used to define the threshold dose for non-oncogenic effects. The NOEL is the experimentally determined highest dose at which no effects were observed.

In acute toxicological studies with two rodent species, imidacloprid caused clinical signs characteristic for nicotine intoxication, such as incoordination, tremors, spasms and respiratory difficulties. Other symptoms included decreased motility and lethargy. Mice appeared to be more sensitive to the acute toxicity of imidacloprid than rats. Presently, there is no specific antidote, which acts as an antagonist to the effects imidacloprid. Imidacloprid did not produce skin or eye irritation in rabbits, or dermal sensitization in guinea pigs. The studies on acute lethality and irritation are summarized in Table 2. NOELs and Lowest-Observed-Effects-Levels (LOELs) for non-lethal effects are presented in Table 3. NOELs and LOELs were based on clinical findings and were determined only from studies, which employed sufficient number of animals (i.e., at least 5 per dose group), included a range of doses and provided experimental details on the treatment protocol and the observations.

### **III.B.1 Acute Toxicity in Animals**

#### **III.B.1.a. Median lethal dose and toxicity category**

**Oral-Rat:** To assess the acute oral toxicity, technical grade imidacloprid (94.2%) was administered by gavage as an aqueous suspension to fasted Wistar rats (strain BOR:WISW SPF Cpb, Bomann, 1989b). There were five animals/sex per each of the eight dose groups, which received a single dose of imidacloprid. The doses were 50 (males only), 100, 250, 315, 400, 475 (females only), 500 and 1800 mg/kg. Clinical signs were evident within 15-40 min after treatment at doses higher than 50 mg/kg in males and 100 mg/kg in females. The main symptoms included apathy, labored breathing, tremors, gait incoordination, decreased motility, nasal and urine staining. Mortality was first observed at 400 mg/kg (20% both sexes) and increased abruptly to 100% at 500 mg/kg. Deaths occurred within 3-7 h following treatment. The median lethal dose (LD<sub>50</sub>) for rats was calculated as 424 mg/kg for male rats and 450-475 mg/kg for the female rats (Table 2). The NOEL for systemic effects was 50 mg/kg, based on the clinical signs observed at the LOEL of 100 mg/kg (Table 3).

**Oral-Mouse:** The acute oral toxicity of imidacloprid was studied in mice (strain Bor:NMRI-SPF, 5/sex/dose; Bomann 1989a). Imidacloprid (94.2%) was given to the mice via gavage at doses of 10, 71 (males only), 100, 120, 140, 160 and 250 mg/kg (Table 1). The animals were observed for clinical signs and gross pathology. Toxic signs were noted at doses higher than 10 mg/kg. All 5 males treated with 71 mg/kg/day imidacloprid showed apathy and labored breathing; decreased motility was noted in 2 males, and one male had tremors. In addition to these toxic signs, staggering gait and severe trembling were also reported at higher doses (100-250 mg/kg). The lowest tested dose, which caused death was 100 mg/kg (20% of the male mice died); 20% of the females died at 120 mg/kg. The toxicity was evident in a relatively brief time (within 5-10 min) following imidacloprid administration. The LD<sub>50</sub> was calculated as 131 mg/kg for male mice and 168 mg/kg for the female mice (Table 2). The NOEL for systemic toxicity was 10 mg/kg, based on clinical signs in the males observed at the LOEL of 71 mg/kg (Table 3).

**Table 1.** Effects of Imidacloprid in Mice After a Single Gavage Dose (Bomann 1989a).

Acute Effect <sup>a</sup>	Time	Males							Females					
		10	71	100	120	140	160	250	10	100	120	140	160	250
<b>Doses mg/kg</b>		10	71	100	120	140	160	250	10	100	120	140	160	250
<b>No. of Mice Tested</b>		5	5	5	5	5	5	5	5	5	5	5	5	5
<b>Mortality</b>	10'-1h	0	0	1	2	2	5	5	0	0	1	1	2	5
<b>Apathy</b>	5'-4h	0	5	5	5	5	5	5	0	5	5	5	5	5
<b>Decreased motility</b>	5'-5h	0	2	5	5	5	5	5	0	5	5	5	5	5
<b>Labored breathing</b>	5'-7h	0	5	5	5	5	5	5	0	5	5	5	5	5
<b>Tremor</b>	1h-2h	0	1	2	3	0	5	5	0	5	1	5	5	5
<b>Spasmodic state</b>	5'-1h	0	0	1	2	2	5	4	0	0	1	1	5	5
<b>Staggering gait</b>	5'-1h	0	0	2	5	5	5	5	0	5	5	5	5	5

a/ Intensity of clinical signs were as 1 for the males at 71 mg/kg/d and 1-2 for the females at 100 mg/kg. The intensity of clinical signs at the higher doses was graded as 2 or 3.

**Inhalation-Rat:** Imidacloprid was assessed for acute inhalation toxicity in Wistar rats (Pauluhn, 1988a). Five animals/sex/dose were exposed by head/nose only to imidacloprid in the form of dust (95.3% a.i.) for 4 hours. The concentrations of imidacloprid were 1220, 2577 and 5323 mg/m<sup>3</sup> (Table 3). The control groups received air alone. At these concentrations, 89%, 94% and 96% of the dust particles, respectively, had an aerodynamic droplet size (MMAD) larger than 5 µm. Particles with MMAD of >5 and up to 10 µm deposit predominantly in the nasopharyngeal region (head airway region) in rats. Particles with MMAD of < 5 µm deposit in the bronchial region and the deeper lung airways of rats (Raabe et al., 1988; SOT, 1992; Pauluhn, 2003). Toxic signs were produced within 4-6 h of the treatment with concentrations higher than 1220 mg/m<sup>3</sup>, and included difficult breathing, reduced motility, piloerection and tremors. None of the animals died as a result of the treatment. The LC<sub>50</sub> was >5323 mg/m<sup>3</sup>. The NOEL for acute inhalation toxicity was 1220 mg/m<sup>3</sup>, based on clinical signs at the LOEL of 2577 mg/m<sup>3</sup>. Using a rat default breathing rate of 0.96 m<sup>3</sup>/kg/day, the LOEL<sup>2</sup> and the NOEL<sup>2</sup> could be calculated as 412 mg/kg/day and 195 mg/kg/day<sup>3</sup>, respectively (Table 3). However, it is uncertain whether the later dose is the NOEL for the acute inhalation toxicity, because of the possible limited

<sup>2</sup> Equivalent dosages were calculated by using the rat default breathing rate of 0.96 m<sup>3</sup>/kg/day in the following equations:

$$\text{Dose (mg/kg/day)} = \text{Concentration (mg/m}^3\text{)} \times \frac{0.96 \text{ m}^3}{\text{kg.day}} \times \frac{4 \text{ hours}}{24 \text{ hours}} \quad (1 \text{ day exposure})$$

bioavailability of imidacloprid due to the large particle size of the dust. For inhalation toxicants causing systemic effects, rather than local toxicity, particles that deposit to any region of the respiratory tract (i.e. MMAD of  $\leq 10 \mu\text{m}$ ) may be considered as bioavailable (Raabe et al., 1988). However, the study provided data on the percentage of particles with MMAD  $\leq 5 \mu\text{m}$ . Adjusting the dose of 195 mg/kg/day for 11% of particles with MMAD  $\leq 5 \mu\text{m}$  would result in an acute inhalation NOEL of 20 mg/kg/day.

In a supplemental study using the same experimental protocol, rats were exposed to a liquid aerosol of imidacloprid (Pauluhn, 1988a). The aerosol was prepared from 2.5% imidacloprid in Lutrol as a vehicle. A single analytical concentration of 69 mg/m<sup>3</sup> was administered to the rats by head/nose only for 4 h. The equivalent dose<sup>2</sup> could be calculated as 11 mg/kg/day. This was reported as the highest concentration of imidacloprid, which was attainable in the form of a liquid aerosol. Control animals received aerosol alone. Clinical signs or mortalities were not observed during the 14 day-observation period. This study was considered unacceptable by the DPR as a fulfillment of the requirement for acute inhalation toxicity data, because the methodology to determine the analytical concentration of imidacloprid was not provided.

In a parallel subacute inhalation toxicity study, 10 Wistar rats/sex/group were exposed by head/nose only to imidacloprid dust 6 hours/day for 5 days (Pauluhn, 1988a). The concentrations of imidacloprid were 20, 109 and 505 mg/m<sup>3</sup> (Table 3). At these concentrations, 46%, 43% and 82% of the dust particles, respectively, exceeded in size the 5  $\mu\text{m}$  respirable range in rats. The control groups received air alone. This study included more elaborated toxicity evaluation (e.g. clinical signs, clinical chemical, hematological and histopathological changes) for a period of 2 weeks after the treatment. The clinical chemistry tests revealed that 5 days of exposure to 109 mg/m<sup>3</sup> imidacloprid induced the mixed-function oxidases (MFO) in the liver of about 28% (p<0.01, males) and 142% (p<0.01, females). In addition, 6% (p<0.01) reduction of the body weights occurred in the females after 4 days of exposure to 109 mg/m<sup>3</sup> imidacloprid. The activities of the liver MFO in the rats from the 505 mg/m<sup>3</sup> were not measured. Mortalities or other cumulative toxic effects were not observed. The author of the study considered the induction of the MFO and the reduction in body weights at 109 mg/m<sup>3</sup> imidacloprid as treatment-related effects and concluded that 20 mg/m<sup>3</sup> imidacloprid did not cause toxicity after 5 days of inhalation exposure. The equivalent dose<sup>4</sup> could be calculated as 3.2 mg/kg/day. Adjusting dose of 3.2 mg/kg/day for 54% of particles with MMAD  $\leq 5 \mu\text{m}$  would result in a NOEL of 1.7 mg/kg/day. This study was considered by the DPR as supplemental information.

**Intraperitoneal-Rat:** Imidacloprid (94.2%) was studied for acute intraperitoneal (i.p.) toxicity in Wistar rats (5 animals/sex/dose) (Krotlinger, 1990). The tested doses were: 10, 100, 160, 170, 180, 200, 250 and 500 mg/kg (males) and 10, 100, 150, 180, 200, 224 and 250 mg/kg (females). Toxic signs were produced within 5 min of treatment with doses higher than 10 mg/kg, and included tremors, apathy, reduced motility, ptosis and labored breathing. Mortalities occurred from a dose of 170 mg/kg. At this dose, 80% percent of the male rats died within 2.5-5 hours of treatment; 40% of the female rats died at 180 mg/kg. The LD<sub>50</sub> for the i.p. administered

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<sup>4</sup> Equivalent dosages were calculated by using the rat default breathing rate of 0.96 m<sup>3</sup>/kg/day in the following equations:

$$\text{Dose (mg/kg/day)} = \text{Concentration (mg/m}^3\text{)} \times \frac{0.96 \text{ m}^3}{\text{kg}\cdot\text{day}} \times \frac{6 \text{ hours}}{24 \text{ hours}} \times \frac{5 \text{ days}}{7 \text{ days}}$$

imidacloprid was estimated as 186 mg/kg/day for female rats and 160-170 mg/kg for male rats (Table 2). The NOEL was 10 mg/kg, based on toxic effects at the LOEL of 100 mg/kg.

**Intraperitoneal-Mouse:** In a study published in the open literature, male Swiss-Webster mice were treated intraperitoneally with imidacloprid and with its metabolite, desnitro-imidacloprid (Chao and Casida, 1997). Both compounds were dissolved in DMSO, however further experimental details such as the number of animals, doses and the treatment protocol were not provided. The LD<sub>50</sub> for imidacloprid was reported as 39-49 mg/kg, whereas the lethal potency of the metabolite desnitro-imidacloprid was significantly higher (7-24 mg/kg, Table 2). Tremors were observed in mice, which were treated with near-lethal or lethal dose levels, but the exact doses were not shown.

**Dermal-Rat:**

In an acute dermal toxicity study, imidacloprid (94.2% in 0.9% NaCl) was applied as a paste to the shaven area of the back of Wistar rats (5/sex) at a dose of 5000 mg/kg (Krotlinger, 1989). The treatment site was covered during the 24-hour exposure period. Imidacloprid did not cause toxic signs and mortalities. The pathological evaluation did not reveal treatment-related changes. The acute dermal LD<sub>50</sub> of imidacloprid in rats was >5000 mg/kg (Table 2).

**Primary Dermal Irritation-Rabbits:** Imidacloprid (94.2% a.i.) was tested for irritation potential on the skin of rabbits (Pauluhn, 1988b). Three animals were treated with 500 mg imidacloprid mixed to a paste in water. The treatment site was covered during the 4-hour exposure period. The skin was then examined for erythema and edema 14 days post-treatment. One animal developed erythema 1 h after treatment, which was graded as 1 (slight) in the scale of 1 to 6; and was cleared within 24 hours. Based on these results, the technical grade imidacloprid was regarded by the DPR as “not an irritant to skin” (Table 2).

**Primary Eye Irritation-Rabbits:** Imidacloprid (94.2% a.i.) was tested for irritation potential in the eyes of rabbits (Pauluhn, 1988c). Three animals received about 60 mg imidacloprid/eye in 0.1 ml physiologic solution. Conjunctival irritation was graded as 2 in a scale of 1 to 3 following 1 h of treatment. The irritation was cleared within 24 h. This study showed that imidacloprid did not possess a local irritant potential to the eye (Table 2).

Based on the LD<sub>50</sub> and LC<sub>50</sub>, technical imidacloprid (94.2% pure) is a Category II oral toxicant (oral LD<sub>50</sub> greater than 50 mg/kg, but lower than 500 mg/kg), Category III dermal toxicant (dermal LD<sub>50</sub> between 2000 to 20,000 mg/kg), Category IV inhalation toxicant (greater than 20 mg/liter or 0.02 mg/m<sup>3</sup>), Category IV eye irritant (no irritation) and a category IV dermal irritant (caused erythema in rabbits that was cleared by 48 hours).

The median lethal doses (LD<sub>50</sub>) or median lethal concentrations (LC<sub>50</sub>) for imidacloprid (technical grade and formulations) and its metabolite desnitro-imidacloprid are listed in Table 2.

**Table 2.** Acute LD<sub>50</sub> and LC<sub>50</sub> Values for Imidacloprid and its Metabolite Desnitro-Imidacloprid.

Animal Species	LD <sub>50</sub> (mg/kg) or LC <sub>50</sub> (mg/m <sup>3</sup> )			References
	Route of Exposure	Males	Females	
<b>Imidacloprid (technical grade 94-98%)</b>				
Mouse	Oral	131	168	Bomann 1989a
Mouse	Intraperitoneal	39	-	Chao and Casida, 1997
Rat	Oral	424	450-475	Bomann, 1989b
Rat	Intraperitoneal	>160 <170	186	Krotlinger, 1990
Rat	Dermal	>5000	>5000	Krotlinger, 1989
Rat	Inhalation 4h dust	>5300 <sup>a,b,e</sup>	>5300	Pauluhn, 1988a
Rat	Inhalation 4h aerosol	>69 <sup>c,d,e</sup>	>69	Pauluhn, 1988a
Rabbit	Dermal	Not an irritant		Pauluhn, 1988b
Rabbit	Eye	Not an irritant		Pauluhn, 1988c
<b>Desnitro-Imidacloprid</b>				
Mouse	Intraperitoneal	7-24	-	Chao and Casida, 1997
<b>Imidacloprid (formulation 23%)</b>				
Rat	Oral	>4870	4143	Sheets, 1990a
Rabbit	Dermal	>2000	>2000	Sheets, 1990b

a/ Only 4-11% of the particles had an aerodynamic droplet size <5 µm.

b/ The equivalent dose could be calculated as > 848 mg/kg/day, using a rat default breathing rate of 0.96 m<sup>3</sup>/kg/day in the following formula:

$$\text{Dose (mg/kg/day)} = \text{Concentration (mg/m}^3\text{)} \times \frac{0.96 \text{ m}^3}{\text{kg.day}} \times \frac{4 \text{ hours}}{24 \text{ hours}}$$

c/ 100% of the particles had an aerodynamic droplet size <5 µm; max concentration

d/ The equivalent dose could be calculated as 11 mg/kg/day, using the formula in b.

e/ No effect at this dose.

**Table 3.** Acute No-Observed-Effect Levels (NOELs) and Lowest-Observed-Effect Levels (LOELs) for Imidacloprid.

Acute Study		NOEL	LOEL	Study Description
Species	Exposure	mg/kg/day		
<b>Rat</b> <b>5/sex/dose</b>	Oral (gavage) 1 dose	50	100	<b>Doses (mg/kg/day):</b> 50 (males only), 100, 250, 315, 400, 475 (females only), 500 and 1800 (Bomann, 1989b) <b>Effects at LOEL:</b> Apathy, labored breathing, tremors, gait incoordination, decreased motility, nasal and urine staining
<b>Mouse</b> <b>5/sex/dose</b>	Oral (gavage) 1 dose	10	71	<b>Doses (mg/kg/day):</b> 10, 71 (males only), 100, 120, 140, 160 and 250 (Bomann, 1989a) <b>Effects at LOEL:</b> labored breathing, decreased motility, staggering gait and trembling
<b>Rat</b> <b>5/sex/dose</b>	Inhalation 4 h (dust)	192 <sup>c</sup>	412	<b>Concentrations (mg/m<sup>3</sup>):</b> 0, 1220, 2577 and 5322 (Pauluhn, 1988a) <b>Doses<sup>a</sup> (mg/kg/day):</b> 0, 192, 412 and 848 <b>Effects at LOEL:</b> Difficult breathing, reduced motility, piloerection and tremors
<b>Rat</b> <b>10/sex/dose</b>	Inhalation 6h/day for 5 days (dust)	3.4 <sup>d</sup>	19 <sup>d</sup>	<b>Concentrations (mg/m<sup>3</sup>):</b> 0, 20, 109 and 505 (Pauluhn, 1988a) <b>Doses<sup>b</sup> (mg/kg/day):</b> 0, 3, 19 and 87 <b>Effects at LOEL:</b> Induction of MFO <sup>f</sup> in the liver (28% <sup>**</sup> males, 142% <sup>**</sup> females; p<0.01); 6% <sup>**</sup> (p<0.01) reduction in body weights of females

a/ The dosages were calculated using a the following formula in Table 1.

b/ The dosages were calculated a rat default breathing rate of 0.96 m<sup>3</sup>/kg/day in the following formula:

$$\text{Dose (mg/kg/day)} = \text{Concentration (mg/m}^3\text{)} \times \frac{0.96 \text{ m}^3}{\text{kg.day}} \times \frac{6 \text{ hours}}{24 \text{ hours}} \times \frac{5 \text{ days}}{7 \text{ days}}$$

c/ Only 4-11% of the particles had the recommended aerodynamic droplet size <5 μm.

d/ Only 57-18 % of the particles had an aerodynamic droplet size <5 μm.

f/ MFO, Mixed-Function Oxidases;

<sup>\*\*</sup>, Statistically significant difference from controls at p ≤ 0.01 (Fisher's Exact test)

Note that the toxic signs were evident in a relatively brief time (within 5-40 min) after an oral exposure and in 4-6 h after an inhalation exposure.

### **III.B.1.b. Additional Acute Toxicity Studies**

Other toxicological studies may also be useful for identifying acute NOELs, if toxic effects are observed after a single dose (e.g., teratological effects) or short-term of exposure (developmental or neurotoxic effects). Because the nervous system is the main target of imidacloprid, the toxicity thresholds established from the neurotoxicity studies (Section III.H) are particularly pertinent. The selection of the critical NOEL for characterizing the risk from acute exposure to imidacloprid is presented in Section IV.A.2. under RISK ASSESSMENT.



### **III.C. SUBCHRONIC TOXICITY**

**Summary:** Seven subchronic toxicity studies were submitted to the DPR to characterize the effects of imidacloprid in rats, mice, dogs and rabbits. These included 96- and 98-Day dietary studies in rats, a 107-Day oral study in mice, 28-Day and 13-Week oral studies in dogs, a 3-Week dermal treatment in rabbits and a 4-Week inhalation study in rats.

The most common toxic effect observed in the subchronic oral toxicological studies in rats, mice and dogs was a reduction in body weight. The liver was the principal target organ as demonstrated by the hepatic necrosis or hypertrophy in rats and dogs. The liver toxicity was further evidenced by the elevated activities of transaminases, alkaline phosphatase and glutamate dehydrogenase in the serum, and alteration of other clinical chemistry parameters such as triglycerides, cholesterol and the blood clotting time. Additional morphological effects included testicular degeneration in rats and dogs; atrophy of thyroid gland and bone marrow, and advanced involution of the thymus in dogs. Imidacloprid was a potent inducer of the hepatic mixed-function oxidases. In the oral toxicity studies, dogs appeared to be the most sensitive species. Subchronic exposure of dogs to imidacloprid resulted in severe tremors, which is characteristic for nicotine intoxication.

#### **III.C.1. Oral Studies – Rat**

The toxicity of imidacloprid (92.8%) was evaluated in Wistar rats for a period of 98 days (Eiben, 1988a). Ten rats/sex/ were exposed daily to imidacloprid at doses of 0, 120, 600 and 3000 ppm. Based on the reported food consumption of the animals, the estimated imidacloprid doses were 0, 11, 57 and 409 mg/kg/day (males) and 14, 78 and 513 mg/kg/day (females).

General Toxicity and Clinical Chemistry. Imidacloprid did not cause death at any dietary level. Body weight reduction (up to 11 %  $p \leq 0.05$ ) starting from Week 2 of treatment was evident in the females at 600 ppm, suggesting that this or higher imidacloprid doses may exceed the maximum tolerated dose (MTD). Indeed, the average body weight of the animals from both sexes in the 3000 ppm group was up to 15-24% ( $p \leq 0.01$ ) less than the control. This effect was seen throughout the treatment period. Interestingly, the food consumption was increased by 41%-51% by these rats. Therefore, the effect on the body weight was clearly treatment-related and could not be attributed to food palatability problems. Other effects in the animals at 3000 ppm included elevated alkaline phosphatase (AP) activity (17-34%,  $p < 0.01$ ) and creatinin levels (22%,  $p < 0.01$ ) in the blood. Decreased levels of glucose (11%,  $p < 0.01$ ) and cholesterol 29% ( $p < 0.01$ ) were measured in the blood of these rats, which is indicative of imidacloprid-induced changes in the metabolism of carbohydrates and fats.

Target organs. Cell necrosis was diagnosed in the liver of one male in the 3000 ppm group. The observed liver change was defined as treatment-related by the authors, because it involved multifocal cell necroses in central, intermediary and peripheral lobular zones. Further histological examination revealed degenerative changes of the testicular tubuli in five of the ten male rats, which were repeatedly exposed to 3000 ppm imidacloprid. This report was considered supplemental by the DPR, because it was not a FIFRA guideline study, lacked analysis of the diet and presented only limited evaluations of the blood and tissues. The subchronic oral NOEL was 120 ppm (14 mg/kg/day), based on 11% reduction in body weight of the female rats at the LOEL of 600 ppm (78 mg/kg/day).

In a 13-Week oral toxicity study, imidacloprid (95.3%) was administered through the diet to Wistar rats (10 rats/sex/group; Eiben, 1989). The dose levels were 0, 150, 600 or 2400 ppm, which corresponded to average daily doses of 0, 14, 61, or 300 mg/kg/day for males and 0, 20, 83 or 422 mg/kg/day for females. The 13-Week dosing period was followed by a 4-Week recovery period (no treatment) for the control group and the high-dose animals.

The findings on the subchronic toxicity of imidacloprid were similar to the earlier, range-finding 98-Day study in rats. Mortality and clinical signs were not evident at any dietary level. Body weights were reduced by about 8% ( $p \leq 0.01$ ) in the males from the 600 ppm group. The average body weight for the males and females at the 2400 ppm group was 14-16% less than control ( $p \leq 0.01$ ), despite their increased food consumption. The body weights of these rats remained reduced on Day 119 (the end of the recovery period). The liver was the principal target organ. The authors concluded that the following changes in the serum chemistry of the animals exposed to 2400 ppm imidacloprid were indicative of hepatotoxicity:

- (1) Elevated activities in the serum of alkaline phosphatase (AP, 15%  $p \leq 0.01$ ) and alanine aminotransferase (ALT, 25%  $p \leq 0.01$ ).
- (2) Decreased levels of protein 8% ( $p \leq 0.05$ ), albumin (6%  $p \leq 0.05$ ), triglycerides (52%,  $p \leq 0.01$ ) and cholesterol (47%  $p \leq 0.05$ ).
- (3) Lengthening of the blood clotting time (9% females; 10% males,  $p \leq 0.01$ ).

The following liver effects were reported for the males in the 2400 ppm dose group: increased incidence of focal necrosis (4 of 8 males), single cell necrosis (8 of 10 males), swollen nuclei and cytoplasmic transformation (9 of 10 males) and round cell infiltration (all males). Round cell infiltration, necrosis of hepatocytes and cytoplasmic changes were also observed in 3 males in the mid-dose (600 ppm). Isolated cell necrosis, necrosis of groups of hepatocytes and round cell infiltrates are indicative of liver damage. Cytoplasmic changes and swelling of nuclei are often caused by an increased liver function (Haschek and Rousseaux, 1998). The subchronic oral NOEL was 150 ppm (14 mg/kg/day), based on liver toxicity and reduced body weight in the male rats at the LOEL of 600 ppm (61 mg/kg/day).

### **III.C.2. Inhalation Studies – Rat**

Imidacloprid (95.2%) was assessed for subchronic inhalation toxicity in Wistar rats (Pauluhn, 1989). Ten rats/sex/dose were exposed by head/nose only to imidacloprid in the form of dust. The exposure time was 6 hours/day, 5 days/week over a period of 4 weeks (Table 4). The concentrations of imidacloprid were 0, 5.5, 30.5 and 191.2 mg/m<sup>3</sup>/day. The control groups received air alone. The selection of doses was based on an earlier 5-day subacute study in rats, which showed a marked induction of MFO in the liver after repeated exposure to 505 mg/m<sup>3</sup>/day imidacloprid (Pauluhn, 1988a). The nominal exposure doses<sup>5</sup> could be calculated as 0.9, 5.2 and 33 mg/kg/day, when using a rat default breathing rate of 0.96 m<sup>3</sup>/kg/day. Characterization of the particles revealed that respirable dust was present in all dose groups (Table 4). More than 95% of the particles in the lowest dose group (5.5 mg/m<sup>3</sup>) had MMAD  $\leq 5 \mu\text{m}$ , about 45% - 57% of the particles in the middle and high dose groups were larger than 5  $\mu\text{m}$ . Particle size of  $\leq 10 \mu\text{m}$  is

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<sup>5</sup> Equivalent dosages were calculated by using the equation in Table 2.

generally recommended to assure bioavailability in rats (Raabe et al., 1988; SOT 1992). The increase in the MMAD with increasing concentrations of imidacloprid was attributed to particle agglomerations.

**Table 4.** Effects of Imidacloprid in Wistar Rats After 4-Weeks of Inhalation Head/Nose-Only Exposure (Pauluhn, 1989).

Effect	Dose							
	Males				Females			
mg/m <sup>3</sup> /day	0	5.5 <sup>a</sup>	30.5 <sup>b</sup>	191.3 <sup>b</sup>	0	5.5	30.5	191.3
mg/kg/day	0	0.9	5.2	33	0	0.9	5.2	33
Body Weight (% of control)								
Week 4	100	100	99	94**	100	100	100	100
Liver Weight (%)								
Absolute	100	97	93	93	100	101	107	114
Relative	100	97	93	97	100	100	109	112
ALT (% of control)	100	100	92	99	100	95	125**	170**
AP (% of control)	100	109	106	111	100	109	120*	146**
GLDH (% of control)	100	98	147*	330*	100	99	200*	732**
Plasma ChE	100	100	100	100	100	107	74	72
MFO (% of control)	100	90	98	183**	100	100	127*	177**
Coagulation Time (sec)	34.2	34.2	35.2	35.5	32.6	32.5	32.9	35.9* 10%↑
TAG (% of control)	100	87	82	50*	100	58	67	27**

**a/** 95% of the particles had MMAD ≤ 5 μm

**b/** 45% - 57% of the particles had MMAD ≤ 5 μm.

ALT, Alanine Aminotransferase; AP, Alkaline Phosphatase; MFO, mixed function oxidases; GLDH, glutamate dehydrogenase; ChE, cholinesterase; \*, \*\* Statistically significant difference from controls at p ≤ 0.05 or p ≤ 0.01, respectively.

The principal toxicological findings were the reduction in body weight gains (6-9%, p ≤ 0.01) of the male rats from the 191.2 mg/m<sup>3</sup>/day group and the concentration-dependent increase of 7-14% in the absolute and relative (to body weight) liver weights of females treated with 30.5 and 191.2 mg/m<sup>3</sup>/day imidacloprid (Table 4). Imidacloprid clearly induced hepatocellular damage and impairment of the liver function in these females. This was demonstrated by (i) increase in the activities of the serum ALT, AP and glutamate dehydrogenase (GLDH) by 25%, 70% and 732% (p ≤ 0.01), respectively; (ii) elevated bilirubin (25%, p ≤ 0.01), (iii) lengthening of coagulation time (10%, p ≤ 0.01) and (iv) elevated urinary pH to a statistically significant extent (from 6.5 in to 7.4). The later effect is generally attributed to a reduced catabolism of hepatic proteins. Finally, marked induction of the hepatic MFO of 34-83% (p ≤ 0.01) was observed in the animals treated with 30.5 and 191.2 mg/m<sup>3</sup>/day imidacloprid. Interestingly, the plasma ChE

activity was reduced by 26% and 28% in the female rats from the 30.5 and 191.2 mg/m<sup>3</sup>/day groups, respectively. The cause of this effect is unknown, because imidacloprid is not a ChE inhibitor. Since plasma ChE is synthesized in the liver, the decrease in the ChE activity may be related to the observed changes in the liver function.

This report was not a FIFRA guideline study and thus was considered by the DPR as supplemental information. Both, the author of the study and the DPR toxicologists established the NOEL for the subchronic inhalation toxicity as 5.5 mg/m<sup>3</sup>/day (0.9 mg/kg/day), based on changes in liver weights, alterations in liver function at the LOEL 30.5 mg/m<sup>3</sup>/day (5.2 mg/kg/day).

### **III.C.3. Oral Studies – Mouse**

The toxicity of imidacloprid (92.8%) was evaluated in B6C3F1 mice (10/sex/dose) for a period of 107 days (Eiben, 1988b). The dietary levels were 120, 600 and 3000 ppm, which reportedly corresponded to 77, 397 and 2323 mg/kg/day (males) and 91, 453 and 3075 mg/kg/day (females). These imidacloprid doses were based upon daily food consumption, which ranged from 16-18 g/animal/day for both sexes from the various study groups.

The animals in the 3000 ppm dose group were in poor general condition, had rough coats and markedly lower body weights. The average body weight of the males and females in this group was 15% and 27% ( $p \leq 0.01$ ), respectively, lower than the control. The food consumption at this dose was distinctly higher (11% males and 51% females) compared to the control, thus indicating that the reduction in body weight was caused by the treatment. Lower body weight (5%,  $p \leq 0.05$ ) was also reported for the males at the 600 ppm dose group. Evaluation of clinical chemistry parameters revealed decreased cholesterol and urea in males (22% and 32%, respectively,  $p \leq 0.01$ ) and higher serum AP activity (up to, 47%  $p \leq 0.01$ ) in males and females treated with 3000 ppm imidacloprid. A total of 16 mice died at the end of the 13 or 14 week of treatment, following blood withdrawal. These included one male from the 120 ppm dose-group, one male from the 600 ppm group, seven males and seven females in the 3000 ppm group. Gross pathological changes were not observed in the mice, which died or were sacrificed at the end of the study. The imidacloprid-induced drastic weight loss was considered a possible reason for the deaths of the mice following blood withdrawal in the 3000 ppm dose group. However, mice died after repeated treatment with 600 and 120 ppm imidacloprid, which caused less or even no reduction in the body weights. Similarly, in a chronic study a significant number of males fed 2000 ppm imidacloprid died during manipulations such as blood withdrawals and tattooing (Watta-Gebert, 1991, 1991a; see Section III.D.2. under CHRONIC TOXICITY). In the later case, the death was reported to be due to hypersensitivity to ether, which was used as anesthesia during these procedures. This report was not a FIFRA guideline study and thus was considered supplemental by the DPR. The LOEL was 3000 ppm, based on poor appearance, reduced body weights and mortality of the animals.

The results from this study indicated that 600 ppm imidacloprid did not cause apparent toxicity. However, there was a substantial uncertainty associated with the reported dose of 397 mg/kg/day as the NOEL for subchronic oral toxicity in mice. This dose was estimated based on unusually high food consumption. The food intake levels represented about 60%-100% of the mice body weight. The report did not indicate whether the calculated quantity of food consumed by the mice was corrected for spillage. Therefore, the presented values may reflect errors in the estimation of both, the actual food consumption and the imidacloprid intake. The DPR

toxicologists adjusted the ingestion of imidacloprid to 1/7 of the mice mean body weight (see Attachment IV), which is similar to a default food consumption of 15% of the body weight of an adult mouse (30 g). The revised NOEL would be 86 mg/kg/day, based on the revised LOEL of 427 mg/kg/day.

It is interesting to note that mice appeared to be less sensitive to the subchronic toxicity of imidacloprid compared to the acute treatment. The subchronic oral NOEL was 9-fold higher than the threshold for acute toxicity (10 mg/kg/day, based on labored breathing, decreased motility, staggering gait and trembling at the LOEL of 71 mg/kg/day).

#### **III.C.4. Oral Studies – Dogs**

The subchronic toxicity of imidacloprid (92.8%) was examined in Beagle dogs by administering it through the diet for a period of 4 or 13 weeks (Tables 5 and 6).

The 4-Week study included four groups of dogs, each containing two males and two females (Block, 1987). The doses were 0, 200 ppm, 1000 ppm and 5000 ppm, which corresponded to 0, 7.3, 31 and 49 mg/kg/day. All animals in the 5000 ppm dose group died or were sacrificed prior to the completion of the study (Table 5). The first dog died after only 2 days of the treatment; the other three dogs died on Day 18 or Day 24. The clinical signs for the dying animals included marked reduction in food intake, weight loss (up to 42%), severe tremor, ataxia and vomiting. One surviving male from the 5000 ppm group had significantly reduced levels of serum triglycerides and alpha-1 globulin (75% and 82%,  $p \leq 0.01$ , respectively). These changes may be associated with the observed hepatocellular atrophy in this dog. Treatment-related hepatocellular atrophy was also diagnosed in the two surviving females from the 5000 ppm group. Additional toxic effects in the 5000 ppm dose group included atrophy of thyroid gland and bone marrow, advanced involution of the thymus (graded as moderate to severe) and testicular tubule degeneration. The involution or decrease in size of the thymus represents loss of lymphoid mass and degeneration of the epithelial cells, which in turn leads to reduced effectiveness of T-lymphocyte function (Aronson, 1993). The involution of the thymus occurs naturally with aging. In this context, imidacloprid may be regarded as causing premature aging of the thymus.

The lower tested dose of imidacloprid 1000 ppm caused a decrease in food consumption (17% compared to the pretest level), however, the body weights of these dogs were not affected by the treatment. Hypertrophy of hepatocytes in one male and follicular atrophy of the thyroid in one female in this group were reported as morphological alterations produced by imidacloprid. This report was considered supplemental by the DPR, because it was not a FIFRA guideline study. Based on the treatment-related morphological changes at the LOEL of 1000 ppm (31 mg/kg/day), the subchronic oral NOEL for dogs was 200 ppm (7.3 mg/kg/day).

In the 13 Week dietary study, imidacloprid was administered to Beagle dogs (Bor:Beag strain; 4 dogs/sex/dietary level) as food mash at doses of 0, 200, 600 or 1800 ppm (Ruf, 1990). The 1800 ppm produced a drastic reduction in body weight (8-20% less than control) within the first 4 weeks (Table 6). This effect was, at least in part, due to the 30-54% decrease in the food intake. Because of the low food consumption, the concentration of imidacloprid was thereafter reduced from 1800 to 1200 ppm until the completion of the study. Nevertheless, the average body weight in the high-dose animals remained lower than the control by 6% (females) and 9% (males) at the completion of the study at week 13. Based on the study report on the weekly imidacloprid intake, the average daily doses corresponding to 200, 600 and 1800/1200 ppm could be calculated as 8, 24 and 46 mg/kg/day. There was no mortality or evidence of tissue damage. Vomiting of food or

mucus occurred at a higher incidence in the females of the 200, 600 and 1800/1200 ppm dose-groups (Table 6). However, the number of vomiting incidents for each of the females never exceeded 1 over the entire treatment period.

Trembling was evident in all males and females treated with 600 and 1800/1200 ppm imidacloprid. The trembling occurred within the first 5 weeks of treatment on 1 to 2 occasions in the animals fed 600 ppm imidacloprid; and as many as 14 times for the dogs of the 1800/1200 ppm group. In addition, severe tremors were reported for all 8 dogs (up to 5 incidents within Weeks 1-5) in the highest dose group (46 mg/kg/day). The same toxic effects (severe tremors and vomiting) were observed in the dogs treated with 49 mg/kg/day imidacloprid in the 4-Week dietary study (Block, 1987; Table 5). The NOEL from this study was 200 (ppm) 8 mg/kg/day, based on clinical symptoms (tremors) at the LOEL of 600 ppm (24 mg/kg/day).

It should be noted that similar doses of imidacloprid produced toxic effects in Beagle dogs, which differed in severity in the 4-Week and 13-Week studies. For example, imidacloprid at 49 mg/kg/day in the 4-Week study caused a marked toxicity, including 100% mortality. In contrast, the effects of 46 mg/kg/day imidacloprid fed to the dogs for four weeks in the 13-Week study were restricted mainly to clinical symptoms, with no deaths and tissue damage. Because these studies were conducted in two different laboratories, the inconsistent results may reflect the use of different protocols and different strains or source of animals.

### **III.C.5. Dermal Studies – Rabbit**

In a subchronic dermal toxicity study, imidacloprid (95%) was applied as a paste to the shaven area of the back and flank of HC:NZW rabbits (5/sex) at a dose of 1000 mg/kg (Flucke, 1990). The control group included vehicle (2% Cremophor EL in physiological saline solution) treated animals. The treatment site was covered with a porous patch 6 hours/day, 5 days/week for 3 weeks. The rabbits were observed for signs of general toxicity, behavioral alterations and skin irritation (evaluated by Draize test). Clinical chemistry examinations were performed prior to and at the end of the treatment period and pathological evaluations were done two or three days after the last dermal dose. Imidacloprid did not cause toxic signs, mortalities or pathology changes in the examined organs. The subchronic dermal NOEL for imidacloprid was >1000 mg/kg/day.

**Table 5.** Effects of Imidacloprid in Beagle Dogs After 4 Weeks of Treatment Through the Diets (Block, 1987).

Effects	Dose								
	Males				Females				
Dog 4-Week Dietary Study	0	200	1000	5000 <sup>b</sup>	0	200	1000	5000 <sup>a</sup>	
ppm	0	200	1000	5000 <sup>b</sup>	0	200	1000	5000 <sup>a</sup>	
mg/kg/day	0	7.3	31	49	0	7.3	31	49	
Death	0/2	0/2	0/2	2/2	0/2	0/2	0/2	2/2	
Body Weight <sup>b</sup> (kg)	Week -1	9.4	8.4	8.4	7.5 <sup>c</sup>	9.3	7.6	8.1	8.1 <sup>c</sup>
	4	9.5	8.7	8.6	5.5 (73%) <sup>d</sup>	9.5	8.0	8.5	6.0 (74%) <sup>d</sup>
Food Intake <sup>c</sup> (g/day)	Week -1	300	289	250	282 <sup>d</sup>	300	295	283	282 <sup>d</sup>
	4	300	294	207 (83%) <sup>e</sup>	93 (33%) <sup>e</sup>	300	295	296	45 (16%) <sup>e</sup>
Severe Tremors	0/2	0/2	0/2	2/2	0/2	0/2	0/2	2/2	
Ataxia	0/2	0/2	0/2	2/2	0/2	0/2	0/2	2/2	
Vomiting	0/2	0/2	0/2	1/2 <sup>f</sup>	0/2	0/2	0/2	2/2 <sup>f</sup>	
Hepatic Hypertrophy	0/2	0/2	1/2	0/2	0/2	0/2	0/2	0/2	
Week									
Hepatocellular Atrophy	0/2	0/2	0/2	1/2	0/2	0/2	0/2	2/2	
Week									
Yolk Follicular Atrophy	0/2	0/2	0/2	1/2	0/2	0/2	1/2	1/2	
Week									
Bone Marrow Atrophy	0/2	0/2	0/2	1/2	0/2	0/2	0/2	1/2	
Involution of Thymus (moderate-to-severe)	0/2	0/2	0/2	2/2	0/2	0/2	0/2	1/2	
Testicular Tubule Degeneration	0/2	0/2	0/2	1/2	-	-	-	-	
Triglycerides	0.37	0.43	0.52	0.09 <sup>d</sup> (24%) <sup>e</sup>	0.34	0.36	0.45	0.34	
Alfa-1-Globulin	0.083	0.101	0.122	0.017 <sup>d</sup> (20%) <sup>e</sup>	0.93	0.111	0.102	0.089	

**a/** One male died on Day 2 and one female died on Day 18; the other two dogs in this group were euthanased on Day 24.

**b/**The body weights or the food consumption are expressed as the mean of two animals.

**c/** level of the one surviving animal in this group. **d/** % of the base-line (pretest at week -1) body weights or food consumption, because the baseline body weights differed substantially between the dose-groups. **e/** percent of the control. **f/** The male dog vomited once in the first week; one female vomited twice and the other female vomited once within the first week.

**Table 6.** Effects of Imidacloprid in Beagle Dogs After 13 Weeks of Treatment Through the Diets (Ruf, 1990)

Dog 13-Week Dietary Study	Dose							
	Males				Females			
ppm	0	200	600	1800/1200	0	200	600	1200/1800
mg/kg/day	0	8	24	64	0	8	24	64
Body Weight <sup>a</sup> (kg) -1 <sup>b</sup>	7.3	7.2	7.1	7.0	6.4	6.6	6.4	6.7
Week	9.6	9.2	9.6	8.7	9.0	9.5	8.5	8.6
Body Weight Gain (kg)	(+2.6)	(+2)	(+2.5)	(+1.7)	(+2.6)	(+2.6)	(+2.1)	(+1.8)
Food Intake <sup>b</sup> (kg/week) Week -1	2.1	2.1	2.1	1.1	2.1	2.1	1.9	2.1
13	2.5	2.5	2.2 (83%) <sup>c</sup>	2.1	2.4	2.4	2.5	2.3
Trembling <sup>d</sup>	0/4	0/4	4/4	4/4	0/4	0/4	4/4	4/4
Severe Tremors <sup>e</sup>	0/4	0/4	0/4	4/4	0/4	0/4	0/4	4/4
Week 13 Vomiting <sup>f</sup>	1/4	1/4	0/4	2/4	0/4	1/4	2/4	3/4

**a/** The body weights or the food consumption are expressed as the mean of four animals.

**b/** The measurements were performed 1 week prior to the treatment (pretest level).

**c/** The number in parentheses represents percent of the control

**d/** Trembling occurred in all males and females in the 600 ppm group within the first week on 1 to 2 occasions; and in all animals in the 1800/1200 ppm group, as many as 14 times within Weeks 1-5.

**e/** Severe tremors (up to 5 incidents) were reported for all males and females in the 1800/1200 ppm group within Weeks 1-5.

**f/** One control male vomited 4 times within the 1<sup>st</sup> week. The number of vomiting incidents in each of the males or females in the imidacloprid-treated groups never exceeded 1 over the entire treatment period.



### **III.D. CHRONIC TOXICITY AND ONCOGENICITY**

Five chronic toxicity/oncogenicity studies with imidacloprid were submitted to the DPR to characterize its long-term toxic effects and potential to cause cancer in rodent and non-rodent species. These included four 2-year dietary studies in rats and mice and one 1-year oral study in dogs.

The most common toxic effect in the chronic oral studies was the reduction in body weight. Rats appeared to be the most sensitive species. The principal morphologic effect was thyroid lesions in rats. An interesting finding in mice was the development of hypersensitivity to anesthesia after chronic treatment with imidacloprid. These mice appeared overall healthy, but died shortly after exposure to ether. It is possible that chronic exposures to imidacloprid may reduce the ability of mice to respond to an additional challenge with xenobiotics. The evidence for carcinogenicity in the chronic studies was not sufficient to implicate imidacloprid as a cancer-causing chemical.

#### **III.D.1. Oral Studies – Rat**

In a 2-year-chronic toxicity/oncogenicity study, imidacloprid (94.3% a.i.) was administered to Wistar rats (50/sex/dose) at dietary levels of 0, 100, 300 and 900 ppm (Eiben and Kaliner, 1991). Ten more rats/sex/dose were used for interim examinations after 1 year of treatment. The selection of doses was based on results from two earlier subchronic feeding studies in rats, which showed necrosis of hepatocytes, changes in the serum chemistry, reduced body weight, and degenerative testicular alterations at 600 or 3000 ppm. In a supplemental study, 50 rats/sex were used as controls or fed with imidacloprid at 1800 ppm for 2 years (Eiben, 1991). The aim of this second chronic toxicity study was to determine the maximum tolerated dose of imidacloprid (MTD) in rats. The two studies were performed in the same laboratory and the protocols of were sufficiently similar to permit an evaluation of the overall results. Consequently, the control group of the combined studies included 100 animals/sex/ and each of the treatment groups had 50 rats/sex/dose. Based on the food consumption, the average daily doses in the chronic studies corresponded to 5.7, 17, 51 or 103 mg/kg/day for males and 7.6, 25, 73 and 144 mg/kg/day for females.

Chronic exposure to 1800 ppm imidacloprid resulted in a substantial reduction in body weights in both sexes at all times. The weight decline reached maximum of 11% -12%, ( $p \leq 0.01$ ) at Week 10. About 5 to 8% ( $p \leq 0.01$ ) decrease in body weight was observed in males and females at the 900 ppm dietary level. The reduction in the body weight was clearly treatment-related, because food intake of the animals from the 900 and 1800 ppm groups was similar to the control. Although changes in liver morphology were not observed, there were some indications of liver toxicity for both sexes at 1800 ppm based on alterations in serum chemistry. These included elevated activities of serum AP (up to 37%,  $p \leq 0.01$ ) at 6, 12 and 18 months, creatine kinase (up to 25%,  $p \leq 0.01$ ) and aspartate aminotransferase (AST, 43%,  $p \leq 0.01$ ), and reduced cholesterol level (38%,  $p \leq 0.01$ ) at 24 months.

The principal treatment-related effect in rats treated for 24 months with imidacloprid was lesions in the thyroid gland. Parafollicular hyperplasia and fewer colloid aggregation sites in the thyroid were diagnosed in the rats from the 1800 ppm dose-group (Table 7). There was a marked, dose-dependent increase in the incidence and severity of mineralized particles in the thyroid follicles. This effect became statistically significant in male rats fed 300 ppm of imidacloprid and in females at 900 ppm ( $p \leq 0.001$ , Table 7). Furthermore, among the 31 males with mineralized particles in the 300 ppm dose-group, 25 exhibited “Grade 1” severity and 6 showed “Grade 2”

severity. The 3 male rats with mineralized colloid from the concurrent control (100 males) showed only minimal severity (“Grade 1”, Table 7). At all doses, the levels of thyroid hormones in plasma (T3, T4 and TSH) in these rats were normal. The occurrence of mineralized colloid indicates involution of follicles and is generally considered as a sign of a biological aging. In this context, imidacloprid may be regarded as causing premature aging of the thyroid follicles. Historical data on the incidence of mineralized particles were available from the Institute of Toxicology at BAER AG in Germany. The database was compiled from four, 2-year toxicity studies (46-48 control rats /sex/per study;) to represent the same period of study (1987-1990, Kaliner, 1991). In the case of the male rats, 8-63% (average  $25\pm 17\%$ ) of the animals could be affected by mineralized particles; and 2-8% of the females could have mineralized particles in the colloid. In general, the severity of occurrence in control rats appeared to be minimal (Grade 1). In view of the historical data, the 100 ppm dose-group males (28% mineralized particles) was in the historical range. The NOEL from this study was 100 ppm (5.7 mg/kg/day), based on an increase in incidence and severity of mineralized particles in thyroid gland in male rats at the LOEL of 300 ppm (17 mg/kg/day).

Various types of tumors were reported in a total of 20 organ/tissue sites. The incidence of neoplasms in the liver and the thyroid gland were of particular interest, because hepatic cell necrosis and thyroid lesions were observed after subchronic or chronic treatment of rats with 1800-3000 ppm imidacloprid. There was no dose-related increase in neoplasms in the thyroid gland (Table 8). Notably, tumors in the liver were found only in the male rats from the 1800 ppm treatment group. These included one rat with adenoma, one with carcinoma and two rats with cholangiocellular carcinomas, the later being rarely seen in aging rat (Table 8; Bomhard and Rinke, 1994). The authors considered the incidences of hepatic adenomas and carcinomas to be within the historical range for these tumors, citing published data by Bomhard et al, (1986). This paper provided incidences of 827 spontaneous tumors (including liver tumors) in 375 male rats from the same Wistar strain, but did not mention the rare cholangiocellular carcinomas. In a later report by the same research group, the historical incidence for cholangiocellular carcinomas was actually zero out of 1270 control male rats (Bomhard and Rinke, 1994). Based on this report the current incidence for cholangiocellular carcinoma (2/50 males) was outside the historical range. Nonetheless, the cholangiocellular carcinoma incidence in the males from the 1800 ppm group was not statistically significant from that for the concurrent controls (0/100 male rats). Altogether, there was no sufficient evidence to indicate that imidacloprid was oncogenic to rats.

**Table 7.** Imidacloprid-Induced Mineralization of the Colloid of Thyroid Follicles in Rats<sup>a</sup>.

	Lesions in Thyroid Gland of Rats									
	24 months									
	Males					Females				
Dose ppm <sup>b</sup>	0	100	300	900	1800	0	100	300	900	1800
Number of thyroids	50	57	17	51	103	50	76	25	73	144
Mineralized particles in colloid	14	50	50	50	50	14	50	50	50	50
Total (absolute percent) mg/kg/day	14%	12	31	44	46	14%	6	11	27	38
	14%	28%	62%***	88%***	92%***	14%	12%	22%	54%***	76%***
	24 months									
Number of thyroids	50	50	50	50	50	50	50	50	50	50
Mineralized particles in colloid										
grade 1						10			19	
grade 2	3	5	25	25	-	1	5	9	6	-
grade 3	0	7	6	16	-	1	1	2	2	-
Parafollicular hyperplasia	0	0	0	3	12	0	0	0	-	8
Total (absolute percent)	4	-	-	-	24%	5				16%
Colloid aggregation	41				20	22	-	-	-	7
Total (absolute percent)	82%	-	-	-	***	44%				14%***

<sup>a</sup>Imidacloprid was administered through the diet to Wister rats for 2 years. The results were based on the incorporation of two 2-year studies with similar protocols (Eiben and Kaliner, 1991). The first study included dose groups of 0, 100, 300 and 900 ppm the second study had 0 and 1800 ppm dose levels (Eiben, 1991). Data for control rats from the two studies were pooled together for analysis.

-, Data were not reported in the study.

\*\*\* Statistically significant different from controls at  $p \leq 0.001$  by Fisher exact test. Note that analysis of the data for male rats affected by mineralized particles indicated that a trend test for dose-response would be significant ( $p \leq 0.001$ ).

**Table 8.** Tumor Incidences from 2-year Dietary Studies with Imidacloprid in Wistar Rats<sup>a</sup>.

Dose (ppm)	Incidence of Neoplastic Lesions									
	24 months									
						Females				
	0	100	300	900	1800	0	100	300	900	1800
<b>Thyroid Gland</b>	0	5.7	17	51	103	0	7.6	25	73	144
Number of thyroids	100	50	50	50	50	100	50	50	50	50
Parafollicular cell adenoma										
Parafollicular carcinoma	5	5	6	3	0	2	4	1	0	4
Follicular adenoma	0	0	1	0	0	1	0	0	1	0
<b>Liver</b>	4	0	0	0	3	0	0	0	0	0
Number of livers	100	50	50	50	50	100	50	50	50	50
Adenoma										
Carcinoma	0	0	0	0	1	2	0	0	0	0
Cholangioma	1	1	1	0	1	0	0	0	0	0
Cholangiocellular carcinoma	0	0	0	0	0	1	0	0	0	2
	0	0	0	0	2	0	0	0	0	0

a/ The results were based on the incorporation of two 2-year studies with similar protocols. The first study included dose groups of 0, 100, 300 and 900 ppm (Eiben and Kaliner, 1991), the second study employed 0 and 1800 ppm dose levels (Eiben, 1991). Data for control rats from the two studies were pooled together for analysis.

### Males

### **III.D.2. Oral Studies – Mouse**

In two chronic toxicity/oncogenicity studies, imidacloprid (95.3% a.i.) was administered to B6C3F1 mice (50/sex/dose) for a period of 24 months. The dietary levels were 0, 100, 330 or 1000 ppm (Watta-Gebert, 1991) and 0 and 2000 ppm (Watta-Gebert, 1991a). Ten more mice/sex/dose were used for interim examinations after 12 months of treatment. The two studies had similar protocols and, therefore, were evaluated together. The reported average daily doses were 0, 20, 66, 208 or 414 mg/kg/day for males and 0, 30, 104, 274 and 424 mg/kg/day for females. The doses were based on the mean daily food consumption ranging from 6.2 to 6.5 g/male/day and from 7.4 to 8.5 g/female day. This food intake represented about 22-28% of the body weight of an adult mouse. These high levels of food consumption (and imidacloprid intake) may be due to not accounting for food spillage in the calculations for the consumed food. Unusually high food consumption was also evident in the subchronic study in mice, (Eiben, 1988b; see Section III.C.2. under SUBCHRONIC TOXICITY).

Mice treated with 2000 ppm imidacloprid had substantially lower body weights (up to 29%,  $p \leq 0.01$ ) than controls from the first week of treatment. The reduction in body weights was, at least in part, due to a decreased food consumption (10-25%). Morphological changes were noted at 2000 ppm, including periacinar hypertrophy of hepatocytes in males and mineralization of thalamus in females. A marked increase in mortality was evident for the males in the 2000 ppm group that died intercurrently (34 % vs. 12% control,  $p=0.002$ ). Interestingly, the number of males, which died simultaneously or were sacrificed in moribund conditions, did not differ from the control mice (14% vs. 12% control). The significant increase in mortality was due to the large number of males, which died during manipulations such as blood withdrawals, tattooing or as a result of being caught in the automatic feeder. The later was attributed by the authors to the general debilitation and major reduction in body weights caused by imidacloprid. The death of the animals after blood withdrawal and tattooing was concluded in the report to be indirectly associated with the treatment. Compared to control mice, males exposed to 2000 ppm imidacloprid developed hypersensitivity to ether, which was used as anesthesia during these procedures. The dying animals exhibited dyspnea, respiratory failure and spasms immediately after administration of ether. Similarly, in a subchronic 107-Day study, all mice fed 3000 ppm imidacloprid and males in the 600 and 120 ppm groups died after blood withdrawal (see Section III.C.2 under Subchronic Toxicity). Overall, these findings suggest that imidacloprid may reduce the ability of mice to respond to an additional challenge with xenobiotics.

Effects at 1000 ppm consisted of reduced body weight for males (up to 10%,  $p \leq 0.01$ ), while the food consumption was not affected by the treatment. On the basis of these results, 1000 ppm imidacloprid appeared to be the MTD for male mice. The type and incidence of tumors in all dose-groups were similar to that for the control animals. Hence, no evidence for oncogenic potential of imidacloprid was indicated in these studies. The NOEL was 330 ppm based on 10% reduction in body weight for male mice at the LOEL of 1000 ppm. The DPR toxicologists adjusted the ingestion of imidacloprid to 1/7 of the mice mean body weight (see Attachment IV), which is similar to a default food consumption of 15 % of the body weight of an adult mouse. The revised NOEL would be 47 mg/kg/day, based on the revised LOEL of 143 mg/kg/day.

### **III.D.3. Oral Studies – Dogs**

Imidacloprid was administered through the diet for a period of 52 weeks to Beagle dogs (4/sex/dietary level) at 200, 500 or 1250 ppm (Allen et al., 1989). The 1250 ppm dose was

increased to 2500 ppm from week 17 to the end of the treatment. These levels correspond to daily doses of 6, 15 and 41/72 mg/kg/day. Food consumption was decreased by 9-14% in the females treated with 1250/2500 ppm imidacloprid. Other effects at 1250/2500 ppm included an increase in the metabolic activity in the liver, as evidenced by the elevated levels of plasma cholesterol in females (up to 91%,  $p \leq 0.01$ ) and liver cytochrome P-450 enzymes for both sexes (51-93%,  $p \leq 0.01$ ). The authors considered the later effect to be associated with the increase in liver weight (10-19%, not statistically significant), which was apparent only when expressed as liver/brain ratio. The more common expression of relative organ weight is the organ weight/body weight ratio, which in this case was not statistically significant. The chronic oral NOEL was established by the authors as 500 ppm (15 mg/kg/day), based on liver changes at the LOEL of 1250/2500 ppm (41 mg/kg/day). It should be noted that unlike the mild effects seen in the chronic study, subchronic treatment for 4 or 13 weeks with similar doses (24-64 mg/kg/day) imidacloprid produced a marked toxicity in dogs, including mortality, severe tremors, morphological changes in liver and thyroid and weight loss.

### III.E. GENOTOXICITY

Thirteen genotoxicity studies with imidacloprid were submitted to the DPR. The results obtained in 11 of these tests were negative, including all *in vitro* point mutation tests, all *in vivo* chromosomal aberration tests and all tests for DNA damage and repair capabilities. Imidacloprid at non-cytotoxic concentration was positive in one of the two *in vitro* assays for sister chromatid exchanges (SCE) in Chinese hamster ovary cells (CHO). In addition, it caused *in vitro* chromosomal aberrations in human lymphocytes, but at concentrations at which cytotoxicity was also evident. There were no published reports on the imidacloprid mutagenic potential in the open literature. The results from the available studies indicated that, under the conditions tested, imidacloprid did not show a clear genotoxic potential. Studies on genotoxicity of imidacloprid are summarized in Table 9.

**Gene Mutation.** Testing of imidacloprid for mutagenicity *in vitro* in *Salmonella typhimurium* provided no evidence that it induced base-pair substitution in strains TA100 and TA1535, or frame shift in *S. typhimurium* strains TA98 and TA1537 and in *Escherichia coli* strain WP2uvr (Herbold, 1989a; Watanabe, 1991). Similarly, in an assay for detection of forward mutations, imidacloprid did not increase the resistance of HGPRT-Chinese hamster ovary cells (CHO) to 6-thioguanidine when incubated at concentrations up to those causing cytotoxicity (Lehn, 1989).

***In Vitro* Chromosome Aberrations:** *In vitro*, imidacloprid was clastogenic to human lymphocytes, causing chromatid gaps and breaks at concentrations at which cell toxicity was also evident (Herbold, 1989c). These results may not be unequivocal for mutagenic potential or carcinogenic properties, because the chromosomal aberrations occurred only at cytotoxicity concentrations. An increased frequency of SCE (44-70%) was reported *in vitro* in CHO cells in the absence or presence of metabolic activation system, starting at concentration of 250 µg/ml (Taalman, 1988). Cytotoxicity was observed at concentrations higher than 500 µg/ml, indicating that imidacloprid caused reciprocal chromatid interchanges at non-lethal doses. In a separate *in vitro* study in CHO, imidacloprid did not induce SCE up to 1250 µg/ml (Putman and Morris, 1989).

Sister chromatid exchanges occur during the S phase. They involve breakage of both DNA strands, followed by an exchange of whole DNA duplexes (Van Veen and Hawley, 2003). Under normal circumstances, SCE are thought to be rare at meioses (Kato, 1974). However, they are efficiently induced by mutagens, which form DNA adducts or interfere with DNA replication. In this respect, SCE are indicative of recombinational repair, induction of point mutations, gene amplification and cytotoxicity. Hence, it is a frequent method of testing for potential DNA damage. On the other hand, it may be argued that the significance of a positive SCE for risk assessment is less certain than other genotoxicity studies, because of the following reasons: (i) If SCE occurs, it has no net effects, since technically it is an exchange of identical genetic material between two chromatids, and (ii) Due of its high sensitivity, the SCE test has a relatively low predictability of both carcinogens and noncarcinogens in the rodent bioassays (0-45%, Ashby and Tennant, 1991; Tennant, 1987; Brusick, 2001).

***In Vivo* Chromosome Aberrations:** Tests of mammals treated *in vivo* with imidacloprid produced negative results for chromosomal aberrations. No significant increases over control were observed in the number of micronucleated erythrocytes isolated from mice treated with 80 mg/kg imidacloprid (Herbold, 1988a). There was no evidence for aberrations or SCE in bone

marrow chromosome preparations from Chinese hamsters, which received 2000-5000 mg/kg imidacloprid via gavage (Herbold, 1989b; Herbold, 1989d). In a mouse-germ cell assay, imidacloprid did not increase the number of structural aberrations in chromosomal preparations from spermatogonial cells up to 80 mg/kg (Volkner, 1990).

**DNA Damage and Repair Capabilities.** Imidacloprid did not show a DNA-damaging potential in a rec assays with *Bacillus subtilis*, as evidenced by the lack of growth inhibition of recombination- and repair-deficient mutants (Watanabe, 1990). Imidacloprid was also tested for induction of mitotic gene recombination in yeast *Saccharomyces cerevisiae* strain D7 (Herbold, 1988b). In this assay, there were no increases in the tryptophan revertants or colonies with red and/or pink sectors, indicating that imidacloprid did not induce mitotic gene conversion and crossing-over. Finally, imidacloprid administered by gavage to rats at doses of 5-500 µg/kg did not increase the nuclear grain counts in the nuclei of primary hepatocytes (Cifone, 1988). This test demonstrated that there was no apparent DNA damage to stimulate a repair response by unscheduled DNA synthesis (USD).



**Table 9.** Mutagenicity Studies with Imidacloprid.

End Point	Test System	Activation/Dose	Results	References
<b>Gene Mutation</b>				
Reverse mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537	+/-S9 rat microsomes <sup>a</sup> 20-12,400 µg/plate	Negative	*Herbold, 1989a; *Watanabe, 1991
Reverse mutation	<i>E.coli</i> WP2uvr	+/-S9 rat microsomes 312.5-5000 µg/plate	Negative	*Watanabe, 1991
Forward mutation	HPRT <sup>b</sup> Chinese hamster ovary cells	+/-S9 rat microsomes 1.25-1225 µg/plate	Negative	*Lehn, 1989
<b><i>In Vitro</i> Chromosome Aberration</b>				
Structural Chromosomal Aberration	Human lymphocytes (cells from 1 male and 1 female)	+/-S9 rat microsomes 50-5200 µg /ml; 24 h	Negative up to 50 µg /ml  Positive (14-29% <sup>c</sup> increased frequency <sup>c</sup> ) at cytotoxic concentrations (500-5200 µg/ml) without S9.	*Herbold, 1989c;
Sister Chromatid Exchange	Chinese hamster ovary cells	+/-S9 rat microsomes 16.7-5000 µg/ml  exposed for 27 h (-S9) and 2h (+S9)	Positive (44-70% increased frequency <sup>c</sup> ) at ≥ 250 µg/ml with or without S9.  Cytotoxic at 500 µg/ml	Taalman, 1988
Sister Chromatid Exchange	Chinese hamster ovary cells	+/-S9 rat microsomes 25-1250 µg/ml  exposed for 29 h (-S9) and 2h (+S9)	Negative up to 1250 µg/ml  Cytotoxic at ≥ 25 µg/ml	*Putman and Morris, 1989

Continued

**Table 6.** Mutagenicity Studies with Imidacloprid. (cont).

End Point	Test System	Activation/Dose	Results	References
<b><i>In Vivo</i> Chromosome Aberration</b>				
Micronucleus test	Mouse bone marrow erythrocytes	Gavage, 80 mg/kg 5 mice/sex Bone marrow examined after 24, 48 and 72 h	Negative	*Herbold, 1988a;
Sister Chromatid Exchange	Chinese hamster bone marrow	Gavage, 500-5000 mg/kg; 5 mice/sex Bone marrow examined after 24 h	Negative	*Herbold, 1989d;
Structural Chromosomal Aberration	Chinese hamster bone marrow	Gavage, 2000 mg/kg 34 animals. Bone marrow examined after 6, 24 and 48 h	Negative	*Herbold, 1989b;
Germ cell damage	Mouse spermatozoid	Gavage, 80 mg/kg 5 males/group Spermatogonia examined after 24, 48 and 72 h	Negative	*Volkner, 1990
<b>Other Genotoxicity Tests</b>				
Mitotic gene recombination	<i>S. Cerevisiae</i> D7	+/-S9 rat microsomes 625-10,000 µg/ml	Negative	*Herbold, 1988b
Rec gene mutation	<i>B. subtilis</i> H17(rec+) and M45 (rec-)	+/-S9 rat microsomes 312.5-5000 µg /disk	Negative	*Watanabe, 1990
Unscheduled DNA synthesis	Primary rat hepatocytes	5-500 µg/ml; 19 h	Negative	*Cifone, 1988

\*, Studies acceptable for filing the SB950 data requirements; **a/** +/- , with and without S9 fraction from rat liver microsomes; **b/** HPRT, Hypoxanthine-Guanine Phosphoribosyl Transferase; **c/** Significantly different than control,  $p \leq 0.05$ ; **d/** rec-, recombination- and repair-deficient *B. subtilis* mutants.

### **III.F. REPRODUCTIVE TOXICITY**

The effects of imidacloprid (95.3%) on reproduction and development were examined in a two-generation, two-litter study in Wistar rats (30/sex/dose in the parental generation, P1). The dietary doses were 100, 250 and 700 ppm (Suter et al., 1990). The rats in the P1 generation were fed imidacloprid during a premating period of 84 days and throughout mating, gestation and lactation for breeding of the offspring (F1A and F1B litters). After weaning on day 21 postpartum, selected F1B animals (26/sex/dose) were fed imidacloprid for 105 days prior to mating, during mating, gestation and lactation for breeding of the F2-generation parental animals.

Maternal toxicity at 700 ppm included decreased body weight gain and food consumption with a marked reduction during lactation (up to 11% and 17%, respectively,  $p \leq 0.05$ ). Liver enzymes participating in the biotransformation of xenobiotics (cytochrome P-450, O-demethylase and N-demethylase) were also induced in the maternal animals (up to 37%,  $p \leq 0.01$ ). The offspring of these dams had a pronounced decrease in body weight gain (up to 13%,  $p \leq 0.05$ ) compared to control until weaning at postnatal day 21. Decreased premating body weights (9%,  $p \leq 0.05$ ) were reported for the P1-F1 males. There were no effects on mating indices, fertility, gestation, litter size, mortality and no evidence of pathology at any dose level. The parental, reproductive and developmental NOELs were 250 ppm, based on significantly decreased body weights of adults and pups at 700 ppm.

It should be noted that the mean daily imidacloprid doses varied greatly within a treatment period (e.g. premating) and between the different treatment periods (premating, mating, gestation and lactation). For example, the report indicated that the parental animals from all dose groups consumed about 50% less imidacloprid from the middle to the end of the premating period, compared to the beginning of the treatment. The reason for the dose variability was not provided. The food consumption was not decreased in the first two dose-groups (100 and 250 ppm) hence; it is not clear how the dose could be reduced. In addition, the imidacloprid intake by the dams was markedly increased toward the end of the lactation period, probably due to the growing pups eating the pesticide-containing pelleted food. The estimated doses corresponding to the NOEL of 250 ppm varied from 13 mg/kg/day to 46 mg/kg/day. The NOEL for adult rats was 13 mg/kg/day based on decreased premating body weights of P1-F1 males and F1 females at the LOEL of 38 mg/kg/day. The offspring NOEL was 13 mg/kg/day, based on a decreased pup body weight of both litters of both generations at the LOEL of 38 mg/kg/day.

### **III.G. DEVELOPMENTAL TOXICITY**

The embryo-, fetal and developmental toxicity of imidacloprid were studied in rats and rabbits. Embryotoxicity was evident only at maternally toxic doses. The main effects on rat fetuses were wavy ribs and disproportionally high number of male fetuses. The developmental effect in the rabbit was reduced fetal weight. The principal effects and the respective toxicity thresholds in the developmental toxicity studies are summarized in Table 10.

#### **III.G.1. Oral – Rat**

In a rat teratology study, imidacloprid (94.2% a.i.) was administered daily by gavage to mated female Wistar rats from gestation days (GD) 6 through 15 (Becker et al., 1992). Each dose group consisted of 25 rats. The respective doses were 0, 10, 30 and 100 mg/kg/day (Table 10). On GD 21 the fetuses were delivered by a cesarean section and examined for developmental abnormalities.

The highest tested dose (100 mg/kg/day) produced maternal toxicity and a delay in embryo development. The maternal toxicity was evidenced by the reduced body weight gain (up to 43% reduction,  $p \leq 0.01$ ) from the third day of treatment to five days after the last dose. The food consumption was also decreased (35%,  $p \leq 0.01$ ) during the treatment period. The authors reported that the offspring of these dams had an increased incidence of wavy ribs (fetal incidence of 4.7% relative to controls (1.2%); this incidence was not statistically significant and was within the historical range (0 to 5.6%). In addition, exposure of dams to 100 mg/kg/day imidacloprid resulted in a disproportionally high number of male fetuses (59%). This effect was statistically significant ( $p \leq 0.05$ ) relative to control animals, which had approximately 1:1 ratio between males and females. Furthermore, the sex ratio in the 100 mg/kg/day group was outside the historical range (range 45-51.9% male fetuses out of 2194 fetuses; mean  $49.5 \pm 1.5\%$ ). The historical database was compiled by the authors from 8 developmental toxicity studies to represent the same period of study (1986-1988).

Presently, it is unclear why the dams at the high-dose group had more male fetuses, since there was no post-implantation loss, e.g. selective loss of female fetuses, to account for the higher number of the male fetuses. It was speculated that imidacloprid may possess androgenic properties, causing virilization of female fetuses, which could explain the profound phenotypic gender change (See Attachment IV and Study Toxicology Summary). Additional information, such as the genotype of the fetuses, measurements of sex differentiation parameters (e.g., anogenital distance), or evaluation of the internal sex organs, is needed to support this hypothesis.

Maternal toxicity at doses of 10 and 30 mg/kg/day included reduction in food intake (10 %,  $p \leq 0.01$ ) and a dose-dependent decrease in body weight gain (4% and 11%, respectively). The decreases in the body weight gain at all doses were noted within the first 5 days of treatment. The authors reported the reduction in food consumption and body weight gain at 10 mg/kg/day as adverse effects on the dams and presented this dose as the maternal LOEL; the developmental NOEL in the study was set at 30 mg/kg/day. The toxicologists at the DPR established the maternal and developmental NOELs at 30 mg/kg/day. The effects at the LOEL of 100 mg/kg/day included reduction in food consumption and body weight gain (dams), and increased incidence of wavy ribs and high number of male fetuses. The USEPA considered the 11% decrease (not statistically significant) in the body weight gain of the dams as the maternal LOEL and used the

NOEL of 10 mg/kg/day to characterize the risk of the short-term oral, dermal and inhalation exposures to imidacloprid.

### **III.G.2. Oral – Rabbit**

The developmental toxicity of imidacloprid was examined in the rabbit. Mated Chinchilla rabbits (16/dose level) were treated by gavage from GD 6 through 18 with daily dosage of 8, 24 or 72 mg/kg/day (Becker and Biedermann, 1992). Cesarean section and examination of the dams and fetuses were performed on GD 28. Severe maternal toxicity was observed at the highest tested dose (72 mg/kg/day). Two dams from this dose-group died on GD 19 and 28, one dam aborted and two dams had complete resorptions at terminal necropsy. All together, the females in the 72 mg/kg/day dose-group had a higher post-implantation loss (32%,  $p \leq 0.01$ ) relative to controls. Consequently, there was a statistically significant reduction in the number of live fetuses per dam. Food consumption for the surviving females was reduced up to 66% ( $p \leq 0.01$ ) compared to control. In turn, there was an overall weight loss during the entire treatment period. The mean body weight was decreased by 4% on day 2 of treatment (GD 8). The weight loss became significantly lower than the controls within 5 days of treatment (8-11%,  $p \leq 0.01$ ). The fetuses from these dams had a reduced body weight (10%,  $p \leq 0.01$ ) and delayed ossification. The next lower dose (24 mg/kg/day) caused a decrease in food consumption (16%,  $p \leq 0.01$ ) and a reduction in body weight gain of the dams (33%, not statistically significant), compared to control animals. The authors considered the reduction in food consumption and body weight gain at 24 mg/kg/day as adverse effects on the dams and established the maternal NOEL as 8 mg/kg/day; the developmental NOEL was 24 mg/kg/day (Table 10). The DPR toxicologists and the USEPA, set both, the maternal and developmental NOELs, at 24 mg/kg/day, based on mortalities and decreased absolute body weights and body weight gain (dams), increased post-implantation loss and a decreased weight of the offspring at the LOEL of 72 mg/kg/day.

**Table 10.** Developmental Toxicity of Imidacloprid in the Rat and Rabbit.

Species	Exposure	NOEL	LOEL	Study Description
<b>Rat<sup>a</sup></b> 25 dams/ dose	Oral (gavage)  10 doses GD 6-15	30	100	<b>Doses (mg/kg/day):</b> 0, 10, 30 and 100 <b>Effects at LOEL: <u>Dams:</u></b> reduction in body weight gain (up to 43% <sup>**</sup> ; within first 3 days of treatment) and reduction in food consumption (35% <sup>**</sup> ) <b><u>Fetuses:</u></b> increased incidence of wavy ribs (5%) and high number of male fetuses (59% <sup>*</sup> )
<b>Rabbit<sup>b</sup></b> 16 dams/ dose	Oral (gavage)  13 doses GD 6-18	24	72	<b>Doses (mg/kg/day):</b> 0, 8, 24 and 72 <b>Effects at LOEL: <u>Dams:</u></b> mortalities (3 of 25 dams), weight loss (up to 11% <sup>**</sup> , start days 2-5), decreased food consumption (66% <sup>**</sup> within first 4 days), post-implantation loss (32% <sup>**</sup> ) <b><u>Fetuses:</u></b> decreased body weight (10% <sup>**</sup> )

<sup>a/</sup> Becker et al., 1992;

<sup>b/</sup> Becker and Biedermann, 1992.

<sup>\*\*</sup>, Statistically significant difference from controls at  $p \leq 0.01$  (Fisher's Exact test)

### **III.H. NEUROTOXICITY**

The acute and subchronic effects of imidacloprid on the nervous system were studied in rats (Sheets, 1994 a,b,c). Imidacloprid caused neurotoxicity, which was evident from clinical signs, alterations in the behavior and decreases in the motor activity in rats. The principal effects were tremors, gait abnormalities, reduced response to stimuli, decreased body temperature, decreased grip strength and rearing, and impaired righting reflex.

#### **III.H. 1. Acute Neurotoxicity**

In an acute neurotoxicity study, imidacloprid (98.8%) was administered by gavage in a single dose to Sprague-Dawley rats (18/sex/dose; Sheets, 1994a). The doses were 0, 42, 151 and 307 mg/kg/day. The control groups included vehicle (0.5% methylcellulose with 0.4% Tween 80)-treated animals. The rats in the neurotoxicity group, (12/sex/group) were evaluated for neurobehavioral signs using the Functional Observational Battery (FOB). Changes in the motor activity were assessed by the figure-8-maze. Additional 6 rats/sex/group were subjected to pathological evaluation. The following tissues were examined for pathology: brain, spinal cord, eyes, peripheral nerves (sciatic, sural and tibial), gasserian ganglion and gastrocnemius muscles. Based on preliminary findings in rats, the Time to Peak Effect (TOPE) for imidacloprid-induced behavioral changes was reported to occur between 90 min to 2 h following treatment. In the current study, the clinical observation and the FOB evaluations were performed at pretest, at the TOPE (90 min after dosing), and 7 and 14 days after treatment. The motor activity was assessed at pretest, from 2.5 to 4.5 h following treatment and at Days 7 and 14.

The highest tested dose (307 mg/kg/day) produced severe toxicity, including lethality. Four males and ten females in this group died within to 24 hours following treatment (Table 11). All animals, which were still alive after four hours of dosing had severe tremors and appeared cool-to-touch, with their body temperature being reduced by 2°C (males) and 5.5°C (females). Autonomic signs in these rats included nasal, perianal and urine stains. The CNS effects in this group were evidenced by the markedly decreased activity and reduced response to stimuli. Additional effects in the rats treated with 307 mg/kg dose included incoordinated gait, decreased rearing and grip strength, and impaired aerial righting. A higher incidence of animals, which were sitting or lying in the cage, tremors and nasal stain was also reported for the 151 mg/kg dose group. The males and females treated with 151 or 307 mg/kg imidacloprid showed 21-89% ( $p \leq 0.05$ ) decrease in the motor and locomotor activity in the figure-8-maze (Table 11). The females from the lowest tested group (42 mg/kg), exhibited 25-27% decrease in their motor activity (Table 11). Some of the effects, such as nasal and urine stains, and a decreased activity of the surviving males at the 307 mg/kg group persisted after 7 to 14 days of treatment. Among the tested clinical chemistry parameters, the authors considered the decrease in serum triglycerides as a treatment related effect. At the lowest tested dose (42 mg/kg) the serum triglycerides were decreased in the males by 23%. This effect became statistically significant in both sexes treated the 151 and 307 mg/kg imidacloprid (up to 73% decrease,  $p \leq 0.05$ ; Table 11). It should be noted that a decrease in the serum triglycerides was consistently observed after acute and the subchronic exposure to imidacloprid, which may be related to the liver toxicity noted in these studies (see next section III.H.2.).

Altogether, the results revealed that imidacloprid caused a range of acute neurotoxic effects including a decreased activity of the females at the lowest tested dose (42 mg/kg) to severe toxicity and mortalities for both sexes at the dose of 307 mg/kg. It should be noted that the TOPE

was determined based on behavioral effects. Limiting the TOPE selection to FOB findings may not be optimal for observing the motor activity.

The Data Review group at the DPR established a study NOEL of 42 mg/kg/day based on statistically significant decreases in the motor and locomotor activity of the female rats at the LOEL of 151 mg/kg/day. For the purpose of risk assessment, a Benchmark Dose (BMD) analysis was performed and established a BMD<sub>05</sub> for acute neurotoxicity of 9 mg/kg/day based on the same endpoint (see detailed discussion in Sections IV.A.2. and V.B.1. under Risk Characterization and Risk Appraisal). The USEPA also considered the dose of 42 mg/kg/day as a LOEL for reduction in motor and locomotor activity.

**Table 11.** Effects of Imidacloprid in Sprague-Dawley Rats After a Single Gavage Dose<sup>a</sup>.

Acute Effect	Males				Females			
	0	42	151	307	0	42	151	307
Dose mg/kg	0	42	151	307	0	42	151	307
Mortality within 24 h <sup>b</sup>	0/18	0/18	0/18	4/18	0/18	0/18	0/18	10/18
<b>FOB Observations at 90 min TOPE<sup>c</sup></b>								
No. Animals Tested	12	12	11	12	12	12	12	12
Tremors	0	0	1	10*	0	0	1	11*
Gait incoordination	0	0	0	5*	0	0	0	10*
Decreased activity	0	0	0	7*	0	0	0	7*
Sitting or lying	7	7	0	11	2	6	4	11*
Decreased arousal	1	1	0	8*	0	0	0	10*
Touch – no response	0	1	0	4	0	0	0	7
Uncoordinated right reflex	0	1	0	2	0	0	0	1
Nasal stains	0	0	2	7	0	0	0	3
Perianal stains	0	0	1	1	0	0	0	0
Urine stains	0	0	0	2	1	0	0	0
Rearing (mean)	1.7	1.9	1.9	0.8*	4.4	4.6	3.6	0.9*
Grip strength (kg)	0.43	0.43	0.43	0.28*	0.3	0.31	0.34	0.25*
<b>Motor Function (figure-8-maze) at 2.5-4.5 h</b>								
Motor activity (% of control)	100	95	75	27	100	73	52*	19 <sup>*d</sup>
Locomotor activity (% of control)	100	91	79*	22*	100	75	54	11 <sup>*d</sup>
<b>Clinical Chemistry (within 24 h)</b>								
Triglycerides (% of control)	100	77	64*	38*	100	91	44*	27*

a/ Data from Sheets, 1994a. The results are expressed as a number of animals, which exhibited a particular effect evaluated by the FOB; b/ All 14 animals (of 36) in the 307 mg/kg dose-group died within 24 h of treatment. c/ TOPE, Time of Peak Effect;

d/ Ten females were tested for motor and locomotor activity due to mortality .

\*, Statistically significant difference from controls at p≤0.05 (Anova or Dunnet test)

In a supplemental study, 12 rats/sex were used as controls or treated with imidacloprid via gavage in a single dose at 20 mg/kg (Sheets, 1994b). The aim of this second study was to determine the NOEL for the acute neurotoxicity of imidacloprid in rats. The supplemental study was performed in the same laboratory 6 months after the main study (Sheets, 1994a) and used a similar protocol. The results indicated that the dose of 20 mg/kg did not cause apparent toxicity, including a decrease in the motor activity, which was observed in females at the LOEL of 42 mg/kg in the main study. However, there was a substantial uncertainty associated with the reported dose of 20 mg/kg as the NOEL for the acute oral toxicity, because this study did not include a high enough dose of imidacloprid to produce toxicity in the rats.

### **III.H. 2. Subchronic Neurotoxicity**

In a subchronic neurotoxicity study, imidacloprid (98.8% a.i.) was administered to Fischer-344 rats (12/sex/dose) at dietary levels of 0, 150, 1000 and 3000 for a period of 13 week (Sheets, 1994c). Based on the food consumption, the average daily doses corresponded to 9.3, 63 and 196 mg/kg/day for males and 10.5, 69, and 213 mg/kg/day for females. The FOB and activity tests on the figure-8-maze were performed at pretest and at week 4, 8 and 13 of treatment.

During most of the exposure period, imidacloprid caused a reduction in body weights in both sexes at 1000 (up to 5%, females; 8%, males;  $p \leq 0.05$ ) and 3000 ppm (up to 9%, females; 17%, males;  $p \leq 0.05$ ). This effect was due, at least in part, to a decrease in food consumption (up to 13% and 29% for the animals at 1000 ppm and 3000 ppm, respectively). Decreases in the TAG in the serum (up to 41%,  $\leq 0.05$ ) were considered by the authors to be treatment-related for both sexes exposed to 1000 and 3000 ppm imidacloprid (Table 12). It should be noted that a significant decrease in the serum triglycerides (55-75%) was consistently observed in most of the subchronic toxicity studies with imidacloprid (33-409 mg/kg/day). These included: 13-Week oral treatment in rats (52% TAG decrease; Eiben, 1989); 13-Week neurotoxicity study in rats (41% decrease, Sheets, 1994c), 4-Week inhalation study in rats (73% decrease, Pauluhn, 1989), and 4-Week oral study in dogs (75% decrease, Block, 1987). In addition, 73% decrease in the serum TAG was also reported in the acute neurotoxicity study in rats (Sheets, 1994a). This effect may reflect imidacloprid-induced changes in the metabolism in liver, as indicated by other studies (Eiben, 1988a and 1989; Pauluhn, 1988a; Eiben 1988b; Block, 1987).

Lower grip strength of the forelimbs was measured in the males exposed to 3000 ppm imidacloprid, which became statistically significant at the 8 week of treatment (23%,  $p \leq 0.05$ ; Table 12). At the end of the study (13 week), a higher incidence of uncoordinated righting response was reported for the males exposed to imidacloprid. While only 1 control male (of 12) showed uncoordinated righting response, there were 2 males from the 150 ppm group, 3 males from the 1000 ppm group and 7 males from the 3000 ppm group ( $p \leq 0.05$ ), which had uncoordinated landing in the FOB. Females treated with 3000 ppm (213 mg/kg/day) imidacloprid showed a decrease in the locomotor activity at all test (at weeks 4, 8 and 13; up to 21%). Although this effect was not statistically significant, it was consistent with the results from the acute neurotoxicity study, where the locomotor activity was reduced by 46% and 89% in the females exposed to single doses of 151 and 307 mg/kg imidacloprid, respectively (Sheets, 1994a). In the acute neurotoxicity study, the marked reduction of the locomotor activity was noted within 2-4 h of treatment. In the subchronic neurotoxicity, the first test on motor activity was performed after 4 weeks of exposure. Therefore, the 21% reduction in the locomotor activity may reflect some degree of adaptation to the blockage of the nAChR by imidacloprid.



The authors established a NOEL of 9.3 mg/kg/day, based on decreased body weights of the male rats and changes in the clinical chemistry parameters at the LOEL of 63 mg/kg/day. The results from the subchronic neurotoxicity study with Fischer-344 rats were comparable with the finding from the subchronic studies in Wistar rats, which established a NOEL of 14 mg/kg/day, based on reduction in body weight (Eiben 1988a, 1989, see Section III.C.1.).

**Table 12.** Effects of Imidacloprid in Fischer-344 Rats In a 13-Week Feeding Study<sup>a</sup>.

Subchronic Effect	Males				Females			
	0	150	1000	3000	0	150	1000	3000
Dose ppm	0	150	1000	3000	0	150	1000	3000
Dose mg/kg/day	0	9.3	63	196	0	10.5	69	213
Body weight - week 13 (g) % of control	100	100	92*	84*	100	98	95*	91*
<b>FOB Observations<sup>b</sup></b>								
No. Animals Tested	12	12	11	12	12	12	12	12
Uncoordinated right reflex	1	2	3	7*	0	0	0	1
<b>Grip strength of forelimb % of control</b>								
Week 4	100	97	100	88*	100	95	95	90
Week 8	100	93	87	77*	100	100 <sup>c</sup>	100 <sup>c</sup>	100 <sup>c</sup>
Week 13	100	100	98	91	100	95	94	95
<b>Motor Function (figure-8-maze)</b>								
<b>Locomotor activity (% of control)</b>								
Week 4	100	95	100	100 <sup>c</sup>	100	95	99	91
Week 8	100	100	100	100	100	91	91	79
Week 13	100	95	100	100	100	100 <sup>c</sup>	100 <sup>c</sup>	82
<b>Clinical Chemistry</b>								
<b>Triglycerides (% of control)</b>								
Week 4	100	100 <sup>c</sup>	100 <sup>c</sup>	64*	100	100 <sup>c</sup>	68	59*
Week 13	100	100 <sup>c</sup>	100	74*	100	91	89	65*

a/ Data from Sheets, 1994c.

b/ The results are expressed as a number of animals, which exhibited a particular effect evaluated by the FOB

c/ The mean value was higher than the levels measured in the control animals.

\*, Statistically significant difference from controls at  $p \leq 0.05$  (Anova or Dunnet's test)

### **III.I. DEVELOPMENTAL NEUROTOXICITY**

Developmental neurotoxicity (DNT) studies are designed to investigate whether pre- or post-natal exposure to a toxicant affects the neural development. The DNT evaluations of imidacloprid were focused on the possible adverse neurodevelopment outcomes, including behavior, learning and memory, and locomotion. Imidacloprid is the first neonicotinoid, for which a DNT study has been completed.

Imidacloprid (98.2%) was administered in the diet to mated Sprague-Dawley rats (about 30 rats/dose; Sheets 2001). The females were treated from the gestation day (GD) 0 to GD 20 and then continued through the lactation day (LD) 21 at doses of 0, 100, 250 and 750 ppm. Based on the food consumption by the dams during the gestation, the average daily intake of imidacloprid was reported as 0, 8, 19 and 54.7 mg/kg/day. The pups were indirectly exposed to imidacloprid for a total of 41 days (20 days *in utero* and 21 days via lactation). Control groups included vehicle (corn oil)-treated animals. After weaning on PND 21, the pups from these litters (4 males and 4 females/litter) were given untreated feed (no pesticide). The dams and the pups were observed for signs of general toxicity throughout the treatment period. All dams were sacrificed on LD 21 following the weaning of the litters. The pups (16 rats/sex/dose) were evaluated for developmental neurotoxicity until about 75 days of age. Six FOB were performed between PND 4 and 60. Motor activity was assessed on the Figure-8-maze on four occasions between PND 13-60. Acoustic startle habituation was tested in a Startle system enclosure on PND 22, 38 and 60. Learning and memory were evaluated using the Passive avoidance test (PND 22 and 29) and the Water maze (PND 60 and 67). Brain tissue from 10 pups/sex/group were analyzed on PND 11 and PND 75.

Dams: The clinical signs in the dams in the 750 ppm group were restricted to a decreased food consumption during the gestation and lactation periods (up to 14%,  $p \leq 0.05$ ). The body weights or body weight gains of these dams were not affected.

Offspring: Male and female pups exposed to 750 ppm imidacloprid *in utero* and via lactation, had reduced body weights (11-13%,  $p \leq 0.05$ ) on PND 4-21; Table 13). Difference in weight at the high dose persisted after weaning, even when imidacloprid was removed from the diet. At the end of the study the body weight was about 4% less than the control. The motor and locomotor activity of males and females from the 750 ppm group were decreased by 31-39% at PND 17, albeit, not statistically significant. The reduction in motion/locomotion persisted in the females on the next test occasion (PND 21; 26-37% reduction compared to controls). The authors ascribed the effects on the motor activity to the treatment, because of the magnitude of the effects and the occurrence at the high dose in both sexes during the period of exposure.

Changes in motor activity were consistently observed in all of the available neurotoxicity studies with imidacloprid (Sheets, 1994a, 1994c and 2001). In all cases, the females appeared to be more susceptible. It is interesting to note that similar doses of imidacloprid for different durations elicited comparable levels of reduction of the motor and locomotor activity in the female rats. For example, a 27% decrease in the motor activity was reported after 2.5-4 h of exposure to 42 mg/kg/day in the acute neurotoxicity study; in the DNT study the decrease was 39% after 37 days of indirect exposure of the pups to 54.7 mg/kg/day imidacloprid.

Brain measurements of the PND11 pups revealed that the caudate putamen width was decreased by 6% in the females from the 750 ppm group (2.769 mm in control vs. 2.617 mm in the treated

females,  $p= 0.037$ ). Furthermore, these females had a substantial reduction (27%) in the thickness of the corpus callosum (0.602 in control vs. 0.436 in the treated females,  $p< 0.05$ ). Despite the significant decreases in these parameters in the female rats at 750 ppm, morphometric brain measurements were not performed in the intermediate and low dose-groups.

**Table 13.** Effects of Imidacloprid in Sprague-Dawley Rats in a Developmental Neurotoxicity Study<sup>a</sup>.

Effect	Males				Females			
	0	100	250	750	0	100	250	750
<b>Dose ppm</b>	0	100	250	750	0	100	250	750
<b>Dose mg/kg/day</b>	0	8	19	54.7	0	8	19	54.7
<b>No. Animals Tested<sup>b</sup></b>	16	16	16	16	16	16	16	16
<b>Body weight – % of control</b>								
<b>PND 4</b>	100	100	100	78*	100	100	100	81*
<b>PND 21</b>	100	100	97	86**	100	100	96	88**
<b>Motor Function (figure-8-maze)</b>								
<b>Locomotor activity (% of control)</b>								
<b>PND 17</b>	100	100 <sup>c</sup>	88	62	100	74	99	69
<b>PND 21</b>	100	100 <sup>c</sup>	100 <sup>c</sup>	100 <sup>c</sup>	100	90	83	63
<b>Brain measurements PND11</b>								
<b>Caudate putamen width (mm)</b>	2.67	- <sup>d</sup>	-	2.71	2.769	-	-	2.617 <sup>#</sup>
<b>Corpus callosum width (mm)</b>	0.54	-	-	0.53	0.602	-	-	0.436 <sup>†</sup>

a/ Data were from Sheets, 2001.

b/ The rats were exposed to imidacloprid for a total of 41 days (20 days *in utero* and 21 days via lactation). After weaning on PND 21, the rats were fed regular diet (no pesticide)

c/ The mean value was higher than the levels measured in the control animals.

d/ Dash (“-”) indicated no data.

\*, \*\* Statistically significant difference from controls at  $p\leq 0.05$  or  $p\leq 0.01$ , respectively (Anova or Dunnett’s test)

<sup>#</sup>, statistically significant different from controls at  $p=0.0374$  (one-tailed test)

<sup>†</sup>, statistically significant different from controls  $p<0.05$  (Mann-Whitney test)

Presently, the biological consequence of the imidacloprid-induced decrease in the caudate putamen width and the thickness of the corpus callosum is not known. However, it has been well established that pathological changes in corpus callosum and basal ganglia (including the caudate nucleus and putamen) affect motor functioning and voluntary motion (Tomimoto et al., 2004; Ding et al., 2001; Middleton and Strick, 2000). The neuronal nAChRs, which are targets for imidacloprid in the CNS have been implicated to be involved in some of these neuropathologies (Cordero-Erausquin et al. 2000; Paterson and Nordberg 2000; Lindstrom 2002). Imidacloprid, its metabolite desnitro-imidacloprid and nicotine, all induced receptor up-regulation of the neuronal nAChR in cell cultures. For nicotine, the receptor up-regulation has been related to the development of tolerance to its effects on the locomotor activity (Marks et al.,

1992). In this respect, a possible link between the decrease in the caudate putamen and the corpus callosum widths in the PND 11 females exposed in utero and via lactation to imidacloprid and the decrease in the motor/locomotor activity in these animals at PND17 should not be dismissed without further investigation.

Decreases in thickness of brain structures of the pups were observed following a total of 32 doses of imidacloprid to the dams (21 doses *in utero* and 11 doses during lactation). Therefore, if the DNT study were to be used to establish a regulatory toxicological level, it would be applicable to repeated (subchronic or chronic) exposures to imidacloprid. However, morphometric brain measurements of the pups were first performed on PND11, and thus, the timeline of the imidacloprid developmental toxicity could not be determined. Because decreases in brain structures could theoretically result from a single exposure *in utero*, a critical NOEL from this study might be pertinent to acute exposures, in particular, to females of childbearing age to protect fetal exposure.

This study was recently submitted to the DPR and was generally expected to provide a NOEL for the effects of imidacloprid on the neural development. However, the study was deficient for the lack of morphometric brain measurements in the females at the intermediate and low dose groups. The LOEL for the marked reduction in the corpus callosum thickness and the decrease in caudate putamen width in the females was 750 ppm (54.7 mg/kg/day). This study could not be used to determine the developmental NOEL. Applying a default factor of 10 to the LOEL of 54.7 mg/kg/day, the estimated NOEL (ENEL) for developmental neurotoxicity could be as low as 5.5 mg/kg/day. The NOEL for the reduction in body weight and decreased motor activity was 250 ppm (19.4 mg/kg/day).

## IV. RISK ASSESSMENT

### IV.A. HAZARD IDENTIFICATION

#### IV.A.1. Introduction

Imidacloprid is classified as a Category II toxicant, based on its acute toxicity. In the available genotoxicity studies and oncogenicity bioassays in rodents, imidacloprid did not show clear potential to cause chromosome damage or cancer. Therefore, the characterization of the risk of imidacloprid in this document was based on non-oncogenic effects.

The experimentally determined highest dose at which no effects were observed (NOEL) was used in delineating the threshold dose for non-oncogenic effects. Therefore, the NOELs were presented in the context of the LOEL, the lowest dose in the experiment, which produced toxicologically significant effects. In a toxicity study, the LOEL is the next higher dose above the NOEL. In some studies, where the lowest tested dose of imidacloprid was the LOEL, a Benchmark Dose (BMD) approach was used to determine the threshold of the imidacloprid toxicity (USEPA, 1995). The BMD method involves fitting a mathematical model to the entire dose-response dataset for a specific endpoint. The BMD is the lower, 95% confidence limit of the effective dose (LED) required to cause a given response (1%, 5% or 10% effect level) in an organism.

#### IV.A.2. Acute Toxicity

##### IV.A.2.a. Acute Oral Toxicity

Acute toxicity studies with imidacloprid were not available in humans. Therefore, studies in laboratory animals were considered for determination of the toxicity thresholds. A list of NOELs and LOELs is shown in Table 14. It includes the thresholds established from all pertinent studies described in Section III.B, and under any other toxicity categories pertinent to acute exposures, e.g., the threshold for neurotoxicity after a single dose (Section III. H.) and the threshold for developmental effects that can potentially occur after a single exposure *in utero* (Section III.G.).

The lowest acute oral NOEL was 10 mg/kg/day in mice, based on clinical signs (labored breathing, decreased motility, staggering gait and trembling) at the LOEL of 71 mg/kg/day (Bomann, 1989a). This single dosing study was designed for determination of the LD<sub>50</sub> and included only evaluations of clinical signs (see Section III.B). A wide dose-range was employed (a total of 7 doses ranging from 10 to 250 mg/kg/day); however the study did not include control (untreated) mice. Because of the dose selection, the NOEL in this study was 7-fold lower than the LOEL. Therefore, a question could be raised regarding the possibility that the NOEL could be higher had the dose interval in the study design been reduced within this region. However, modeling of the data on tremors with the quantal BMD Probit model produced an LED<sub>05</sub> of 14 mg/kg/day, which is close to the NOEL of 10 mg/kg/day. It is interesting to note that mice appeared to be very sensitive to the acute treatment with imidacloprid (acute NOEL of 10 mg/kg/day), but were less sensitive in the subchronic and chronic studies (NOELs of 86 and 47 mg/kg/day, respectively; see Sections III.C.2. and III.D.2)

The NOEL of 10 mg/kg from the acute study in mice was used by the DPR in the health risk assessment in 1993, which evaluated imidacloprid for an emergency use on cotton under the

Section 18 of the FIFRA (Lewis et al., 1993). Following the completion of the 1993 health risk assessment, new acute studies became available to the DPR for defining the critical NOEL.

**Table 14.** Acute No-Observed-Effect Levels (NOELs) and Lowest-Observed-Effect Levels (LOELs) of Imidacloprid.

Acute Study		NOEL	LOEL	Toxic Effects at LOEL
Species	Exposure	mg/kg		
<b>Rat</b> <b>5/sex/dose</b>	Oral (gavage) 1 dose	50	100	<b>Effects at LOEL:</b> Apathy, labored breathing, tremors, gait incoordination, decreased motility, nasal and urine staining (Bomann, 1989b <sup>#</sup> )
<b>Rat</b> <b>5/sex/dose</b>	Inhalation 4 h (dust; 95% a.i.)	192 <sup>a,b</sup>	412	<b>Effects at LOEL:</b> Difficult breathing, reduced motility, piloerection and tremors (Pauluhn, 1988a <sup>#</sup> )
<b>Rat</b> <b>10/sex/dose</b>	Inhalation 6h/day for 5 days (dust; 95% a.i.)	3.4 <sup>a,c</sup>	19	<b>Effects at LOEL at day 5:</b> Reduction in body weights (6%**) and induction of MFO <sup>d</sup> (142%**) in the liver (Pauluhn, 1988a)
<b>Rat</b> <b>18/sex/dose</b> Acute Neurotox.	Oral (gavage) 1 dose	9 <sup>e</sup>	42	<b>Effects at LOEL:</b> Decrease in motor and locomotor activity (25-27%), decreased TAG (23%, Sheets, 1994a) <sup>#</sup>
<b>Mouse</b> <b>5/sex/dose</b>	Oral (gavage) 1 dose	10	71	<b>Effects at LOEL:</b> apathy and labored breathing), decreased motility, staggering gait and trembling (Bomann, 1989a <sup>#</sup> )
<b>Rat</b> <b>25 dams/dose</b> Dev. Tox. Study	Oral (gavage) 10 doses (GD 6-15)	30 <sup>f</sup>	100	<b>Effects at LOEL:</b> <u>Dams:</u> reduction in body weight gain (43% ** within first 3 days) and reduction in food consumption (35%**) <u>Fetuses:</u> increased incidence of wavy ribs (5%) and high number of male fetuses (59%*; Becker et al., 1992 <sup>#</sup> )
<b>Rabbit</b> <b>16 dams/dose</b> Dev. Tox. Study	Oral (gavage) 13 doses (GD 6-18)	24	72	<b>Effects at LOEL:</b> <u>Dams:</u> mortalities (3 of 25 dams), weight loss (up to 11%**, start day 2), decreased food consumption (66%** within first 4 days), post-implantation loss (32%**, Becker and Biedermann, 1992 <sup>#</sup> ) <u>Fetuses:</u> decreased body weight (10%**)

**a/** For inhalation studies, the dosages were calculated using the formula in Table 1. **b/** Only 4-11% of the particles had the recommended MMAD <5 µm. **c/** Only 57-18 % of the particles had MMAD <5 µm. **e/** LED<sub>05</sub> estimated by the BMD model. **f/** 11% reduction in body weight gain of dams at this dose. USEPA established the NOEL at 10 mg/kg/day.

**\*\***, Statistically significant difference from controls at  $p \leq 0.01$  (Fisher's Exact test).

The next higher oral LOEL was from the acute neurotoxicity study in rats (Sheets, 1994a). The experimental protocol consisted of a single gavage treatment and extensive toxicity evaluations, including neurobehavior and motor activity. The selected doses produced dose-groups with a gradation of the toxic effects, however, they did not include a level of no effect. The principal finding at the LOEL of 42 mg/kg was the 25-27% decrease in the motor and locomotor activity in the females (Table 11). This effect became statistically significant for both sexes (up to 89% decrease) in the next higher doses (151 and 307 mg/kg/day).

In a subsequent study performed in the same laboratory, the dose of 20 mg/kg did not produce apparent toxicity, including the effects seen at the LOEL of 42 mg/kg in the main study (Sheets, 1994a). However, there was a substantial uncertainty in the NOEL of 20 mg/kg because the study did not include a high enough dose of imidacloprid to produce toxicity in the rats. The USEPA applied an uncertainty factor of 3 to the LOEL of 42 mg/kg/day to estimate an oral acute NOEL (ENEL) for imidacloprid of 14 mg/kg/day (USEPA, 2003).

As an alternative to the ENEL, the Benchmark Dose (BMD) approach could be considered in determining the threshold of the imidacloprid acute toxicity. In this approach, the BMD is the lower 95% confidence limit of the effective dose (LED) required to cause a given response in an organism (USEPA, 1995). Depending on the characteristics and/or the severity of the toxic responses, a 95% lower bound estimate of the 1%, 5% or 10% effect level may be selected as the LED<sub>01</sub>, LED<sub>05</sub>, or LED<sub>10</sub>, respectively. Unlike the ENEL, which is determined based on one data point, the LOEL, the BMD method utilizes response levels at all tested doses and hence minimizes the uncertainty in the determination of the toxicity threshold.

Benchmark Dose Modeling of the Motor Activity Data: The USEPA Benchmark Dose Software version 1.3.2 (available at <http://cfpub.epa.gov/ncea/cfm/bmds.cfm>) was used to calculate the LED for imidacloprid. LEDs were derived from the data on motor activity of the female rats measured in the figure-8-maze (Sheets, 1994a, Section III.H.1. under Acute Neurotoxicity; Table 11). The current DPR default of 5% response level was used to determine the LED for the motor effects (DPR MT-1, 2004). Of the several available algorithms, the Polynomial model generated a good curve fit, as indicated by the AIC value (Akaike's Information Criterion; see Attachment III). The LED<sub>05</sub> was estimated as 9 mg/kg/day (Table 14). The effective dose ED<sub>05</sub> corresponding to the above LED<sub>05</sub> was 12 mg/kg/day. Both, the LED<sub>05</sub> and the ED<sub>05</sub> were close to the USEPA NOEL of 14 mg/kg/day, which was estimated by applying an uncertainty factor of 3 to the LOEL of 42 mg/kg/day (USEPA, 2003).

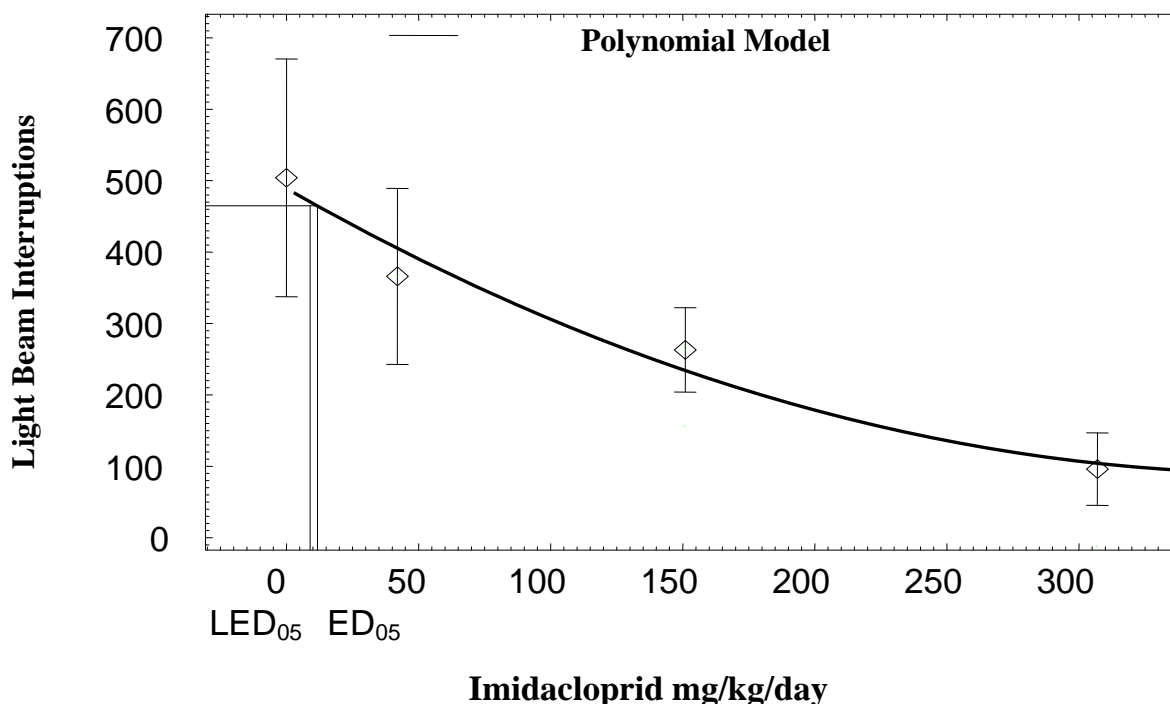
The DNT study might also be pertinent for establishing a threshold for effects on the developing nervous system, which can potentially occur after a single exposure *in utero*. A NOEL of 5.5 mg/kg/day could be estimated from the LOEL of 54.7 mg/kg/day for significant decreases in dimensions in brain structures (up to 27%) of the female pups (Sheets, 2001, see Sections III.I. and IV.A.3.). However, there was a much greater uncertainty associated with the DNT endpoint, because it was approximated from the LOEL by using a 10-fold default factor.

### **Conclusions**

The two lowest acute oral NOELs for imidacloprid were 9 mg/kg/day and 10 mg/kg/day. The LED<sub>05</sub> of 9 mg/kg/day was estimated from the data on motor activity of the females from the acute neurotoxicity study in rats (Sheets, 1994a; Table 14). The NOEL of 10 mg/kg/day was based on the LOEL of 71 mg/kg/day for clinical signs, which was established in the acute

toxicity study in mice (Bomann, 1989a). The acute neurotoxicity study in rats had higher quality data than the mouse study. It employed more sensitive toxicity evaluation (e.g. clinical observations, FOB, motor activity, neuropathology, etc.; Sheets 1994a). The acute neurotoxicity included a control group and more animals per dose group; and had a clearer dose-response relationship, which could be described by the continuous BMD model (from USEPA NCEA, 2002). Based on these considerations, the LED<sub>05</sub> of 9 mg/kg/day for decreases in motor activity in rat was selected as equivalence to the NOEL to characterize the acute risk due to oral exposure to imidacloprid. The ENEL of 5.5 mg/kg/day for decreases in dimensions in brain structures in rats from the DNT study (Sheets, 2001) could be applicable to acute exposures to imidacloprid in women of childbearing age to protect against fetal exposure.

**Figure 4.** Estimation of the Threshold of the Imidacloprid Acute Oral Toxicity with the BMD model.



**Imidacloprid-Induced Decrease in the Motor Activity in Rats.** Imidacloprid was administered by gavage in a single dose to Sprague-Dawley rats (Sheets, 1994a). The doses were 0, 42, 151 and 307 mg/kg/day. The lowest tested dose produced 27% decrease in the motor activity of the female rats. The motor activity was assessed using the figure-8-maze by counting light beam interruptions. The BMD approach was used to calculate the effective dose (ED) and the 95% confidence limit of the effective dose (LED), which were required to cause a 5% reduction in the motor activity. The Polynomial model generated the best curve fit among the several available algorithms. The LED<sub>05</sub> and ED<sub>05</sub> were estimated as 9 and 12 mg/kg/day, respectively.



#### **IV.A.2.b. Acute Inhalation Toxicity**

Two acute inhalation toxicity studies with imidacloprid in Wistar rats were available for the NOEL and LOEL determinations (Table 14).

In the study by Pauluhn (1988a), the rats were exposed head/nose only to imidacloprid in the form of dust for 4 hours. The effects at the LOEL of 412 mg/kg/day included difficult breathing, reduced motility, piloerection and tremors. The same clinical signs were observed at the LOEL of 100 mg/kg/day in the acute oral study in Wistar rats (Bomann, 1989b, see Table 3 and Table 14). The NOEL was 192 mg/kg/day, which was 21-fold higher than the acute oral NOEL of 9 mg/kg/day from the neurotoxicity study in rats (Sheets, 1994a). This study was designed for determination of the LC<sub>50</sub> and thus more subtle toxic effects might have been missed. In addition, the data suggested that an adjustment of the NOEL was needed to correct for the bioavailability of imidacloprid due to the large particle size of the dust. The study reported that at the NOEL, only 11% of the dust particles had an aerodynamic particle size less than 5 µm. If only particles with MMAD ≤ 5 µm were to be considered, the adjusted NOEL would be 21 mg/kg/day. Nevertheless, the adjusted dose could be higher, since the observed toxicity may be due to larger particles as well. For toxicants causing systemic effects, a particle size range that deposit throughout the entire rodent respiratory tract (i.e. MMAD up to 10 µm) is of toxicologic concern (Raabe et al., 1988; SOT, 1992; Pauluhn, 2003). However, data on the percentage of larger particle size, which could contribute to the systemic toxicity of imidacloprid, were not provided.

In the second inhalation toxicity study, Wistar rats were exposed by head/nose only to imidacloprid dust for 6 hours/day for 5 days (Pauluhn, 1988a). This study included more extensive toxicity evaluation (e.g. clinical signs, clinical chemistry, hematological and histopathological changes). Clinical signs were not observed at any of the tested doses. However, the highest tested dose in this study (87 mg/kg/day) was 5-fold lower than the dose at which clinical signs were to be expected (e.g. the LOEL of 412 mg/kg/day from the 4-hour inhalation study; Pauluhn, 1988a). The reported NOEL was 3.2 mg/kg/day, based on statistically significant reduction of body weights (6%) and induction of liver MFO in the liver (28%) at the LOEL of 19 mg/kg/day. This NOEL was 56-fold lower than the NOEL from the 4-hour inhalation study (192 mg/kg/day). It was also 3-fold lower than the oral NOEL from the acute neurotoxicity study in rats (9 mg/kg/day; Sheets, 1994a). Adjusting dose of 3.2 mg/kg/day for 54% of particles with MMAD ≤ 5 µm would result in a NOEL of 1.7 mg/kg/day.

For characterizing the risk of inhalation exposures of contaminants in the air, data from inhalation toxicity studies are preferable. There was, however, a substantial uncertainty associated with the bioavailability of imidacloprid in both inhalation studies. The 5-Day study had provided more elaborate evaluations. Nevertheless, there was a greater uncertainty in the reported effects at the LOEL of 19 mg/kg/day (Pauluhn, 1988a), as they may have required repeated exposures. In this regard, induction of the liver MFO and reduction in body weights were consistently observed in the subchronic oral and inhalation studies. Thus, the adjusted NOEL of 1.7 mg/kg/day may not be appropriate for use as an acute inhalation no effect level. Since the toxicological effects identified in the inhalation studies were systemic rather than localized (i.e., at the site of contact), the oral NOELs and LOELs can reasonably be assumed to be the thresholds for inhalation exposures. There were no pharmacokinetic studies to determine the extent of the imidacloprid absorption upon inhalation exposure. In the absence of data, both DPR and USEPA assumed a default of 100% for the inhalation uptake. Based on the comparable

acute toxicity between the oral and inhalation routes, it is possible to extrapolate a threshold from the oral route based on the absorbed dose. In conclusion, the oral NOEL of 9 mg/kg/day from the acute neurotoxicity study in rats (Sheets, 1994a) was selected for characterizing the acute risk due to inhalation exposure to imidacloprid.

#### **IV.A.2.c. Acute Dermal Toxicity**

There were no available studies to determine the acute dermal NOEL and LOEL or the extent of the dermal absorption. The oral NOEL of 9 mg/kg/day from the acute neurotoxicity study in rats (Sheets, 1994a) was selected for characterizing the risk due to the acute dermal exposure to imidacloprid.

#### **IV.A.3. Subchronic Toxicity**

The subchronic NOELs and LOELs for imidacloprid are presented in Table 13. The list included pertinent studies described in Section III.C., SUBCHRONIC TOXICITY and under any other toxicity categories pertinent to subchronic exposures, e.g., the threshold for subchronic neurotoxicity and the threshold for reproductive toxicities.

##### **IV.A.3.a. Subchronic Oral Toxicity**

Five oral toxicity studies in rats, one study in mice and two studies in dogs were available for the selection of the critical subchronic NOEL.

The lowest NOEL of 7.3 mg/kg/day was established in Beagle dogs, after 4 weeks of treatment with imidacloprid (Table 15). This NOEL was based on morphological changes in the liver and the thyroid gland (hypertrophy of hepatocytes and follicular atrophy) at the LOEL of 31 mg/kg/day (Block, 1987). The toxicity increased abruptly at the next tested dose (49 mg/kg/day) and included mortality, weight loss, severe tremors, ataxia and pathological changes of the liver, thymus, thyroid and testis. The same NOEL in Beagle dogs (8 mg/kg/day) was determined following 13 weeks of dosing with imidacloprid (Table 15). Tremors were reported at the LOEL of 24 mg/kg/day.

In a DNT study in rats, statistically significant decreases (up to 27%) in thickness of brain structures of the PND11 pups were found at the highest tested dose of 54.7 mg/kg/day, following 32 daily oral doses of imidacloprid to the dams (Sheets, 2001). Pups from the intermediate and low dose-groups were not evaluated for developmental brain effects. Assuming that the LOEL for DNT is 54.7 mg/kg/day and applying a 10-fold default uncertainty factor, the NOEL could be estimated as 5.5 mg/kg/day. The ENEL of 5.5 mg/kg/day is close to the NOEL of 7.3 mg/kg/day established in dogs, but with a greater uncertainty due to the application of a 10-fold default factor.

The next set of higher NOELs, ranging from 9.3-19.4 mg/kg/day, were identified in studies in rats. Reduction in body weights was consistently observed in all subchronic and reproductive toxicity studies in rats. The lowest NOEL (9.3 mg/kg/day) was from a subchronic neurotoxicity study in Fischer-344 rats (Sheets, 1994c). The experimental protocol included 13 weeks of dosing with imidacloprid and extensive evaluations, such as assessments of the neurobehavioral and the motor activity. The reported effect at the LOEL of 63 mg/kg/day was a statistically significant reduction (6%) in body weights of the male rats. In a reproductive toxicity study in Wistar rats, the NOEL was 13 mg/kg/day rats based on significantly decreased body weights

(13-17%) of the parental animals and the pups from all generations at the LOEL of 38 mg/kg/day (Suter et al., 1990). Statistically significant decreases in body weight (8-11%) were also observed in the 13- or 14-Week subchronic dietary studies in Wistar rats at the LOELs of 57 and 61mg/kg/day (Eiben, 1988a; 1989). In the 13-week study, an additional effect at the LOEL was liver toxicity (necrosis of hepatocytes). Both studies established a NOEL of 14 mg/kg/day. A NOEL of 19.4 mg/kg/day was determined from the developmental neurotoxicity study in Sprague-Dawley rats (Sheets, 2001). It was based on a statistically significant reduction in body weights of the pups (13%) and a decreased motor activity LOEL of 54.7 mg/kg/day.

The highest of all subchronic NOELs was determined in B6C3F1 mice treated with imidacloprid for 107 days (Eiben, 1988b). The effects at the LOEL included mortality, clinical signs and a marked reduction in the body weight (up to 27%). There was a substantial uncertainty associated with the reported doses in this study. The imidacloprid doses were estimated based upon unusually high food consumption, representing about 60%-100% of the mice body weight. The DPR toxicologists adjusted the ingestion of imidacloprid based on a default food consumption of 15% of the body weight of an adult mouse (30 g). The revised NOEL was 86 mg/kg/day, based on the revised LOEL of 427.

### **Conclusions**

With the exception of the NOEL from the mouse study, the rest of the subchronic oral NOELs in rats and dogs were in the range of 7.3-19.4 mg/kg/day. The lowest NOEL (7.3 mg/kg/day) was established from two studies in the dog, based on morphological changes of the liver and the thyroid gland, and tremors at the LOEL of 24-31 mg/kg/day. The two dog studies included extensive toxicity evaluations and the endpoints were relevant, as liver, thyroid effects and tremors were seen in other studies with imidacloprid.

The most common effect in the five studies in rats was decreases in the body weight at the LOEL of 38-63 mg/kg/day. It should be noted that a reduction in body weights was also observed in the dogs at similar doses (49-63 mg/kg/day). The lowest NOEL in rats was 13 mg/kg/day from the reproductive toxicity study (Suter et al, 1990). Because the rats had higher NOEL than dogs, it could be argued that the subchronic no effect level is closer to the dose of 13 mg/kg/day than to the NOEL of 7.3 mg/kg/day in dogs. However the toxicity endpoint defining the NOELs in rats and dogs were different. In addition, the NOEL of 7.3 mg/kg/day was supported by the ENEL of 5.5 mg/kg/day for developmental neurotoxicity (Sheets, 2001). Thus, the subchronic oral NOEL of 7.3 mg/kg/day from the 4- and 13-Week studies in Beagle dogs (Block, 1987; Ruf, 1990) was selected for characterizing the risk due to subchronic dietary exposures to imidacloprid.

### **IV.A.3.b. Subchronic Inhalation Toxicity**

One subchronic inhalation toxicity study with imidacloprid in Wistar rats was available for the NOEL and LOEL determinations (Pauluhn, 1989, presented in Section III.C.3. under Subchronic Toxicity). In this study, the rats were exposed by head/nose only to imidacloprid in the form of dust over a period of 4 weeks (Tables 4). The NOEL was established as 0.9 mg/kg/day. The principal effects at the LOEL of 5.2 mg/kg/day were concentration-dependent 7-9% increases in the absolute and relative liver weights, statistically significant increases in the activities of the serum ALT, AP and GLDH (25%-200%) and induction of the hepatic MFO (27%).

This study included extensive toxicity evaluations. The endpoints were relevant, as changes in liver weights, clinical chemistry parameters and liver function were seen in oral subchronic or

chronic studies. The subchronic inhalation NOEL was 8-fold lower than the subchronic oral NOEL in dogs (7.3 mg/kg/day). However, the subchronic inhalation NOEL was close to the NOEL of 1.7 mg/kg/day defined in the 5-Day inhalation study in rats. In the 5-Day inhalation study, the reported effects were induction of the liver MFO and reduction in body weights (Pauluhn, 1988a; Table 14). Both, the 4-Week and the 5-Day inhalation studies suggested that inhalation may be a more toxic route. Based on these considerations, the NOEL of 0.9 mg/kg/day from the 4 week-inhalation study in rats was selected for characterizing the subchronic risk due to inhalation exposure to imidacloprid (Table 15).

The DPR employed the subchronic inhalation LOEL of 5.2 mg/kg/day to calculate the risk of the pesticide workers in the health risk assessment in 1993, which evaluated imidacloprid for an emergency use on cotton under the Section 18 of the FIFRA (Lewis et al., 1993).

#### **IV.A.3.c. Subchronic Dermal Toxicity**

One subchronic dermal toxicity study was available in rabbits, which were treated with the dose of 1000 mg/kg/day imidacloprid (Flucke, 1990). No effects were observed after 3 weeks of treatment. Since a subchronic dermal NOEL could not be clearly defined from this study, the oral NOEL of 7.3 mg/kg/day, from the 4-Week study in dogs (Block, 1987) was selected for characterizing the risk due to subchronic dermal exposures to imidacloprid.

**Table 15.** Subchronic No-Observed-Effect Levels (NOELs) and Lowest-Observed-Effect Levels (LOELs) for Imidacloprid.

Subchronic Study		NOEL <sup>a</sup>	LOEL <sup>b</sup>	Toxic Effects at LOEL
Species	Exposure	mg/kg		
Rat 10 sex/dose	Oral 14 weeks	14	57	11%* body weight reduction (females, food intake increased, Eiben, 1988a)
Rat 10 sex/dose	Oral 13 weeks	14	61	Liver toxicity (necrosis of hepatocytes) and reduced body weight (8%*) in male rats, (Eiben, 1989 <sup>#</sup> )
Rat 12 sex/dose	Oral 13 weeks Subchr. Neurotox	9.3	63	Reduction in body weights (8%** in male rats (Sheets, 1994b)
Rat 30 sex/dose/dose	Oral Repro. Toxicity	13	38	Reduction in body weights (13-17%** in adults and pups (start: Day 1 of premating and PND 4-throughout lactation; Suter et al., 1990 <sup>#</sup> )
Rat 12 sex/dose	Oral 41days <sup>a</sup> ; Dev.Neurot	19.4	54.7 <sup>a</sup>	Reduction in body weights (13%** in pups, decreased motor activity in females (Sheets, 2001)
Rat 10 sex/dose	Inhalation, dust 6 h/5days/4 weeks	0.9	5.2	Increased liver weights (9% absolute and 7% relative) and liver toxicity: (↑ ALT 25% **; ↑ AP 20%*; ↑ GLDH 200%**); plasma ChE ↓ 26%), induction of hepatic MFO (27%*; Pauluhn, 1989)
Mouse 10 sex/dose	Oral 107 days	86	427	Mortality, reduced body weight (15-27%**), poor general condition, rough coats, changes in clinical chemistry (↑ ALT 47%**; ↓ cholesterol 22%** and ↓ urea 32%**; Eiben, 1988b)
Dog 2 sex/dose	Oral 4 Weeks	7.3	31	Morphological changes: hepatocyte hypertrophy (one male) and thyroid follicular atrophy (one female; Block, 1987)
Dog 4 sex/dose	Oral 13 Weeks	8	24	Tremors (Ruf, 1990 <sup>#</sup> )

**a/** Decreases in thickness of corpus callosum (27%, p< 0.05) and the width of caudate putamen (6%, p< 0.05) were found in the PND11 females. Brain measurements were not performed in the intermediate and low dose-groups. A NOEL for developmental neurotoxicity could be estimated (ENEL) as low as 5.5 mg/kg/day by applying a default factor of 10 to the LOEL of 54.7 mg/kg/day.

ALT, alanine aminotransferase; AP, alkaline phosphatase; GLDH, glutamate dehydrogenase; ChE, cholinesterase; MFO, mixed function oxidases; \*, \*\* Statistically significant difference from controls at p ≤ 0.05 or p ≤ 0.01, respectively

#### **IV.A.4. Chronic Toxicity**

Three chronic oral studies in rats, mice and dogs were available for determination of NOELs and LOELs for imidacloprid (Table 16; also see Section III.D., under CHRONIC TOXICITY). Chronic inhalation and dermal toxicity studies with imidacloprid were not available. Therefore, oral studies were used to define the critical NOEL for chronic exposures from all routes.

The lowest oral NOEL of 5.7 mg/kg/day was from a 2-year chronic toxicity/oncogenicity study in Wistar rats (Eiben and Kaliner, 1991; Eiben, 1991). The principal effect at the LOEL of 17 mg/kg/day was a statistically significant increase (62%) in the incidence and severity of mineralized particles in thyroid gland in male rats (Tables 7 and 16). In the subchronic studies in rats, the most common effect was body weight decreases at doses of 38-63 mg/kg/day (Table 15). In the chronic rat study, statistically significant reduction in body weight (12%) was also seen at a similar dose level (51 mg/kg/day, see Section III.D). The NOEL of 5.7 mg/kg/day was employed by the DPR to calculate the risk of chronic exposures in the health risk assessment in 1993, which evaluated imidacloprid for an emergency use on cotton under the Section 18 of the FIFRA (Lewis et al., 1993). The same NOEL was also used by the USEPA to assess the chronic risk of imidacloprid exposures (USEPA, 2003).

The next higher oral NOEL of 15 mg/kg/day was from a study in Beagle dogs, which were treated with imidacloprid for a period of 52 weeks (Allen et al., 1989). The reported effects at the LOEL of 41 mg/kg/day included statistically significant changes in the liver metabolic function (91% increase in the cholesterol level and 200% induction of the liver MFO) and a decrease of food consumption (14%, Table 16). The effects in this study were relatively mild, compared to the marked toxicity observed in dogs after subchronic treatment (4 and 13-Weeks) with similar doses with imidacloprid, including mortality, severe tremors, morphological changes in liver and thyroid and weight loss (Block, 1987; Ruf, 1990, Tables 5, 6 and 15).

Similar to the subchronic NOELs, the highest chronic NOEL was determined in mice fed with imidacloprid for 24 months (Watta-Gebert, 1991). There was a substantial uncertainty associated with the reported doses in this study, because the food intake and, in turn the imidacloprid intake, was unusually high (about 22-28% of the body weight of an adult mouse). The DPR toxicologists adjusted the ingestion of imidacloprid to a default food consumption of 15% of the body weight of an adult mouse. The main effect at the LOEL was statistically significantly reduced body weights of the males (10%). The revised NOEL was 47 mg/kg/day, based on the revised LOEL of 143 mg/kg/day (Table 16).

#### **Conclusions**

The lowest NOEL for imidacloprid of 5.7 mg/kg/day was in rats, based on an increase in incidence and severity of mineralized particles in thyroid gland (Eiben and Kaliner, 1991; Eiben, 1991). The NOEL established in dogs was higher (15 mg/kg/day), but was based upon different endpoints (i.e. changes in the liver metabolic function). Although thyroid effects were not observed at any of the doses tested in the chronic dog study (Allen et al., 1989), subchronic toxicity studies in dogs established a NOEL of 7.3 mg/kg/day based on thyroid follicular atrophy, among other toxic endpoints (Block, 1987; Ruf, 1990). Thus, the subchronic NOEL in dogs was in support of the chronic NOEL of 5.7 mg/kg/day for thyroid lesions in rats. In conclusion, the oral NOEL of 5.7 mg/kg/day in rats was selected for characterizing the risk due to chronic exposures to imidacloprid. This NOEL is sufficiently close to the ENEL of 5.5 for

developmental neurotoxicity (Sheets, 2001), and therefore, would be adequate for protection against the potential effects of imidacloprid on the developing nervous system.

**Table 16.** Chronic No-Observed Effect Levels (NOELs) and Lowest-Observed-Effect Levels (LOELs) of Imidacloprid.

Chronic Study		NOEL	LOEL	Toxic Effects at LOEL	References
Species	Exposure	mg/kg/day			
Rat	Oral 2 year	5.7	17	Mineralized particles in thyroid gland (males, 62%** increase)	Eiben and Kaliner <sup>#</sup> , 1991; Eiben, 1991
Mouse	Oral 2 year	47 <sup>a</sup>	143 <sup>a</sup>	Reduced body weight (10%*, males)	Watta-Gebert, 1991; 1991a <sup>#</sup>
Dog	Oral 52 Weeks	15	41	Liver metabolic changes: ↑ liver cytochrome P-450 enzymes (200 fold*); ↑ cholesterol (91%**)	Allen et al., 1989 <sup>#</sup>

a/ The reported food intake levels represented about 22-28% of the mice body weight. Because of the unusually high food consumption (and imidacloprid intake), the doses were revised by the DPR, based on a default food consumption of 15% of the body weight of an adult mouse (30 g).

\*, \*\* Statistically significant difference from controls at  $p \leq 0.05$  or  $p \leq 0.01$ , respectively.

# The study fulfilled the SB950 data requirement for a specific type testing.

#### **IV.A.5. Oncogenicity Weight of Evidence**

Two oncogenicity bioassays were available for imidacloprid in rats and mice. In the rat study, rare liver tumors (cholangiocellular carcinoma) were found in the males (Eiben, 1991). The incidence for cholangiocellular carcinoma was outside the historical range, albeit, not statistically significant from the concurrent controls. The lack of clear evidence of oncogenicity at sufficiently high doses, together with the negative genotoxicity under laboratory conditions, precluded further considerations of the oncogenicity potential of imidacloprid.

Nevertheless, it should be noted that cholinergic agonists such as ACh and nicotine are known to stimulate the growth of human cancer cells from lung, colon and gingival origin (Song et al., 2003a; Ye et al., 2004; Argentin and Cicchetti, 2004). Importantly, human lung carcinomas have been shown to express nicotinic AChRs and to secrete and degrade ACh. Both ACh and nicotine stimulated the growth of these cells via activation of the nAChRs, thus suggesting that other nicotinic agonists may have the same effect (Song et al., 2003a,b). The current hypothesis is that ACh may function as an autocrine growth factor for lung carcinomas (Song et al., 2003b). Recent studies revealed that nicotine enhanced the proliferation of human lung cancer cells by blocking the programmed cell death (apoptosis; Jin et al., 2004). Nicotine has also been shown to promote the growth of pre-existing tumors *in vivo* (Seppa, 2002; Heeschen et al., 2001; Natori et al, 2003). This effect was attributed to the ability of nicotine to induce growth of new blood vessels (angiogenesis), which supply oxygen and nourishment to tumors. In fact, the angiogenic properties of nicotine have been linked to the development of lung and mouth cancers (Seppa, 2002). These data should be considered when assessing the oncogenicity of imidacloprid, because it binds to the ACh binding site on the AChR and is structurally and functionally similar to nicotine. However, the available bioassays were not designed to test whether imidacloprid promotes the growth of pre-existing tumors. In conclusion, the current data on imidacloprid may be insufficient to thoroughly evaluate its tumorigenic properties through a promotion mechanism.



## **IV.B. EXPOSURE ASSESSMENT**

Human non-occupational exposure to imidacloprid could result from consuming food and water containing the pesticide residues (dietary exposure). The general population may be also exposed to airborne imidacloprid in agricultural regions with extensive application of imidacloprid.

This document pertains only to the assessment of the dietary exposure. The lack of monitoring data precluded the assessment of the ambient air exposure to imidacloprid at this time. The occupational exposure and the exposure from residential uses will be addressed subsequently in an addendum to this document.

### **IV. B.1. Dietary and Drinking Water Exposure**

#### **IV. B.1.a. Introduction**

The Department of Pesticide Regulation (DPR) conducts acute and chronic dietary exposure assessments to evaluate the risk of human exposure to pesticide residues in food in California (Bronzan and Jones, 1989). Two types of dietary exposure assessments are conducted: (1) the total dietary exposure is determined based on residue levels on all label-approved commodities and (2) exposure to an individual commodity at the tolerance level (DPR MT-3, 2004).

Dietary exposure is a product of the amount of food that is consumed and the concentration of the pesticide residue in that food. The total exposure in an individual's diet during a defined period of time (e.g., a day) is the sum of exposure from all foods (in various forms and as ingredients in food items) consumed within that period:

$$\text{Exposure} = \sum_{i=1}^n (\text{Residue}_i \times \text{consumption}_i \text{ of foods}),$$

where  $n$  is the number of foods items in the diet.

Data on the amount of the pesticide residue on food and the food consumption provide dietary exposures for various population subgroups based on age, gender, ethnicity, and season and pregnancy/lactation status.

For estimating the acute exposure, the highest residue values at or below the tolerance, or the distribution of residues are considered. In contrast, for chronic exposure, the mean residue values are appropriate. Acute exposure is calculated on a per-user basis, i.e., including in the distribution of exposures only the days of survey that at least one commodity with potential pesticide residues is consumed. Chronic exposure to pesticides is generally calculated using per-capita mean consumption estimates to include the entire population (DPR MT-3, 2004).

The imidacloprid acute and chronic dietary risk assessments, along with the acute tolerance assessment, are discussed below. Acute and chronic exposure analyses were carried out for all combined imidacloprid food uses. USEPA tolerances for residues of imidacloprid are presently established on a large number (over 270) of fruit and vegetable crops, and animal commodities (Table 18, CFR 2003 a). As of December 2004, there are 21 active products containing imidacloprid approved for use in California. Bayer Inc. and

Miles Inc. hold the registration for agricultural food use of these products containing 0.5-75% imidacloprid as an active ingredient (see Section II.C. TECHNICAL AND PRODUCT FORMULATIONS).

#### **IV. B.1.b. Consumption Data and Dietary Exposure**

The Dietary Exposure Evaluation Model (DEEM™ v. 7.74; Exponent Inc. <http://www.exponent.com/home.html>) was used to calculate the dietary risk. The food consumption pattern was based on data generated by the United States Department of Agriculture (USDA) during the 1994-1998 Continuing Survey of Food Intake by Individuals (CSFII). The CSFII 1994-98 is the most recent and representative consumption database, which provides information on a 2-day food intake by 20,607 individuals of all ages from 62 geographical areas. The database consists of the 1994-1996 food consumption survey, along with the 1998 Supplemental Children's Survey (CSFII 1998), which includes an additional 5,559 children from birth to 9 years old. <http://www.barc.usda.gov/bhnrc/foodsurvey/pdf/Csfii98.pdf>

Dietary exposure and risk estimates were provided for the average U.S. population and 15 selected population subgroups, including all infants, nursing or non-nursing infants and children. Subgroups were defined by geographic regions, age, gender or ethnicity.

In addition to calculating the dietary exposure, the DEEM™ Acute Module was used to determine those foods having the greatest contribution to the total exposure of the individuals. The Critical Exposure Commodity (CEC) analysis provides consumption records for individuals at the high end of dietary exposure (in the top 5% or less). The CEC analysis also identifies the commodities contributing to the high end of the dietary exposure. The records include the amount of food(s) consumed, body weight, age, residue values and the exposure estimate by food.

For acute exposure estimates, one-day consumption data comprised all the commodities with imidacloprid tolerances. The consumption of each commodity by each individual in a population subgroup was multiplied by a single residue value (point estimate) for a deterministic risk assessment. For chronic exposure estimates, the average food consumption of each population subgroup was multiplied by the mean residue value. The estimates for both acute and chronic exposure were expressed as a dosage in µg/kg/day.

#### **IV. B.1.c. Exposure to Imidacloprid from Food.**

Imidacloprid residues, which are of toxicological significance in plant and animal commodities, include imidacloprid and its metabolites containing the 6-chloropyridinyl moiety. This moiety is common for several insecticidal neonicotinoids, which exert neurotoxicity via blockage of the nAChRs (Tomizawa et al, 2001). The major 6-chloropyridinyl metabolites of imidacloprid are desnitro-imidacloprid, olefinic-imidacloprid, 4- and 5-hydroxy-imidacloprid, imidacloprid urea and 6-chloronicotinic acid. The published tolerances for imidacloprid are listed in 40 CFR 180.121 and are expressed for plant and animal commodities as combined residues of imidacloprid parent compound and its 6-chloropyridinyl metabolites (CFR, 2003a)

#### **IV. B.1.d. Residue Data Sources**

The residue data for imidacloprid used in the current risk assessment were based on the following sources: USDA Pesticide Data Program (PDP), DPR Market Basket Surveillance Programs and Field Trial Residue Studies (submitted by the imidacloprid registrants to support tolerances). Although monitoring data are preferred for risk assessment, only a few commodities with imidacloprid registrations were screened for residues under the Federal and State monitoring programs.

##### **1. Pesticide Data Program (PDP)**

The PDP ([www.ams.usda.gov/science/pdp/download.htm](http://www.ams.usda.gov/science/pdp/download.htm)) is the most representative monitoring residue database, because it is designed to obtain pesticide residue data for risk assessments. The PDP samples are collected in ten states, including California.

In 1999, PDP for the first time monitored raw agricultural (RAC) and processed commodities for the combined residues of imidacloprid and its 6-chloropyridinyl metabolites. From 1999 to 2002, PDP examined 5 commodities with tolerances for imidacloprid (USDA, 1999-2002). Detectable residues were reported in 2000 and 2001 for oranges. In contrast, quantifiable imidacloprid residues were not reported on the following commodities: nectarines (during the 2000-2001 surveillance period); oats (examined in 1999); sweet peas (analyzed in 2001 and 2002), and tomato paste (canned; screened in 2001; Table 17). The residue limit of detection (LOD) varied from 0.025-0.008 ppm among the national laboratories contracted by USDA to perform the analysis (Table 17).

In 2001 and 2002, PDP analyzed drinking water systems for imidacloprid residues in two states, New York and California. A total of 329 water samples were screened in 2001 and 2002 from wells in the New York state. One sample had quantifiable imidacloprid residues. The residue LOD varied from 1.5-22.5 ppt. In 2002, the community water system in California was analyzed at the USDA contract laboratory at Sacramento, California. A total of 51 samples were screened for imidacloprid and there were no detectable residues. The residue LOD was 15 ppt (Table 17).

##### **2. DPR Marketplace Surveillance Program.**

The DPR monitoring program (<http://www.cdpr.ca.gov/docs/pstrsmon/rsmonmnu.htm>) includes commodities, which are not monitored by other programs, and reflects the wide variety of foods consumed by Californians (DPR, 2002). It is mainly a tool for enforcement, as it focuses on commodities with known violations of tolerance. Under the California DPR surveillance program, imidacloprid is analyzed as the parent compound only (CDFA analytical method No. RES-SM-7). Detectable residues were reported in 2002 for lettuce. There were no detected imidacloprid residues in the following commodities: cantaloupes, cucumbers, grapes, peppers and chili peppers, strawberries and tomatillos. The residue limit of detection was 0.4 ppm.

In 2001, preliminary surface water monitoring studies did not detect imidacloprid residues in the California. The detection limit was 0.05 ppb (see section II.G.4.d. under Environmental Fate).

### 3. Field Trial Residue Studies.

Bayer Corporation and Miles Inc. (the basic registrant of imidacloprid-containing products in the US) have submitted field studies evaluating the residues on RAC treated with imidacloprid at various label rates, including the maximum. These studies were conducted for support in the setting of tolerances and measured imidacloprid as combined residues of the parent compound and its 6-chloropyridinyl metabolites. Field trial data were available to DPR for selected commodities representing the following crop groups, as defined in the 40 CFR 180.41: Crop Group 1 (Root and tuber vegetables); Crop Group 2 (leaves of root and tuber vegetables); Crop Group 5 (Brassica vegetables); Crop Group 6 (Legumes, succulent and dry vegetables); Crop Group 8 (Fruiting vegetables); Crop Group 9 (Cucurbit Vegetables); Crop Group 10 (Citrus Fruit), Crop Group 11 (Pome Fruit); Crop Group 15 (Cereal grain); Subgroup 4-A (Leafy greens) and Subgroup 4-B (Leaf petioles; Tables 17 and 18). Residue data from field trial studies were available to DPR for an additional 57 RAC and animal commodities (Table 18).

**Table 17.** Anticipated Imidacloprid Residues From Monitoring Databases Used For Acute And Chronic Dietary Exposure Assessments

Commodity	Source of Data	Year	Number Samples	Number Detected Samples	Detected Residues (ppm)	Range LOD <sup>a</sup> (ppm)	% Crop Treated <sup>b</sup>	Adj. Factor <sup>c</sup>	Acute Point Est. Residue (ppm)	Chronic Average Residue (ppm)
<b>Cantaloupe (fresh, juice and pulp; honeydew, Persian)</b>	DPR	2002	33	0	No detectable residues	0.40	45	1	0.400	0.200
<b>Citrus Fruit Group 10<sup>d</sup> (except oranges)</b>	PDP <sup>e</sup>	See Data for Oranges				0.01	100	2 - 11.4 <sup>f</sup> juice and juice conc.	0.120	0.038
<b>Cucumbers</b>	DPR <sup>g</sup>	2002	34	0	No detectable residues	0.4	50	1	0.400	0.200
<b>Grapes (juice, juice-conc., leaves, raisins, wine, sherry)</b>	DPR for grapes	2002	71	0	No detectable residues	0.4	50	1.2 x juice 4.3 x raisin	0.400	0.200
<b>Ground-cherry</b>	DPR	2002	18	0	No detectable residues	0.4	100 <sup>i</sup>	1	0.400	0.200

Continued

**Table 17.** Anticipated Imidacloprid Residues From Monitoring Databases Used For Acute And Chronic Dietary Exposure Assessments (continued).

Commodity	Source of Data	Year	Number Samples	Number Detected Samples	Detected Residues (ppm)	Range LOD (ppm)	% Crop Treated <sup>b</sup>	Adj. Factor <sup>c</sup>	Acute Point Est. Residue (ppm)	Chronic Average Residue (ppm)
<b>Lettuce (head, leaf)</b>	DPR	2002	45	3	0.11-0.4	0.4	85	1	0.400	0.200
<b>Nectarines</b>	PDP	2000	249	0	No detectable residues	0.01	1	1	0.010	0.005
		2001	259	0						
<b>Oats</b>	PDP	1999	332	0	No detectable residues	0.08	100	1	0.008	0.004
<b>Oranges</b>	PDP	2000	528	3	0.014-0.12	0.01	1	1.8x juice 6.7x juice conc.	0.120	0.038
		2001	531							
<b>Peas (garden dry and green; succulent/blackeye/co wpea, snowpeas)</b>	PDP	2000	131	10	No detectable residues	0.01	1	1	0.010	0.005
		2001	499	0						

Continued

**Table 17.** Anticipated Imidacloprid Residues From Monitoring Databases Used For Acute And Chronic Dietary Exposure Assessments (continued).

Commodity	Source of Data	Year	Number Samples	Number Detected Samples	Detected Residues (ppm)	Range LOD <sup>a</sup> (ppm)	% Crop Treated <sup>b</sup>	Adj. Factor <sup>c</sup>	Acute Point Est. Residue (ppm)	Chronic Average Residue (ppm)
<b>Peaches (fresh, dried, juice)</b>	PDP for nectarines	See	Data	for	Nectarine	0.01	1	7x dried peaches	0.010	0.005
<b>Peppers (chilly, sweet)</b>	DPR	2002	74	0	No detectable residues	0.40	62	1.0	0.400	0.200
<b>Strawberry (fresh, juice)</b>	DPR	2002	28	0	No detectable residues	0.400	100	1.0	0.400	0.200
<b>Tomato, paste</b>	PDP data for tomato paste canned	2001	369	0	No detectable residues	0.025	70	-	0.025	0.013
<b>Tomato, puree and catsup</b>	PDP	See	Data for	Tomato	Paste	0.025	70	-	0.025	0.013
<b>Drinking Water</b>	PDP in CA	2002	51	0	No detectable residues	15 ppt*	-	-	15 ppt	7.5 ppt

a/ LOD, Limit of Detection.

b/ PCT was from the 2003 report by the USDA Biological and Economical Analysis Division (BEAD; USEPA, 2003b); or the highest value from the 1998-2003 Agricultural Chemical Usage Reports by the USDA National Agricultural Statistical Service.

Continued

c/ DEEM™ default factors to account for changes in the hydration state of foods.

d/ Citrus Fruit Group 10 as defined in the 40 CFR 180.41: Calamondin\*, Citrus citron, Citrus hybrids\*, Grapefruit, Kumquat, Lemon, Lime, Mandarin (tangerine), Orange (sweet and sour), Pummelo, Satsuma mandarin\* ; \* No consumption data in DEEM™

e/ Pesticide Data Program (PDP) implemented by the United States Department of Agriculture (USDA).

f/ Hydration factors were: 2.1 and 8.26 for grapefruit juice and juice-concentrate; 2.0 and 11.4 for lemon juice and juice-concentrate; 2.0 and 6.0 for lime juice and juice-concentrate; 2.3 and 7.35 for tangerine juice and juice-concentrate.

g/ Residue Distribution File (RDF) containing all detected residues to determine the exposure distribution in Monte Carlo analyses.

h) Department of Pesticide Regulation (DPR) Priority Pesticide and Market Basket Surveillance Programs.

i/ 100% PCT was assumed for all crops, for which information on the percentage of the crops treated with imidacloprid was not available.

\***ppt** , Part per Trillion



**Table 18.** Imidacloprid Residues from Field Trial Studies Used for Acute and Chronic Dietary Exposure Assessments<sup>a</sup>.

Commodity	% Crop Treated <sup>b</sup>	Acute Residue Point Estimate (ppm)	Chronic Average Residue (ppm)
Acerola	100	1.00	0.500
Almonds	100	0.05	0.025
Apple (fresh, dried, juice/cider, juice-conc.)	34	0.50	0.250
Artichokes, globe	100	2.50	1.250
Avocado	100	1.00	0.500
Banana (fresh, dried, juice)	100	0.02	0.010
Barley (grain)	100	0.05	0.025
Beet (sugar roots)	100	0.05	0.025
Beet (sugar molasses)	100	0.30	0.150
Blueberries	100	3.50	1.750
Brassica Vegetables Crop Group 5 <sup>c,d</sup>	35 broccoli 56 brussels sprout 20 cabbage 60 cauliflow. 10 collards 30 kale	3.50	1.750
Canola oil (rape seed)	100	0.05	0.025
Cattle (dried, fat, kidney, liver meat, meat byproducts)	-	0.30	0.150
Coriander	100	3.50	1.750
Corn grain (bran, endosperm, oil), sweet corn, popcorn)	100	0.05	0.025
Cottonseed -meal	3	8.00	4.000
Cottonseed -oil	3	6.00	3.000
Cranberries (fresh, juice, juice-concentrate)	100	0.05	0.025
Currant	100	3.50	1.750
Egg (whole, white and yolk)	-	0.02	0.010
Elderberry	100	3.50	1.750
Fruit, Pome Group 11 <sup>e</sup> (except apples)	20 pears	0.60	0.300
Fruit, Stone Group 12 <sup>f</sup> (except nectarines and peaches)	100	0.30	0.150
Goat (dried, fat, kidney, liver meat, meat byproducts)	-	0.30	0.150

Continued

**Table 18.** Imidacloprid Residues from Field Trial Studies Used for Acute and Chronic Dietary Exposure Assessments<sup>a</sup> (continued).

<b>Commodity</b>	<b>% Crop Treated<sup>b</sup></b>	<b>Acute Residue Point Estimate (ppm)</b>	<b>Chronic Average Residue (ppm)</b>
Gooseberries	100	3.50	1.750
Grain, Cereal Group 15 <sup>g</sup>	100	0.05	0.025
Guava (fruit and juice)	100	1.00	0.500
Hog (dried, fat, kidney, liver meat, meat byproducts)	-	0.30	0.150
Hops	100	6.00	3.000
Horse (horsemeat)	-	0.30	0.150
Huckleberries	100	3.50	1.750
Juneberry	100	3.50	1.750
Leaf Petioles Subgroup 4B <sup>h</sup>	100	6.00	3.000
Leafy Greens Subgroup 4A <sup>i</sup> (except lettuce)	100	3.50	1.750
Longan Fruit	100	3.00	1.500
Lychee (fresh and dried)	100	3.00	1.500
Mango	100	1.00	0.500
Milk (water, fat solids, non-fat solids; milk sugar)	-	0.10	0.050
Milk (water, fat solids, non-fat solids; milk sugar)	-	0.10	0.050
Mustard seeds	100	0.05	0.025
Okra	100	1.00	0.500
Passionfruit (fruit and juice)	100	1.00	0.500
Papaya (pulp, juice, dried)	100	1.00	0.500
Pecans	100	0.05	0.025
Persimmons	100	3.00	1.500
Potatoes (white peeled, peel only, whole, white dry)	46	0.40	0.200
Poultry (fat, liver, meat-lean)	-	0.05	0.025
Safflower-oil	100	0.50	0.25
Safflower-seed	100	0.05	0.025
Sapodilla	100	1.00	0.500
Sheep (fat, kidney, liver, lean meat, meat byproducts; other organ meats)	-	0.30	0.150
Soybeans (flour defatted, full fat, low fat)	100	0.50	0.250

Continued

**Table 18.** Imidacloprid Residues from Field Trial Studies Used for Acute and Chronic Dietary Exposure Assessments<sup>a</sup> (continued).

Commodity	% Crop Treated <sup>b</sup>	Acute Residue Point Estimate (ppm)	Chronic Average Residue (ppm)
<b>Soybeans (mature seeds dry, oil, sprouted seeds)</b>	100	1.00	0.500
<b>Sorghum</b>	100	0.05	0.025
<b>Starfruit (carambola)</b>	100	1.00	0.500
<b>Vegetables, Cucurbit Group 9<sup>l</sup> (except cucumbers and cantaloupes)</b>	6 watermelon 7 pumpkin 10 squash	0.50	0.250
<b>Vegetable, Fruiting Group 8<sup>k</sup> (except peppers, groundcherries and processed tomatoes)</b>	36 eggplant	1.00	0.500
<b>Vegetable, Leaves of root and tuber Group 2<sup>l</sup></b>	100	4.00	2.000
<b>Vegetable, Legume, Group 6<sup>m</sup> (except peas and soybeans)</b>	6 beans	4.00	2.000
<b>Vegetable, root and tuber, Group 1<sup>n</sup> (except sugar beet)</b>	100	0.40	0.200
<b>Watercress</b>	100	3.50	1.750
<b>Wheat (bran, germ, germ oil, flour; rough)</b>	100	0.05	0.025

a/ Field trial studies were submitted to the DPR for support in the setting of tolerances. The residue concentrations on the commodities were at a tolerance level for the acute assessment and ½ of the tolerance for the chronic assessment.

b/ Percent of the crop treated (PCT) adjustments were used only in the chronic analysis for non-blended foods. The average PCT was from the 2003 report by the USDA Biological and Economical Analysis Division (BEAD; USEPA 2003b) or from the 1998-2003 Agricultural Chemical Usage Reports by the USDA National Agricultural Statistical Service.

c/ Tolerances for imidacloprid were established for 12 crop groups of related commodities, as defined in the 40 CFR 180.41

d/ Brassica Vegetables Crop Group 5: Broccoli, Broccoli, Chinese (gai lon), Broccoli raab (rapini), Brussels sprouts, Cabbage, Cabbage, Chinese (bok choy and napa), Cabbage, Chinese mustard (gai choy), Cauliflower, Collards, Kale, Kohlrabi, Mizuna, Mustard greens, Mustard spinach, Rape greens

e/ Fruit Pome Group 11: Apple, Crabapple, Loquat, Pear, Quince

f/ Fruit Stone Group 12: Apricot; Cherry, sweet and tart; Nectarine; Peach; Plum (Chickasaw, Damson, Japanese); Plumcot\*; Prune

g/ Grain, Cereal, Group 15: Barley; Buckwheat; Corn; Millet, pearl; Millet, proso; Oats; Popcorn; Rice; Rye; Sorghum (milo); Teosinte; Triticale; Wheat; Wild rice.

h/ Leaf Petioles Subgroup 4-B. Cardoon\*; Celery; Celery, Chinese; Celtuce\*; Fennel\*, Florence\*; Rhubarb; Swiss chard

i/ Leafy Greens Subgroup 4-A. Amaranth; Arugula; Chervil; Chrysanthemum (edible-leaved and garland); Corn salad; Cress (garden and upland); Dandelion; Dock\*; Endive; Lettuce; Orach\*; Parsley; Purslane (garden and winter)\*; Radicchio (Chicory; Belgian endive), Spinach; Spinach (New Zealand and vine).

Continued

j/ Vegetables, Cucurbit Group 9. Chayote\*; Chinese waxgourd\*; Citron melon\*; Cucumber; Gherkin\*; Gourd\*; Momordica spp. (balsam apple, balsam pear, bitter melon, chinese cucumber\* Muskmelon (true cantaloupe, cantaloupe, casaba, crenshaw melon, golden pershaw melon, honeydew melon, honey balls, mango melon, Persian melon, pineapple melon, Santa Claus melon, and snake melon); Pumpkin; Squash, summer; Squash, winter (acorn squash; spaghetti squash); Watermelon.

k/ Vegetable, Fruiting, Group 8. Eggplant; Groundcherry; Pepino; Pepper (bell pepper, chili pepper, cooking pepper, pimento, sweet pepper); Tomatillo; Tomato.

l/ Vegetables, Leaves of root and tuber, Group 2: Beet, garden; Beet, sugar; Burdock\*; Carrot\*; Cassava\*, bitter and sweet; Celeriac\* (celery root); Chervil\*, turnip-rooted; Chicory\*; Dasheen (taro); Parsnip\*; Radish; Radish, oriental; Rutabaga; Salsify\*; Sweet potato; Tanier\*; Turnip; Yam, true

m/ Vegetables, Legumes, succulent and dry, Group 6. Bean (lupin, sweet lupin, white lupin, and white sweet lupin); Bean (field bean, kidney bean, lima bean, navy bean, pinto bean, runner bean, snap bean, tepary bean, wax bean); Bean (adzuki bean, asparagus, bean, blackeyed pea, catjang, Chinese longbean, cowpea, Crowder pea, moth bean, mung bean, rice bean, southern pea, urd bean, yardlong bean); Broad bean (fava bean); Chickpea (garbanzo bean); Guar; Jackbean; Lablab bean; Lentil, Pea (dwarf pea, edible-pod pea, English pea, field pea, garden pea, green pea, snowpea, sugar snap pea); Pigeon pea; Soybean; Soybean (immature seed); Sword bean.

n/Vegetables, Root and Tuber, Group 1. Beet sugar; Beet garden; Burdock; Canna\*; Carrot; Cassava, bitter and sweet; Celeriac; Chayote; Chervil; Chicory; Chufa\*; Dasheen (taro); Ginger; Ginseng; Horseradish; Leren\*; Parsley; Parsnip; Potato; Radish; Radish, oriental; Rutabaga; Salsify (oyster plant); Salsify, black; Salsify, Spanish; Skirret\*; Sweet potato; Tanier; Turmeric; Turnip; Yam bean; Yam, true.

\* No consumption data in DEEM™

## **IV. B.2. Acute Exposure**

The acute dietary exposure to a pesticide is estimated using the tiered approach in the selection of the appropriate residue values (DPR MT-3, 2004). The tiered approach begins with the point estimate (deterministic) steps, which are generally less time-consuming and less labor intensive than the refining assessment. The Point Estimate Model (Tiers 1-3) employs the tolerance, the upper bound value or the mean residue value. The Monte Carlo probabilistic approach (Tier 4) can be subsequently used to refine the assessment, taking into account the occurrence and distribution of residue levels, and provides the probability distribution of exposure.

The DPR uses two thresholds for indicating that the next tier of assessment is needed (DPR MT-3, 2004): (1) the MOE at the 99<sup>th</sup> percentile exposure is within 5-fold of the health protective level, or (2) the MOE at the 95<sup>th</sup> percentile exposure is 10-fold of the health protective level. For imidacloprid, the acceptable MOE is 100. Therefore, the threshold MOE for the next tier of assessment would be 500 at the 99<sup>th</sup> or 1000 at the 95<sup>th</sup> percentiles. These thresholds provide room for exposures from other potential routes; and the 5-and 10-fold distance from the acceptable MOE ensures the likelihood that dietary exposure would not be a major contributor to the aggregate risk. In the event that this is not the case, the next tier of exposure may be needed.

### **IV. B.2.a. Acute Deterministic (Point Estimate) Exposure Assessment**

The acute dietary exposure to imidacloprid of the US population and various population subgroups was assessed using the deterministic approach (Tiers 1 and 2). In this model, a single value (referred to as a point estimate) was selected to represent the concentration of imidacloprid on each of the registered commodities.

Tier 1 Point Estimate Assessment: This model assumes that all foods consumed in a given day contain pesticide residues at the tolerance level. For imidacloprid, this analysis produced exposures ranging from 73 to 26 µg/kg/day at the 95<sup>th</sup>; and 115 to 32 µg/kg/day at the 99<sup>th</sup> percentiles, respectively (Table 19). These exposures resulted in MOEs below the thresholds of 1000 and 500 at the 95<sup>th</sup> or 99<sup>th</sup> percentiles, respectively, for all of the population subgroups (see Table 22 in Section IV. C.2). Therefore, Tier 2 point estimate assessment was used as a next refining step to calculate the exposure to imidacloprid.

Tier 2 Point Estimate Assessment: The typical assumptions in the Tier 2 are: (i) all consumed foods contain the highest reported residue at or below the tolerance (ii) pesticide residues below the LOD are equal to that limit, (iii) All crops are treated with the pesticide and (iv) residue concentrations do not vary from the time of sampling to the time of consumption (DPR MT-3, 2004).

Consequently, the highest measured residues or the highest LOD within a program were selected for the commodities nectarines, oats, oranges, peas, processed tomatoes (tomato paste canned) and drinking water from the PDP databases (Table 17).

In cases where PDP data were not available, DPR monitoring studies on imidacloprid were considered for the residue selection. The highest imidacloprid concentration or the LOD were chosen for the commodities cucumbers, grapes, groundcherries, lettuce, cantaloupe, peppers and strawberries from the DPR Marketplace Surveillance Program (Table 17).

For several commodities regulatory monitoring data were not available, however, residues reported for similar foods were used as surrogates. The imidacloprid concentration on the foods

from the Citrus Fruit Group 10 (citrus citron, grapefruit, kumquat, lemon, lime, tangerine and pummelo) was assumed to be equal to the highest concentration measured by the PDP on oranges (Table 17). The pesticide residue on peaches was set equal to the LOD for nectarines reported by the PDP (Table 17). No imidacloprid residues were detected on 508 nectarine samples analyzed by the PDP in 2000 and 2001. The residues on tomato puree and catsup were considered equal to the LOD reported by the PDP for canned tomato paste. Imidacloprid residues were not detected on 369 samples of canned tomato paste in 2001. The choice of the most appropriate surrogate commodity was based on the classification of related raw agricultural commodities into crop groups, established in 40 CFR 180.40, and according to the agricultural practices specified in the product label.

Federal or state multi-year monitoring data were not available for rest of the commodities, for which imidacloprid is registered for use. The published tolerances for these foods were chosen to represent the residues for the Tier 2 acute exposure analysis (Table 18).

Changes in the hydration state of foods can alter the residue concentration compared to the raw commodities, which were monitored. The following default factors, provided in the DEEM™ Acute Module, were utilized to account for concentration of imidacloprid residues due to changes in food hydration: 2.1 and 8.26 for grapefruit juice and juice-concentrate; 2 and 11.4 for lemon juice and juice-concentrate; 2 and 6 for lime juice and juice-concentrate; 2.3 and 7.35 for tangerine juice and juice-concentrate; 1.8 and 6.7 for orange juice and juice-concentrate; 1.2 for grape juice; 4.3 for raisins and 7 for dried peaches. No other adjustment factors were employed in the evaluation of the acute dietary exposure.

The DEEM™ hydration factor was not used (i.e., set to 1) for the commodities with imidacloprid residues at the tolerance level. Applying the hydration factor to account for residue concentration could result in a residue level higher than the tolerance, which is illegal.

Based on the paradigms used in this dietary assessment, the 95<sup>th</sup> percentile of user-day exposures to imidacloprid ranged from 15 µg/kg/day to 51 µg/kg/day. At the 99<sup>th</sup> percentile the exposures ranged from 23 µg/kg/day to 78 µg/kg/day. At both, the 95<sup>th</sup> and 99<sup>th</sup> exposure percentiles, the population subgroups “Children 1-2 years” and “All Infants” were identified as the most highly exposed among the evaluated subgroups (Table 19; see also Attachment I).

The acute Critical Exposure Commodity (CEC) analysis identified several commodities, including beans, broccoli, apples, tomatoes, spinach and apricots as making substantial contributions to the overall acute dietary exposure. Beans appeared as the most significant contributor to the dietary exposure for the majority of the evaluated population subgroups. The respective food-forms were: Beans-succulent-green-Canned: Cooked or Boiled, Beans-dry-pinto-Boiled and Beans-dry-kidney-Canned: Boiled. The contribution of beans to the total dietary exposure to imidacloprid was the highest for the following population subgroups: All Infants (up to 66% of the total dietary exposure), Children 6-12 yrs. (22%) and Non-Hispanic Whites (18%). The contribution of Broccoli (in the food-forms of Broccoli-Frozen: Cooked; Broccoli-Boiled) was the highest for Females 13-49 yrs. (19%), Non-Hispanic Other (14%), Western Region (13%) and Children 6-12 yrs. (12%). Apples in the food forms of Apples-juice/cider-Uncooked also made a significant contribution to the dietary exposure for the most of the population subgroups. The contribution was the highest for Non-Hispanic Whites (15%), US Population, Western Region, Children 1-2 yrs. (13%). It is important to note that spinach (Boiled/Canned and Cooked) and canned apricots were significant contributors to the total

dietary exposure of the infants (nursing and non-nursing up to 12%). Tomatoes in the food-forms of Tomatoes- Puree; Tomatoes- juice-Canned and Canned: Boiled; and Tomatoes-whole-Canned: Boiled contributed to the high total dietary exposure of Adults 20-49 yrs. (14%), Females 13-49 yrs (13%), Adults 50+ yrs. (10%) Children 3-15 and 6-12 yrs., Western Region and Hispanics (up to 7%)

**Table 19.** Acute Dietary Exposure Estimates for Imidacloprid.

Population Subgroup	ACUTE DIETARY EXPOSURE <sup>a</sup> (µg/kg/day)			
	Point Estimate Tier 1		Point Estimate Tier 2	
	95 <sup>th</sup> Percentile	99 <sup>th</sup> Percentile	95 <sup>th</sup> Percentile	99 <sup>th</sup> Percentile
US Population (all seasons)	30	54	20	38
Western Region	31	54	23	39
Hispanics	33	57	24	43
Non-Hispanic Whites	28	51	20	36
Non-Hispanic Blacks	33	61	24	41
Non-Hispanic Other	35	55	27	43
All infants	66	98	45	70
Infants (nursing, <1yr.)	60	79	36	65
Infants (non-nursing, <1yr.)	65	101	46	71
Children (1-2 yrs)	<b>73</b>	<b>115</b>	<b>51</b>	<b>78</b>
Children (3-5 yrs)	57	87	38	57
Children (6-12 yrs)	36	57	24	42
Youth 13-19	23	35	16	24
Adults 20-49	22	32	15	23
Adults 50+	22	34	26	25
Females (13-49 yrs)	22	32	15	23

a/ DEEM™ program was used for the analysis with the USDA CSFII from 1994-1998.

b/ The acute Point Estimate dietary exposure from all commodities with imidacloprid registrations was calculated at the 95<sup>th</sup> and 99<sup>th</sup> percentiles of user-days for all population subgroups. The highest exposures are indicated in bold.

#### **IV. B.2.b. Acute Probabilistic (Monte Carlo) Exposure Assessment**

Because of lack of monitoring data, the residue level on all of these contributors was represented by the tolerance. The contribution of these commodities to the high daily exposure of individuals was a result of: (i) use of imidacloprid tolerances as surrogate for residue concentration and (ii) the consumption of the respective food-forms determined during 1994-1998 CSFII. The current

tolerances for these contributors are: 4 ppm for beans, 3.5 ppm for broccoli and spinach, 3 ppm for tomato and apricots and 0.5 ppm for apples.

The Tier 2 analysis produced exposures, which resulted in MOEs below the thresholds of 1000 or 500 at the 95<sup>th</sup> or 99<sup>th</sup> percentiles, respectively, for all of the population subgroups (See Section IV. C.2. under RISK CHARACTERIZATION). As part of the DPR's tiered approach, the probabilistic analysis can be used as the next refining step of the acute dietary exposure assessment. The probabilistic evaluation, also known as Monte Carlo analysis, uses the entire range of pesticide residues available from a data source to calculate the distribution of exposure for selected population subgroups. The food exposure estimates could be improved by incorporating information on the pesticide use and agricultural or processing practices. Probabilistically, Monte Carlo exposures at high-end percentiles are often lower than the high-end Point Estimate exposures. However, the outcome is largely dependent on the residue database, especially when residue values could not be treated probabilistically for all food commodities.

For imidacloprid, residue distribution data were available only for cucumbers, grapes, nectarines, oats, oranges, peaches and tomato paste. Distributional data were not available for any of the high contributing commodities. Consequently, the resultant high-end exposure distribution from the Monte Carlo analysis was not significantly different from the pattern of the point estimate, and, thus was not presented in this document.

#### **IV. B.3. Chronic Exposure**

For chronic risk assessments, the residue concentration for each food is represented by a single value. This residue is multiplied by the average consumption of each population subgroup. Total exposure is the sum of the individual exposures for each selected food and food form. DPR uses certain assumptions when conducting chronic dietary assessment (DPR MT-3, 2004). Typical ones are: (i) commodities that could contain imidacloprid residues contain the average residue levels and (ii) the population average daily consumption distribution reflects the longitudinal consumption patterns of individuals.

Therefore, the arithmetic average of the reported pesticide concentrations was used to estimate the combined exposure from all commodities with current imidacloprid tolerances. In order to account for possible unquantifiable exposures, samples with residues below the limit of detection were assigned ½ of the LOD. For commodities for which monitoring data were not available, the chronic residue concentration was set equal to ½ of the tolerance. The anticipated chronic imidacloprid residues are presented in Tables 17 and 18.

This chronic analysis employed percent-crop-treated adjustments to account for the fact that only a fraction of the total cropland was treated. The PCT data were available to refine the residue values on the following non-blended commodities: apple, broccoli, Brussels sprouts, cabbage, cauliflower, collards, kale, pears, potatoes, watermelon, pumpkin, squash, eggplant, beans, cantaloupe, cucumber, grapes, lettuce, nectarines, oranges, peaches, peppers, strawberry and tomatoes. The PCT ranged from 1 to 85% (Tables 17 and 18). PCT adjustments were not applied for blended foods (DPR MT-3, 2004).

Based on the paradigms used in this analysis, the estimated chronic exposures to imidacloprid ranged from 1.75 µg/kg/day (Females 13-49 yrs.) to 7.41 µg/kg/day (Children 1-2 yrs.; Table 20).



**Table 20.** Chronic Dietary Exposure Estimates for Imidacloprid.

<b>Population Subgroup</b>	<b>Chronic Exposure (<math>\mu\text{g}/\text{kg}/\text{day}</math>)<sup>a</sup></b>
<b>US Population (all seasons)</b>	2.37
<b>Western Region</b>	2.64
<b>Hispanics</b>	2.66
<b>Non-Hispanic Whites</b>	2.28
<b>Non-Hispanic Blacks</b>	2.37
<b>Non-Hispanic Other</b>	3.40
<b>All infants</b>	4.35
<b>Infants (nursing, &lt;1yr.)</b>	1.98
<b>Infants (non-nursing, &lt;1yr.)</b>	5.25
<b>Children (1-2 yrs)</b>	<b>7.41</b>
<b>Children (3-5 yrs)</b>	5.47
<b>Children (6-12 yrs)</b>	3.24
<b>Youth 13-19</b>	1.93
<b>Adults 20-49</b>	1.79
<b>Adults 50+</b>	1.89
<b>Females (13-49 yrs)</b>	1.75

a/ The DEEM™ program was used for the analysis with the USDA CSFII from 1994-1998. The highest exposures are indicated in bold.

c/ The percent crop treated adjustment factors were used for the commodities: apples; beans, broccoli, Brussels sprouts, cabbage, cantaloupes, cauliflower, collards, cucumbers, eggplant, grapes, kale, lettuce, nectarines, oranges, peaches, pears, peppers, potatoes, pumpkin, squash, tomato and watermelon.

## **IV.C. RISK CHARACTERIZATION**

In the case of imidacloprid, the process of risk characterization involved estimating the margin of exposure (MOE). The MOE for exposure to imidacloprid was calculated as the ratio of the critical NOEL, established for specific exposure duration and an estimate of a human exposure. The critical NOELs were determined from oral and inhalation studies (Table 21); NOELs for the dermal route were not available. This document pertains only to the assessment of the dietary exposure. Therefore, the critical oral NOEL was utilized in the calculation of the MOE for oral route. The exposures were estimated from the oral (dietary) exposure.

The acute, subchronic and chronic NOELs employed for the characterization of the risk from exposure to imidacloprid were derived from studies with laboratory animals. Consequently, a calculated MOE of 100 was considered prudent for protection against the imidacloprid toxicity. The benchmark of 100 includes an uncertainty factor of 10 for interspecies sensitivity and 10 for intraspecies variability.

**Table 21.** Critical NOELs and Endpoints for the Risk Characterization of Imidacloprid

<b>Duration/Route</b>	<b>NOEL mg/kg/day</b>	<b>Critical Endpoint</b>	<b>Reference Dose<sup>a</sup> mg/kg/day</b>
Acute Oral	9.0 <sup>b</sup>	Decreased motor activity in rat; (Sheets, 1994a)	0.09
32-day Oral <sup>c</sup>	5.5 <sup>d</sup>	Decreased widths of corpus callosum and caudate putamen in PND11 rats (Sheets, 2001)	0.06
Subchronic Oral	7.3	Morphologic changes in liver and thyroid and tremors in dog (Block, 1987, Ruf, 1990 <sup>#</sup> )	0.07
Chronic Oral	5.7	Thyroid lesions in rat; Eiben and Kaliner, 1991 <sup>#</sup> )	0.06

**a/** Reference Dose (RfD) was estimated as NOEL/uncertainty factor (UF). RfD was based on a UF of 100, 10 each for inter and intra-species extrapolation.

**b/** LED<sub>05</sub> was used as equivalence to the NOEL. LED<sub>05</sub> was calculated with the BMD approach as the 95% confidence limit of the effective dose (ED), which was required to cause a 5% reduction in the motor activity in rats.

**c/** This NOEL was estimated from the LOEL of 54.7 mg/kg/day by applying a 10-fold default factor. The ENEL of 5.5 mg/kg/day was used for acute exposures to imidacloprid in women of childbearing age to protect against fetal exposure.

**d/** Pups were indirectly exposed to imidacloprid for a total of 41 days (20 days *in utero* and 21 days via lactation). Decreases in thickness of brain structures of the pups were observed following 32 doses of imidacloprid to the dams (21 doses *in utero* and 11 doses during lactation).

<sup>#</sup> Study was considered acceptable by the DPR according to FIFRA guidelines.

### **IV.C.1. Dietary Exposure**

#### **IV.C.1.a. Acute Dietary Exposure**

The acute dietary exposure to imidacloprid was estimated using the deterministic (Point Estimate) model.

**Tier 1 Point Estimate Assessment:** In this analysis, the imidacloprid residues in all foods were set equal to the tolerance. The Tier 1 acute dietary exposures were presented in the Table 19. The corresponding MOEs were calculated using the acute NOEL of 9 mg/kg/day for decrease in

motor and locomotor activity in rats (Sheets, 1994a). The MOEs ranged from 122 to 417 at the 95<sup>th</sup> percentile and 78 to 281 at the 99<sup>th</sup> percentile (Table 22). These MOEs were below the threshold MOE of 1000 at the 95<sup>th</sup> percentile; or below the threshold MOE of 500 at the 99<sup>th</sup> percentiles. Consequently, the Tier 2 was used to refine the dietary exposure (DPR MT-3, 2004).

Tier 2 Point Estimate Assessment: In this analysis all consumed foods were assumed to contain the highest reported residue at or below the tolerance. The Tier 2 acute dietary exposures were presented in Table 19. The corresponding MOEs ranged from 175 to 614 at the 95<sup>th</sup> exposure percentile; and 115 to 394 at the 99<sup>th</sup> percentile. Children 1-2 yrs were identified as the most highly exposed population (Table 22).

**Table 22.** Acute (Point Estimate) Dietary Risk Estimates for Imidacloprid.

Population Subgroup	ACUTE MOE <sup>a</sup>			
	Point Estimate Tier 1		Point Estimate Tier 2	
	95 <sup>th</sup> Percentile	99 <sup>th</sup> Percentile	95 <sup>th</sup> Percentile	99 <sup>th</sup> Percentile
US Population (all seasons)	302	167	429	237
Western Region	288	167	399	230
Hispanics	274	157	375	206
Non-Hispanic Whites	318	175	462	250
Non-Hispanic Blacks	275	145	383	221
Non-Hispanic Other	257	162	327	210
All infants	139	92	198	128
Infants (nursing, <1yr.)	150	112	250	138
Infants (non-nursing, <1yr.)	137	88	195	127
Children (1-2 yrs)	<b>122</b>	<b>78</b>	<b>175</b>	<b>115</b>
Children (3-5 yrs)	159	103	234	157
Children (6-12 yrs)	249	159	370	186
Youth 13-19	394	254	575	370
Adults 20-49	409	276	595	390
Adults 50+	415	268	554	359
Females (13-49 yrs)	417	281	614	394

a/ DEEM<sup>TM</sup> program was used for the analysis with the following input parameters: (i) USDA CSFII from 1994-1998, (ii) acute NOEL of 9 mg/kg (Sheets, 1994a). MOE is defined as NOEL/Acute Dietary Intake. Acute dietary exposure was calculated at the 95<sup>th</sup> and 99<sup>th</sup> percentiles of user-days for all population subgroups. The lowest MOEs are indicated in bold.

These MOEs were calculated based on the acute NOEL of 9 mg/kg/day for decreases in motor activity in rats (Sheets, 1994a). Using the ENEL of 5.5 mg/kg/day for developmental neurotoxicity (Sheets, 2001) to estimate the risk for acute dietary exposure to women in childbearing age (Females 13-49 yrs.) would result in an MOE of 306 and 239 at the 95<sup>th</sup> and 99<sup>th</sup> percentiles.

The DPR concludes the acute dietary exposure, when the MOE are within 5-fold of the health protective level at the 99<sup>th</sup> percentile, or 10-fold of the health protective level at the 95<sup>th</sup> percentile. This was clearly not the case with imidacloprid, where the lowest MOEs (115 and 175 at the 99<sup>th</sup> and 95<sup>th</sup> percentiles, respectively) were only marginally above the benchmark of 100. The dietary exposure could be refined further when the single residue concentration for the high contributing commodities is replaced with residue distribution in the probabilistic Monte Carlo modeling. However, distributional data for imidacloprid were not available for any of the high contributing commodities to the dietary risk. In conclusion, the lack of sufficient residue data for imidacloprid precludes a further refinement of the dietary assessment at this time.

#### **IV.C.1.b. Chronic Dietary Exposure**

The estimated chronic exposures to imidacloprid are presented in the Table 20. The corresponding MOEs ranged from 770 for “Children 1-2 yrs” to 3251 for “Females 13-49”, based on the chronic NOEL of 5.7 mg/kg/day for thyroid lesions in rat (Eiben and Kaliner, 1991). The NOEL of 5.7 mg/kg/day is sufficiently close to the ENEL of 5.5 mg/kg/day for developmental neurotoxicity (Sheets, 2001), and therefore, would be adequate for protection against the potential effects of imidacloprid on the developing nervous system.

**Table 23. Chronic Dietary Risk Estimates for Imidacloprid.**

<b>Population Subgroup</b>	<b>Chronic MOE <sup>a</sup> (µg/kg/day)<sup>a</sup></b>
<b>US Population (all seasons)</b>	2407
<b>Western Region</b>	2159
<b>Hispanics</b>	2145
<b>Non-Hispanic Whites</b>	2500
<b>Non-Hispanic Blacks</b>	2516
<b>Non-Hispanic Other</b>	1676
<b>All infants</b>	1311
<b>Infants (nursing, &lt;1yr.)</b>	2875
<b>Infants (non-nursing, &lt;1yr.)</b>	1087
<b>Children (1-2 yrs)</b>	<b>770</b>
<b>Children (3-5 yrs)</b>	1041
<b>Children (6-12 yrs)</b>	1762
<b>Youth 13-19</b>	2960
<b>Adults 20-49</b>	3177
<b>Adults 50+</b>	3015
<b>Females (13-49 yrs)</b>	3251

**a/** The DEEM<sup>TM</sup> program was used for the analysis with the following input parameters: (i) USDA CSFII from 1994-1998, and (ii) Chronic NOEL of 5.7 mg/kg/day (based on increased mineralized particles in thyroid gland in two-year feeding study in rats; Eiben and Kaliner 1991; Eiben 1991). MOE is defined as NOEL/Chronic Dietary Intake. The lowest MOE is indicated in bold.

**c/** The percent crop treated adjustment factors were used for the commodities: apples, beans, broccoli, Brussels sprouts, cabbage, cantaloupes, cauliflower, collards, cottonseed, cucumbers, eggplant, grapes, kale, lettuce, nectarines, oranges, peaches, pears, peppers, potatoes, pumpkin, squash and watermelon.

## **V. RISK APPRAISAL**

### **V.A. INTRODUCTION**

This risk assessment for imidacloprid evaluated the risk to 16 population subgroups from potential residues in food and drinking water. Dietary exposures were estimated under acute and chronic scenarios. Every risk assessment has inherent uncertainties, which reflects limitations in the knowledge to estimate the potential risk to human health. Assumptions and extrapolations are made when the available data are insufficient to identify the hazard, to adequately characterize the dose-response, or to assess the exposure. These, in turn, result in uncertainty in the risk characterization. Specific areas of uncertainty associated with this risk assessment for imidacloprid are delineated in the following discussion.

### **V.B. HAZARD IDENTIFICATION**

The most appropriate toxicity data for the hazard identification of imidacloprid would be from human studies. However, toxicity studies with imidacloprid were not available in humans. Consequently, studies in laboratory animals were used as a source of information at this time. Critical NOELs derived from oral studies were employed to assess the risk from dietary exposure to imidacloprid.

#### **V.B.1. Acute Oral Toxicity**

The LED<sub>05</sub> of 9 mg/kg/day was selected as an equivalence of the NOEL to estimate the risk for the acute dietary exposure of the US population to imidacloprid. This critical acute oral NOEL was derived from an acute neurotoxicity study in rats (Sheets, 1994a). The study included elaborated toxicity evaluation (e.g., neurobehavior, motor activity, neuropathology, clinical observations and clinical chemistry). The reported effects were consistent with the toxicity observed in other toxicity studies with imidacloprid. The range of effects included typical cholinergic signs, changes in the neurobehavior and motor activity, severe toxicity and mortalities. The most sensitive toxicological endpoint at the LOEL of 42 mg/kg/day was the 25-27% decrease in the motor and locomotor activity of the females. This effect became statistically significant (up to 89% decrease,  $p \leq 0.05$ ) in both sexes in the next higher doses. Importantly, for imidacloprid, reduction in motor/locomotor activity was observed in all of the available (acute and subchronic) neurotoxicity studies. Altogether, the presented findings could be used to determine acute toxicity endpoints.

In this study, toxicological effects were observed at the lowest tested dose, hence, an experimental NOEL could not be defined. The general default approach for estimating a NOEL would be to scale down from the LOEL using an uncertainty factor. USEPA estimated the acute NOEL for imidacloprid as 14 mg/kg/day, by applying an uncertainty factor of 3 to the LOEL of 42 mg/kg/day (USEPA, 2003). This approach carries greater uncertainties, because it does not take into account the dose response curve, but rather focuses on only one dose (the LOEL). These limitations could be overcome with the BMD modeling, which involves fitting a mathematical model to the entire dose-response dataset for an endpoint. The model estimates the threshold dose LED at a defined level of benchmark response (BMR; DPR MT-2, 2004). The LED is the 95<sup>th</sup> percent lower bound of the effective dose (ED). The acute neurotoxicity study had a large sample size (n=18) and a clear dose-response relationship, and thus, was suitable for BMD modeling. The calculated LED<sub>05</sub> of 9 mg/kg/day represented the 5% change in the group

mean relative to the control. The difference between the ED<sub>05</sub> and the LED<sub>05</sub> and (12 vs. 9 mg/kg/day) was small (i.e., ED/LED ratio <5), which was indicative of good quality experimental data and a good model fit (DPR MT-2, 2004).

The choice of 5% benchmark response level was based on the current DPR default BMR (DPR MT-2, 2004). However, the BMR could vary from 1 to 10, depending on the endpoint severity. Severity considerations could suggest a lower BMR for the imidacloprid-induced reduction in the motor activity levels. First, decreases in the motor and locomotor activity are known acute effects of nicotinic agonists. Second, the Time to Peak Effect (TOPE, 90 min after dosing) was determined based on FOB findings and thus, may not be optimal for observing the motor activity (Sheets, 1994a). Third, this effect was reported in all of the available neurotoxicity studies. Similar doses of imidacloprid for different durations induced comparable levels of reduction of the motor/locomotor activity. In all cases, the female rats were more sensitive. Finally, data from the developmental neurotoxicity study suggested that the decrease in the motor/locomotor activity in the female rats may be related to changes in dimensions of brain areas, which control motor functioning and voluntary motion (Sheets, 2001); see Section III.I. DEVELOPMENTAL NEUROTOXICITY. Had a 1% BMR been chosen to model the decrease in the motor activity in the acute neurotoxicity study, the LED<sub>01</sub> and ED<sub>01</sub> would have been 1.8 and 2.4 mg/kg/day, respectively. The LED<sub>01</sub> is 5-fold lower than the LED<sub>05</sub>.

Regardless of these considerations, the choice of the LED<sub>05</sub> of 9 mg/kg/day as the acute critical oral NOEL was supported by the NOEL of 10 mg/kg/day, which was established from the acute toxicity study in mice (Bomann, 1989a). In addition, the available imidacloprid toxicological database revealed that the majority of the estimated or established oral NOELs were in the range of 5.5-30 mg/kg/day for all endpoints and exposure times.

The estimated NOEL for developmental neurotoxicity was 5.5 mg/kg/day (Sheets, 2001). This ENEL could be applicable to acute exposures to females of childbearing age. However, there is a much greater uncertainty associated with the DNT endpoint, because it was approximated from the LOEL by using a 10-fold default factor.

### **V.B.2. Chronic Oral Toxicity**

The NOEL of 5.7 mg/kg/day was utilized to estimate the risk of chronic dietary exposure to imidacloprid. This critical oral NOEL was derived from a 2-year chronic toxicity/oncogenicity study in Wistar rats (Eiben and Kaliner, 1991; Eiben, 1991).

The reported effects were consistent with the toxicity observed in other toxicity studies with imidacloprid. These included reduction in body weight, thyroid toxicity and changes in serum chemistry. The principal effect at the LOEL of 17 mg/kg/day was a statistically significant increase (62%) in the incidence and severity of mineralized particles in thyroid gland in male rats. The NOEL of 5.7 mg/kg/day was the lowest from the three available chronic toxicity studies. While thyroid effects were not observed in the other two chronic studies (in dogs and mice), subchronic toxicity studies in dogs established a NOEL of 7.3 mg/kg/day based on thyroid toxicity, among other toxic endpoints (Block, 1987; Ruf, 1990). Finally, the NOEL of 5.7 mg/kg/day was sufficiently close to the ENEL of 5.5 mg/kg/day for developmental neurotoxicity (Sheets, 2001), and therefore, would be adequate for protection against the potential effects of imidacloprid on the developing nervous system.

## **V.C. EXPOSURE ASSESSMENT**

### **V.C.1. Dietary Exposure Assessment**

The uncertainty in the exposure assessment is classified in three major categories: (i) parameter uncertainty, (ii) model uncertainty and (iii) scenario uncertainty (USEPA 1992, Peterson et al, 2001).

**V.C.1.a. Parameter Uncertainty:** Sources of parameter uncertainty in the dietary exposure assessment include completeness of the food residue database, the use of surrogate data and measurement, sampling or reporting errors.

The food exposure estimates could be improved if the residue data for the major contributors to the dietary risk are available. In general, the USDA PDP program is preferred, because it is specifically designed for generating data for risk assessments. The current food residue database for imidacloprid is very limited. In the US, imidacloprid is registered for protection of a large number of crops (more than 270). Only 14 of them have been tested for imidacloprid residues by the Federal and State Monitoring programs (USDA and DPR). Residue levels measured by the PDP and DPR were employed for the following commodities: oranges, nectarines, oats, peas, canned tomato paste, drinking water, cantaloupes, cucumbers, grapes, lettuce, peppers, chili peppers, strawberries and tomatillos (Table 17). Attempts were made to decrease the degree of uncertainty by selecting surrogate commodities from the crop groups of related commodities established in 40 CFR 180.40. The residues measured by the PDP on oranges and canned tomato paste were used to model the exposure for the foods from the Citrus Fruit Group 10 and tomato puree and catsup, respectively (Table 17). The residue on peaches was refined by assigning the LOD of the PDP for nectarines. The use of more refined data for these commodities in the Tier 2 analysis resulted in 1.3-1.5-fold lower exposure estimates, compared to the Tier 1-exposures, which were based on residues at the tolerance level (see Tiers 1 and 2 under Section IV.B.2.5.a). It should be emphasized, that none of these commodities emerged as a major contributor to the total dietary exposure, even when the residue levels were set at the tolerance in Tier 1. Altogether, replacing the tolerance with the available measured concentrations for foods with small impact on the dietary exposure did not significantly refine the 95<sup>th</sup>-99<sup>th</sup> acute exposures.

Because of lack of residue data, the rest of the commodities were represented by the tolerance as surrogate for residue concentration. The tolerance is established based on field trial-measured residues, following maximum application rate and frequency. Typically, these conditions do not reflect the actual use pattern. Therefore, the total acute exposure was a result from consumption of foods, most of which contained the maximum allowed residue level. Consequently, the high end of exposure was likely reflective of the tolerance for these commodities. Importantly, all of the foods, which emerged as major contributors (beans, broccoli, apples, tomatoes, spinach and apricots), were represented by the tolerance. With the exception of apples (tolerance of 0.5 ppm), the tolerances for the rest of the major contributors are high (3-4 ppm). The aforementioned high contributing commodities should be considered for monitoring of imidacloprid residues.

The dietary exposure assessment may exhibit a level of uncertainty in the consumption data contained in the 1994-1998 USDA survey. The uncertainty may result from under-representation of actual dietary consumption, reporting errors, response and variation in the culinary habits over the consumption period.

**V.C.1.b. Scenario and Model Uncertainty:** Three Point Estimate dietary exposure scenarios were evaluated for imidacloprid under acute and chronic conditions. The acute dietary exposure estimates for imidacloprid were calculated using the tiered approach in the selection of the appropriate residue values.

Acute Dietary Exposure. In the initial scenario, the Tier 1 Point Estimate analysis, the concentration of imidacloprid on all commodities was assumed to be equal to the tolerance. The MOEs were at or above 100 for all population subgroups at the 95<sup>th</sup> percentile. However, the MOEs at the 99<sup>th</sup> percentile were less than 100 for the following population subgroups: Children 1-2 yrs, Non-nursing Infants, All Infants and Children 3-5 yrs. (Table 22). It is highly unlikely that all the commodities, consumed in a given day, can contain imidacloprid residues at the highest legally allowed residue level.

Because of the low MOEs, additional refinements of the acute scenario were carried out. In the Tier 2 acute analysis, the refinement involved the use of imidacloprid concentrations measured by the PDP and DPR. This analysis produced only a slight increase of the MOE values. The lowest MOEs were 175 and 115 at the 95<sup>th</sup> and 99<sup>th</sup> percentiles, respectively. These MOEs were only marginally above the health protective level (MOE of 100). The reasons for not achieving a significant refinement of the Tier 2-exposures were as follows: (i) Imidacloprid is registered for a very large number of foods; (ii) The high-end exposure mostly reflected residues at the tolerance. The established tolerances for many of the foods, including high consumption commodities, are high (3-6 ppm) and (iii) The high contributing commodities were represented by the tolerance, whereas foods which were assigned measured residues had much less impact on the dietary exposure.

Additional models could be used to refine the acute dietary exposure. The Monte Carlo techniques employ residue distribution and PCT information to produce more realistic exposure estimates. However, the lack of sufficient residue data for imidacloprid precluded a further refinement of the dietary assessment at this time.

Chronic Dietary Exposure. The available data on PCT was used to refine the chronic residue levels. A major assumption in both scenarios was that chronic residue levels below the LOD were at ½ of that limit. The chronic dietary MOEs were all greater than 770 (Table 23).

## **V.D. RISK CHARACTERIZATION**

A margin of exposure of 100 is considered sufficiently protective of human health when data are derived from animal studies. The MOE of 100 assumes that humans are 10 times more sensitive than the laboratory animals and that the sensitivity among human population could vary as much as 10-fold.

### **V.D.1. Dietary Exposure**

The uncertainties associated with the dietary exposure estimates and the critical NOELs, which were used to calculate the dietary MOEs, were discussed in detail in the sections V.B.1-3 and V.C.1.

#### **V.D.1.a. Acute MOE**

The acute dietary MOEs for the DPR high-end percentiles are presented in Table 22 (DPR MT-3, 2004). The MOE values ranged from 175 to 614 at the 95<sup>th</sup> percentile, and from 115-394 at the



99<sup>th</sup> percentile. The dietary exposure was assessed by the deterministic (Point Estimate, Tier 2) model. The MOEs were estimated using the acute rat NOEL of 9 mg/kg/day (Sheets, 1994a). Children 1-2 yrs. and Infants were identified as the most highly exposed population subgroup. The MOEs for these population subgroups were 175 and 195 at the 95<sup>th</sup> percentile, and 115 and 128 at the 99<sup>th</sup> percentile. Using the ENEL of 5.5 mg/kg/day for women in childbearing age to protect against fetal exposure would result in acute MOEs of 366 at the 95<sup>th</sup> and 239 at 99<sup>th</sup> percentiles, which exceed the benchmark MOE of 100.

It should be noted that in the BMD modeling, the effective dose ED<sub>05</sub> corresponding to the above LED<sub>05</sub> was 12 mg/kg/day. This ED<sub>05</sub> was in the same range as the USEPA NOEL of 14 mg/kg/day, which was estimated by applying an uncertainty factor of 3 to the LOEL of 42 mg/kg/day (USEPA, 2003). If the ED<sub>05</sub> of 12 mg/kg/day was used in the estimation of the acute dietary risk, the MOE values for the highest exposure group (Children 1-2 yrs.) would be 235 and 154 at 95<sup>th</sup> and 99<sup>th</sup> percentiles, respectively. For comparison, the USEPA estimated NOEL of 14 mg/kg/day would produce MOEs of 275 and 179 at 95<sup>th</sup> and 99<sup>th</sup> percentiles, respectively, for this exposure group.

These MOEs reflect only the risk from the dietary and drinking water exposure. The aggregate (i.e., combined) exposures from ambient air, occupational activities and residential uses of imidacloprid remain to be assessed.

#### **V.D.1.b. Chronic MOEs**

The chronic MOEs for exposure to imidacloprid were over 700. These MOEs were estimated using the chronic rat NOEL of 5.7 mg/kg/day (Eiben and Kaliner 1991; Eiben 1991). PCT assumptions were employed to refine the chronic exposure. The conventional benchmark for the MOE using a NOEL from an animal study is 100, thus indicating that the chronic dietary exposure to imidacloprid would not present a potential health risk.

#### **V.D.2. Aggregate Inhalation and Dietary Exposure**

The DPR began monitoring for imidacloprid residues in the ambient air in California in 2002. These studies were preliminary and the information was not sufficient to estimate the acute inhalation exposure to imidacloprid. The aggregate risk for humans from inhalation and dietary exposure will be assessed when data become available. Discussion on the choice of the inhalation NOEL will accompany the aggregate assessment.

#### **V.D.3. Aggregate Occupational and Dietary Exposure and Residential and Dietary Exposure**

The aggregate risk for humans from occupational and dietary exposure and from residential and dietary exposure will be subsequently evaluated in an addendum to this RCD.

### **V.E. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT**

#### **V.E.1. Pre- and Post- Natal Sensitivity**

The FQPA requires considerations of an additional safety factor of up to 10 to account for pre- and post-natal toxicity and the completeness of the database. The extent of pre- and post-natal sensitivity can be evaluated based on the completed submission of toxicity studies required under

the Senate Bill 950 (SB950), particularly the studies on developmental and reproductive toxicities.

One reproductive and two developmental toxicity studies were available for imidacloprid. In rats, the main fetal effects were wavy ribs and disproportionately high number of male fetuses (Becker et al., 1992). Both effects occurred at the same doses as the maternal toxicity, which was a decreased weight gain. In a rabbit teratology study, imidacloprid doses caused reduction in survival, body weight and delayed ossification in fetuses (Becker and Biedermann, 1992). The same doses were also toxic to the dams (weight loss and death). In a reproductive toxicity study in rats, decreased body weight gain of pups was observed on PND 4 and 21. The reduction of maternal body weight gain and pup survival occurred at the same doses of imidacloprid (Suter et al., 1990). Altogether, a higher pre- and post-natal sensitivity was not indicated in these studies. Based on these findings, the USEPA in their 2003 risk assessment concluded that an additional safety factor is not required to protect infants and children from exposure to imidacloprid (USEPA, 2003).

A developmental neurotoxicity study was recently completed for imidacloprid, which investigated whether pre- or post-natal exposure affected the neural development (Sheets, 2001). The principal effects were reduction in body weights in pups at PND 4 and up to 75 days of age, decreased motor activity at PND 17 and 21, and decreased width of the caudate putamen and corpus callosum in females at PND 11. These effects could not be directly compared to the toxicity in the adult animals. Therefore, conclusions on whether immature rats are more sensitive to imidacloprid than the adults could not be drawn from this study.

Imidacloprid is structurally and functionally related to nicotine, which pre- and postnatal toxicity has been well documented. Both nicotine and imidacloprid act via the nAChRs that are present in the fetal brain, autonomic ganglia and adrenal medulla (Sugiyama et al., 1985; Cairns and Wonnacott, 1988).

Nicotine is a known neuroteratogen. In rats, prenatal nicotine exposure causes mitotic arrests, cell death and a decline in the CNS cell number (Slotkin, 1998). Prenatally, nicotine disrupts the serotonergic systems, which are involved in mood disorders and depression (Xu et al., 2001). Nicotine inhibits the spontaneous release of catecholamines from the adrenal medulla during hypoxia (Slotkin et al., 1995). Massive release of catecholamines is needed to maintain the cardiac rhythm during oxygen starvation. In fact in humans, prenatal nicotine exposure has been correlated with the Sudden Infant Death Syndrome, in which cardiorespiratory failure occurs in a hypoxic episode, as in sleep apnea. Prenatal and postnatal nicotine exposure in rats has been linked to growth retardation, learning disabilities, cognitive deficits and hyperactivity (DiFranza and Lew, 1995). Females appeared to be more affected, thus suggesting that the nicotine effects could be sex-selective (Xu et al., 2003). Interestingly, the neurotoxicity studies with imidacloprid revealed changes in the size of brain structure in female rats, which in general were more sensitive to its effect on the motor/locomotor activity (Sheets, 1994a; 1994b and 2001).

These data should be considered when assessing the effects of imidacloprid on the developing organisms. The available bioassays were not designed to test the more subtle effects of imidacloprid such as mood disorders, depression and cardiac function during hypoxia. In conclusion, the current data on imidacloprid may be insufficient to thoroughly evaluate its pre- and post-natal toxicity.

### **V.E.2. Aggregate Exposures**

For total non-occupational exposure, the DPR considers contributions to risk from various exposure sources. These include exposures from food, drinking water, air, and residential sources. The lack of monitoring data on imidacloprid residues in air precluded an ambient air exposure assessment at this time and will be assessed when data become available. The exposure from residential uses will also be addressed subsequently in an addendum to this document. Therefore, the non-occupational aggregate risk was evaluated from imidacloprid residues in the food and in the drinking water. The total dietary exposure was calculated with the deterministic (Point Estimate, Tier 2) model. The MOEs ranged from 175 to 614 at the 95<sup>th</sup> percentile, and from 115-394 at the 99<sup>th</sup> percentile (Table 22). Drinking water did not emerge as a major contributor to the total dietary exposure.

While the estimated MOEs for exposure from the oral route (food and drinking water) were at or above the benchmark of 100, they reflect only the risk from the dietary exposure. The aggregate (i.e., combined) exposures from ambient air, occupational activities and residential uses of imidacloprid remain to be assessed. These additional exposures will lead to reductions in the MOEs estimated in this assessment.

### **V.E.3. Cumulative Toxicity**

The USEPA recently developed methodology to evaluate the exposure to multiple chemicals from multiple pathways. The USEPA is required under the FQPA of 1996 to assess the cumulative risk to human health, which could result from exposure to pesticides with a common mechanism of toxicity (USEPA, 1999c). The organophosphate (OP) pesticides were the first group with common mechanism of toxicity to undergo a cumulative risk assessment (USEPA, 2002b). Certain members of the carbamate pesticides and triazine-containing pesticides are also being evaluated for cumulative toxic effects (USEPA, 2002c).

Imidacloprid belongs to the family of the neonicotinoids, which are structurally similar to nicotine. Both the neonicotinoids and nicotinoids have a common mode of action as agonists of the nicotinic AChRs (Tomizawa and Casida, 2003). In addition to imidacloprid, four other neonicotinoids (acetamiprid, thiacloprid, thiamethoxam and nitenpyram) are currently used as insecticides worldwide (Tomizawa and Casida, 2003). USEPA tolerances are presently established for the residues of acetamiprid, thiamethoxam and thiacloprid on various crops and animal commodities (CFR 2003b; CFR 2003c; FR 2003). The same commodities are also registered for imidacloprid use. In California, the neonicotinoids acetamiprid and thiamethoxam are registered for food uses. Most of the nicotine-containing pesticide food uses have been cancelled to reduce human risk from dietary exposures. Presently, nicotine-containing pesticides have tolerances on three commodities: cucumber, lettuce and tomato (CFR 2003d). The same three crops are also registered for imidacloprid use (CFR 2003a). Therefore, commodities with imidacloprid residues could potentially contain other neonicotinoid and nicotinoid pesticides. This indicates that a possible multiple chemical exposure could result from the consumption of foods with neonicotinoid and nicotinoid residues.

Quality monitoring residue data would be required for a comprehensive cumulative dietary risk assessment. Although imidacloprid is one of the most extensively used insecticides, its current monitoring database is very limited (see section IV. B.2.4. under EXPOSURE ASSESSMENT and Table 17). The federal and state monitoring programs do not presently screen for residues of the other three neonicotinoids, which also have a modest agricultural use. In California, the first

reported use for acetamiprid and thiamethoxam was in 2002 of 6,632 lb and 11,091 lb, respectively (DPR, 2003). Finally, monitoring residue data are available for the nicotinoid-containing insecticides, however, their present use on crops is very limited (only on three commodities with less than 2 lb in 2002; DPR, 2003). In conclusion, the risk of concomitant dietary exposure to multiple neonicotinoid and nicotinoid pesticides would be addressed when residue data become available.

#### **V.E.4. Endocrine Effects**

Information pertinent for the evaluation of endocrine disruption potential of imidacloprid in animals is limited. The developmental and reproductive toxicity database in rats and rabbits showed lower fetal body weight, increased resorption, reduced pup survival, and skeletal alterations (see: Section III.G. and III.F). Testicular effects in rat and dogs were also reported (Eiben, 1988a, Block, 1987). In a rat DNT study, there were indications of changes in the dimensions of brain structures in female pups (Sheets, 2001). A disproportionately high number of male fetuses were observed in a rat teratology study (Becker et al., 1992). This effect was statistically significant, with the sex ratio (59% males) being outside the historical range. The underlying mechanisms for these effects are not known. In addition, evaluation of endocrine activities was not part of the protocols in the available studies. More information is needed about the aforementioned imidacloprid effects and whether they could be occurring via endocrine disruption.

Imidacloprid is an agonist of the nicotinic AChRs. In the brain, nAChRs regulate the endocrine system. Other nicotinic agonists, including the structurally related nicotine, are known to have neuroendocrine effects through interacting with the brain nAChRs (Rhodes, et al., 2001, Andersson et al., 1988). Nicotine is listed under the California Safe Drinking Water And Toxic Enforcement Act of 1986 as a chemical known to the State of California cause reproductive toxicity. These data should be considered when assessing the effects of imidacloprid on the endocrine systems. Testing guidelines and criteria for hazard identification are needed for a clear evaluation of the endocrine disruption potential.

## **VI. TOLERANCE ASSESSMENT**

### **VI.A. BACKGROUND**

A tolerance is the legal maximum residue concentration of a pesticide, which may exist in or on a raw agricultural commodity or processed food. USEPA is responsible under the Federal Food, Drug, and Cosmetic Act (FFDCA) for setting tolerances for pesticide residues in raw agricultural commodities (Section 408 of FFDCA) and processed commodities. The tolerances are established at levels necessary for the maximum application rate and frequency, and are not expected to produce deleterious health effects in humans from chronic dietary exposure (USEPA, 1991).

The data requirements for the registration of pesticides and for establishment of tolerances include: (1) residue chemistry which includes measured residue levels from field studies, (2) environmental fate, (3) toxicology, (4) product performance such as efficacy, and (5) product chemistry (Code of Federal Regulations, 2001). The field studies must reflect the proposed use with respect to the rate and mode of application, number and timing of applications and the proposed formulations (USEPA, 1982).

In 1996, the Food Quality Protection Act (FQPA) amended the overall regulation of pesticide residues under FIFRA and FFDCA (USEPA, 1997a and b). One major change was the removal of the Delaney Clause that prohibited residues of cancer-causing pesticides in processed foods. FQPA requires scientific evidence to show that tolerances are safe for children. USEPA must consider applying an additional uncertainty factor of up to 10-fold to take into account potential pre- and post-natal developmental toxicity and the completeness of the data.

Under FQPA, USEPA is also required to reassess all existing tolerances and exemptions from tolerances for both active and inert ingredients by 2006 (USEPA, 1997c; 1998). Previously, USEPA reassessed tolerances as part of its reregistration and Special Review processes. In the evaluation of tolerances, the USEPA uses a tiered approach and the assessment includes all label-use commodities.

In California, Assembly Bill 2161 (referred to as the Food Safety Act) requires DPR to “conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides” (Bronzan and Jones, 1989). In the situation where “any pesticide represents a dietary risk that is deleterious to health of humans, the DPR shall prohibit or take action to modify that use or modify the tolerance.”

### **VI.B. ACUTE EXPOSURE**

The acute tolerance analysis evaluates the health protectiveness of the tolerance for a commodity in which a pesticide is allowed to be used. It does not include all labeled commodities at their respective tolerance levels in the same analysis, because the probability is low for diets to contain multiple foods at the tolerance levels.

The DPR estimates the acute tolerance exposure as the sum of the 95<sup>th</sup> percentile exposure for the commodity of concern at the tolerance and a background exposure (DPR MT 3, 2004). The background exposure is added to account for residues in other commodities, which may also be treated with the same pesticide. In the first step, the chronic dietary exposure from total dietary

exposures is used as a surrogate for background exposure. In this step, the exposure contribution of the commodity of interest is “double counted” (e.g. having pesticide residues at the tolerance and having average “chronic” residues). If the margin of exposure for any population subgroup at this step is above the benchmark for acceptable exposure (i.e., MOE of 100), the acute tolerance assessment is concluded. If the MOE is below the benchmark, the background dietary exposure is assessed again but without the commodity for which the tolerance is being evaluated.

In the US, imidacloprid is registered for use on more than 270 individual plant and animal commodities (CFR 2003a). Because of the large number of registered commodities, tolerance assessment was carried out only for foods, which had a significant impact on the dietary exposure. The commodities making substantial contributions to the acute dietary exposure were selected based on the CEC report from the total (all food) acute dietary analysis (see section IV. B.2.5.). These included apples, apricots, beans, broccoli and spinach and tomato puree. In addition, the health protectiveness of the tolerance was assessed for foods with very high USEPA tolerances (i.e., >5 ppm). These included celery, tomato paste and cotton (tolerance of 6 ppm). Tolerance assessment was conducted for two more commodities, lettuce and blueberry, although these foods were not identified as high contributors to the acute dietary exposure. Imidacloprid major use in California is on lettuce; and blueberry is a high consumption food for infants and children (FDA, 1991). The imidacloprid tolerance for both commodities is high (3.5 ppm).

Consequently, the residue levels for imidacloprid were set equal to the tolerance to estimate the potential dietary exposure for each of the 11 commodities described above. The tolerance exposure was calculated at the 95<sup>th</sup> percentile for each of the evaluated 16 population subgroups. The chronic exposure from total dietary exposures was added as a surrogate for background exposure.

The consumption patterns of a given population subgroup is better represented when the survey sample size is large (i.e. >100 user-days). DPR currently would exclude from the tolerance assessment population subgroups with less than 25 user days in the 1994-1998 CSFII database, because of the high uncertainty associated with consumption data. Accordingly, the following population subgroups were not included in the tolerance assessment: All Infants and Non-nursing Infants (lettuce) and Nursing Infants (broccoli, lettuce, spinach, tomato paste and tomato puree).

Six population subgroups had more than 25, but less than 100 user days for some of the evaluated commodities. Although these subgroups were included in the analysis, the exposure and MOE values should be interpreted with caution, because of the relatively small dietary sample size. These included: All Infants (broccoli and spinach), Nursing Infants (beans, blueberry and celery) and Non-nursing Infants (broccoli, spinach and tomato puree), Hispanics, Children 1-2 yrs. and Youth 13-19 yrs. (spinach).

The range of the exposure and MOE values at the 95<sup>th</sup> percentile for each of the evaluated commodity with imidacloprid at the tolerance level, in the background of the chronic dietary exposure, is presented in Table 22. The MOEs were calculated using the acute NOEL of 9 mg/kg/day for decrease in motor and locomotor activity in rats (Sheets, 1994a). The MOEs were at or above the benchmark of 100 for all population subgroups for all of the analyzed foods.

The commodities with the highest amount of dietary exposure at tolerance were tomato paste, spinach, and broccoli. The exposure range was 52.9-15.5, 51.4-12.3, and 46.0-12.7 µg/kg/day, respectively. These exposures resulted in MOE values ranging from 170-582 (tomato paste), 175-730 (spinach), and 196-709 (broccoli). The population subgroups with the lowest MOEs

were Children 1-2 yrs (tomato paste and spinach) and All Infants (broccoli). It should be noted that while the population subgroup All Infants had a relatively small dietary sample size for broccoli (47 user-days), the consumption patterns of Children 1-2 yrs. for tomato paste and spinach were represented by a large survey sample size (i.e. >100 user-days). In conclusion, the MOE levels (170, 175 and 196) for Children 1-2 yrs and Infants, which consumed tomato paste, spinach and broccoli with tolerance levels of imidacloprid were above the benchmark of 100.

These MOEs were calculated based on the acute NOEL of 9 mg/kg/day for decreases in motor activity in rats (Sheets, 1994a). Using the ENEL of 5.5 mg/kg/day for developmental brain effects (Sheets, 2001) to estimate the risk of dietary exposure at tolerance to women in childbearing age (Females 13-49 yrs.) would result in MOEs ranging from 355 (tomato paste) to 2542 (cottonseed oil).

**Table 24.** Acute Dietary Risk Estimates for Imidacloprid Residues at the Tolerance Level.

<b>Commodity</b>	<b>Range of Exposure (µg/kg/day)<sup>a</sup></b>	<b>Range of Margin of Exposure<sup>b,c</sup></b>	<b>Tolerance (ppm)</b>
<b>Apples</b>	29.3- 4.1	307-2200	0.5
<b>Apricot(12)</b>	35.2- 2.3	256-3995	3.0
<b>Beans (6)</b>	56.6-11.6	159- 774	4.0
<b>Blueberry(5)</b>	11.0- 3.8	818-2396	3.5
<b>Broccoli</b>	45.0-12.7	196 <sup>d</sup> - 709	3.5
<b>Celery(4b)</b>	16.6- 6.2	543-1454	6.0
<b>Cotton</b>	7.5- 2.2	1209-4110	6.0
<b>Lettuce</b>	20.5- 8.4	429- 1068	3.5
<b>Spinach(4a)</b>	51.4-12.3 <sup>d</sup>	175- 730 <sup>d</sup>	3.5
<b>Tomato paste</b>	52.9-15.5	170- 582	6.0
<b>Tomato puree</b>	30.6- 9.1	295- 989	3.0

**a/** Acute dietary exposure assessment was conducted for imidacloprid residues on 11 commodities at a level equal to the USEPA tolerance. DEEM™ program was used for the analysis with the following input parameters: (i) USDA CSFII from 1994-1988 and (ii) acute NOEL of 9 mg/kg (decrease in motor and locomotor activity in rats, Sheets, 1994a). The exposure was calculated as the sum of the 95<sup>th</sup> percentile exposure for each commodity at the tolerance and the chronic dietary exposure, as a surrogate for background exposure.

**b/** Margin of Exposure (MOE) is defined as NOEL/Acute Dietary Intake; The number of user-days ranged from 3 to 37173.

**c/** Total of 16 consumer groups were considered to be exposed to tolerance levels of imidacloprid residue. These include: US Population (all seasons), Western Region, Hispanics, Non-Hispanic Whites, Non-Hispanic Blacks, Non-Hispanic Other, All infants, Infants (nursing, <1yr.), Infants (non nursing,<1yr.), Children (1-2 yrs), Children (3-5 yrs), Children (6-12 yrs), Youth 13-19 yrs, Adults 20-49 yrs, Adults 50+ yrs and Females (13-49 yrs).

The following population subgroups had less than 25 user-days and were not included in the tolerance assessment: Nursing Infants (broccoli, lettuce, spinach, tomato paste and tomato puree), All Infants (lettuce) and Non-Nursing Infants (lettuce)

**d/** Exposure estimates were based on ≥ 25 but <100 user-days, therefore the risk estimates may not be representative of the population.

## **VI.C. CHRONIC EXPOSURE**

A chronic exposure assessment using residues equal to the established tolerances for individual or combinations of commodities is not conducted, because it is highly improbable that an individual would habitually consume single or multiple commodities with pesticide residues at tolerance levels. This conclusion is supported by data from both federal and DPR pesticide monitoring programs, which indicate that less than one percent of all sampled commodities have residue levels at or above the established tolerance (PDP 1999-2002; DPR 2002e).



## VII. CONCLUSIONS

This health risk assessment for imidacloprid evaluated the risk to 16 population subgroups from potential residues in food and drinking water. Dietary exposures were estimated under acute and chronic scenarios. The exposure estimates were based primarily on the maximum allowed residue level (tolerance) as surrogate for residue concentration. The critical NOELs were derived from studies with laboratory animals; therefore, a MOE of 100 was used as the benchmark to determine the level of human health protection.

The acute point estimate MOEs ranged from 115 to 614 at the DPR high-end percentiles (95<sup>th</sup> and 99<sup>th</sup>), and thus, were greater than the benchmark MOE of 100. Children 1-2 yrs. and Infants were identified as the most highly exposed population subgroups, with MOEs of 175 and 195 at the 95<sup>th</sup> percentile, and 115 and 128 at the 99<sup>th</sup> percentile. The acute MOEs were estimated based on the acute NOEL of 9 mg/kg/day for decreases in motor activity in rats.

The risk from acute dietary exposure to imidacloprid in women of childbearing age requires further consideration. Evidence from the developmental neurotoxicity study in rats, suggested that imidacloprid may affect the neural development. The estimated NOEL for decreases in dimensions of brain structures was 5.5 mg/kg/day. This ENEL might be pertinent to acute exposures of women of childbearing age to protect for fetal exposure. Based on the ENEL of 5.5 mg/kg/day, the acute dietary MOEs for females 13-49 yrs. would be 366 at the 95<sup>th</sup> and 239 at 99<sup>th</sup> percentiles, which exceed the general health protective benchmark MOE of 100.

The MOEs for all of the evaluated population subgroups from chronic dietary exposure were greater than 770, based on the chronic NOEL of 5.7 mg/kg/day for thyroid effects in rats. This NOEL is sufficiently similar to the estimated NOEL for developmental neurotoxicity (5.5 mg/kg/day), and thus, would be adequate for protection against potential developmental effects of imidacloprid.

The acute tolerance exposure was calculated as the sum of the 95<sup>th</sup> percentile exposure for the commodity of concern at the tolerance and a background exposure. The MOEs for exposure to tolerance level imidacloprid were at or above the benchmark of 100. The lowest MOEs were 170-196 for Children 1-2 yrs. and Infants, who consumed tomato paste, spinach and broccoli.

The MOEs in this RCD reflect only the risk from the dietary exposure. The potential human exposures from ambient air, occupational activities and residential uses of imidacloprid will be subsequently evaluated in an addendum to this RCD. Aggregate exposures to specific population subgroups from various combined scenarios will also be determined. These additional exposures will lead to reductions in the MOEs estimated in this assessment. Dietary exposure may have to be reevaluated using refinements such as measured residue levels from monitoring studies, when data become available.

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# ATTACHMENT I: DEEM Acute Point Estimate Dietary Exposure Assessment

## I.1. Tier 1 Residue Data Files

Filename: H:\svetlana\Imidacloprid\DEEM\IMI Acute Tier1 final\Tier 1 Res\_Adj Fl\_1.RS7  
 Chemical:  
 RfD(Chronic): 0 mg/kg bw/day NOEL(Chronic): 0 mg/kg bw/day  
 RfD(Acute): 0 mg/kg bw/day NOEL(Acute): 0 mg/kg bw/day  
 Date created/last modified: 03-03-2005/15:03:19/14 Program ver. 7.87

Food Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	Adj.Factors #2	Comment
98	O	Acerola	1.000000	1.000	1.000	CFR 03
40	14	Almonds	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03; Nov26 03 Sec 18 CA exp June 22 04				
498	4A	Amaranth	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
52	11	Apples	0.500000	1.000	1.000	CFR 03
53	11	Apples-dried	0.500000	1.000	1.000	CFR 03
54	11	Apples-juice/cider	0.500000	1.000	1.000	CFR 03
377	11	Apples-juice-concentrate	0.500000	1.000	1.000	CFR 03
410	12	Apricot juice	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
59	12	Apricots	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
60	12	Apricots-dried	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
181	O	Artichokes-globe	2.500000	1.000	1.000	CFR 03
203	1CD	Artichokes-jerusalem	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
70	O	Avocados	1.000000	1.000	1.000	CFR 03
497	9B	Balsam pear	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
72	O	Bananas	0.020000	1.000	1.000	CFR 03
		Full comment: CFR 03 imported tolearnce				
73	O	Bananas-dried	0.020000	1.000	1.000	CFR 03
		Full comment: CFR 03 imported tolearnce				
378	O	Bananas-juice	0.020000	1.000	1.000	CFR 03
		Full comment: CFR 03 imported tolearnce				
265	15	Barley	0.050000	1.000	1.000	CFR 03
258	6C	Beans-dry-blackeye peas/cowpea	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
249	6C	Beans-dry-broadbeans	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
259	6C	Beans-dry-garbanzo/chick pea	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
227	6C	Beans-dry-great northern	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
228	6C	Beans-dry-kidney	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
229	6C	Beans-dry-lima	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
230	6C	Beans-dry-navy (pea)	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
231	6C	Beans-dry-other	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
251	6C	Beans-dry-pigeon beans	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
232	6C	Beans-dry-pinto	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
250	6B	Beans-succulent-broadbeans	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
234	6A	Beans-succulent-green	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				

233	6B	Beans-succulent-lima	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
235	6A	Beans-succulent-other	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
236	6A	Beans-succulent-yellow/wax	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
253	6	Beans-unspecified	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
323	M	Beef-dried	0.300000	1.000	1.000	CFR 03
324	M	Beef-fat w/o bones	0.300000	1.000	1.000	CFR 03
325	M	Beef-kidney	0.300000	1.000	1.000	CFR 03
327	M	Beef-lean (fat/free) w/o bones	0.300000	1.000	1.000	CFR 03
326	M	Beef-liver	0.300000	1.000	1.000	CFR 03
321	M	Beef-meat byproducts	0.300000	1.000	1.000	CFR 03
322	M	Beef-other organ meats	0.300000	1.000	1.000	CFR 03
197	1AB	Beets-garden-roots	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
165	2	Beets-garden-tops(greens)	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 2 leaves root & tuber				
152	9B	Bitter melon	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
7	13B	Blueberries	3.500000	1.000	1.000	FR May
		Full comment: FR May 26 04				
452	5B	Bok choy	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
168	5A	Broccoli	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
451	5A	Broccoli-chinese	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
169	5A	Brussels sprouts	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
286	15	Buckwheat	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
382	1AB	Burdock	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
170	5A	Cabbage-green and red	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
383	5B	Cabbage-savoy	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
301	O	Canola oil (rape seed oil)	0.050000	1.000	1.000	CFR 03
106	O	Carambola (starfruit)	1.000000	1.000	1.000	CFR 03
198	1AB	Carrots	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
143	9A	Casabas	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
222	1CD	Cassava (yuca blanca)	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
171	5A	Cauliflower	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
199	1AB	Celeriac	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
166	4B	Celery	6.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4b petioles				
384	4B	Celery juice	6.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4b petioles				
61	12	Cherries	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
62	12	Cherries-dried	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
63	12	Cherries-juice	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
447	4A	Chervil	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
366	P	Chicken-byproducts	0.050000	1.000	1.000	CFR 03
368	P	Chicken-fat w/o bones	0.050000	1.000	1.000	CFR 03
367	P	Chicken-giblets(liver)	0.050000	1.000	1.000	CFR 03
385	P	Chicken-giblets (excl. liver)	0.050000	1.000	1.000	CFR 03

369	P	Chicken-lean/fat free w/o bones	0.050000	1.000	1.000	CFR 03
114	1AB	Chicory	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
167	4A	Chicory(french/belgian endive)	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
386	9B	Christophine	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
892	O	Chrysanthemum	3.500000	1.000	1.000	
495	O	Cilantro	3.500000	1.000	1.000	CFR 02
20	10	Citrus citron	0.070000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
172	5B	Collards	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
121	19B	Coriander	3.500000	1.000	1.000	CFR 03
267	15	Corn grain-bran	0.050000	1.000	1.000	CFR 03
266	15	Corn grain-endosperm	0.050000	1.000	1.000	CFR 03
289	15	Corn grain-oil	0.050000	1.000	1.000	CFR 03
268	15	Corn grain/sugar/hfcs	0.050000	1.000	1.000	CFR 03
388	15	Corn grain/sugar-molasses	0.050000	1.000	1.000	CFR 03
237	15	Corn/pop	0.050000	1.000	1.000	CFR 03
238	15	Corn/sweet	0.050000	1.000	1.000	CFR 03
291	O	Cottonseed-meal	8.000000	1.000	1.000	CFR 03
290	O	Cottonseed-oil	6.000000	1.000	1.000	CFR 03
55	11	Crabapples	0.600000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 11				
8	O	Cranberries	0.050000	1.000	1.000	June 1
		Full comment: June 13 03				
9	O	Cranberries-juice	0.050000	1.000	1.000	June 1
		Full comment: June 13 03				
389	O	Cranberries-juice-concentrate	0.050000	1.000	1.000	June 1
		Full comment: June 13 03				
144	9A	Crenshaws	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
180	4A	Cress-garden/field	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
191	4A	Cress-upland	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
148	9B	Cucumbers	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
10	13B	Currants	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 13B				
177	4A	Dandelion-greens	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
154	8	Eggplant	1.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 8 Fruiting Veg				
364	P	Eggs-white only	0.020000	1.000	1.000	CFR 03
363	P	Eggs-whole	0.020000	1.000	1.000	CFR 03
365	P	Eggs-yolk only	0.020000	1.000	1.000	CFR 03
11	13B	Elderberries	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 13B				
178	4A	Endive-curley and escarole	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
124	1CD	Ginger	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
450	1AB	Ginseng	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
330	M	Goat-fat w/o bone	0.300000	1.000	1.000	CFR 03
331	M	Goat-kidney	0.300000	1.000	1.000	CFR 03
333	M	Goat-lean (fat/free) w/o bone	0.300000	1.000	1.000	CFR 03
332	M	Goat-liver	0.300000	1.000	1.000	CFR 03
328	M	Goat-meat byproducts	0.300000	1.000	1.000	CFR 03
329	M	Goat-other organ meats	0.300000	1.000	1.000	CFR 03
12	13B	Gooseberries	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 13B				
23	10	Grapefruit-juice	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
441	10	Grapefruit-juice-concentrate	0.023000	1.000	1.000	CFR 03

		Full comment: CFR 03 Group 10				
448	10	Grapefruit peel	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
22	10	Grapefruit-peeled fruit	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
13	O	Grapes	1.000000	1.000	1.000	CFR 03
15	O	Grapes-juice	1.500000	1.000	1.000	CFR 03
392	O	Grapes-juice-concentrate	1.500000	1.000	1.000	CFR 03
195	O	Grapes-leaves	1.500000	1.000	1.000	CFR 03
14	O	Grapes-raisins	1.500000	1.000	1.000	CFR 03
315	O	Grapes-wine and sherry	1.500000	1.000	1.000	CFR 03
164	8	Groundcherries	1.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 8 Fruiting Veg				
287	6C	Guar beans	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
393	O	Guava-juice	1.000000	1.000	1.000	CFR 03
79	O	Guava	1.000000	1.000	1.000	CFR 03
125	O	Hops	6.000000	1.000	1.000	CFR 03
334	M	Horsemeat	0.300000	1.000	1.000	CFR 03
126	1AB	Horseradish	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
16	13B	Huckleberries	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 13B				
18	O	Juneberry	3.500000	1.000	1.000	CFR 03
174	5B	Kale	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
175	5A	Kohlrabi	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
24	10	Kumquats	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
28	10	Lemons-juice	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
442	10	Lemons-juice-concentrate	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
27	10	Lemons-peel	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
26	10	Lemons-peeled fruit	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
243	6C	Lentils	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
182	4A	Lettuce-unspecified	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
176	4A	Lettuce-leafy varieties	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
192	4A	Lettuce-head varieties	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
32	10	Limes-juice	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
443	10	Limes-juice-concentrate	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
31	10	Limes-peel	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
30	10	Limes-peeled fruit	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
108	O	Longan fruit	3.000000	1.000	1.000	CFR 03
81	11	Loquats	0.600000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 11				
96	O	Lychee-dried	3.000000	1.000	1.000	CFR 03
95	O	Lychees (litchi)/fresh	3.000000	1.000	1.000	CFR 03
80	O	Mangoes	1.000000	1.000	1.000	CFR 03
141	9A	Melons-cantaloupes-juice	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
142	9A	Melons-cantaloupes-pulp	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
145	9A	Melons-honeydew	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
146	9A	Melons-persian	0.500000	1.000	1.000	CFR 03

		Full comment: CFR 03 group 9 cucurbit				
398	D	Milk-based water	0.100000	1.000	1.000	CFR 03
319	D	Milk-fat solids	0.100000	1.000	1.000	CFR 03
318	D	Milk-nonfat solids	0.100000	1.000	1.000	CFR 03
320	D	Milk sugar (lactose)	0.100000	1.000	1.000	CFR 03
280	15	Millet	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
244	6C	Mung beans (sprouts)	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
183	5B	Mustard greens	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
130	19B	Mustard seed	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03				
64	12	Nectarines	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
399	15	Oats-bran	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
269	15	Oats	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
245	O	Okra	1.000000	1.000	1.000	CFR 03
397	9B	Okra/chinese (luffa)	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
36	10	Oranges-juice	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
33	10	Oranges-juice-concentrate	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
35	10	Oranges-peel	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
34	10	Oranges-peeled fruit	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
85	O	Papayas-dried	1.000000	1.000	1.000	CFR 03
86	O	Papayas-juice	1.000000	1.000	1.000	CFR 03
84	O	Papayas-pulp	1.000000	1.000	1.000	CFR 03
139	8	Paprika	1.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 8 Fruiting Veg				
184	4A	Parsley	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
225	1AB	Parsley roots	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
220	1AB	Parsnips	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
401	O	Passion fruit-juice	1.000000	1.000	1.000	CFR 03
92	O	Passion fruit (granadilla)	1.000000	1.000	1.000	CFR 03
65	12	Peaches	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
66	12	Peaches-dried	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
402	12	Peaches-juice	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
56	11	Pears	0.600000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 11				
57	11	Pears-dried	0.600000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 11				
404	11	Pears-juice	0.600000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 11				
240	6C	Peas (garden)-dry	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
241	6AB	Peas (garden)-green	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
405	6B	Peas-succulent/blackeye/cowpea	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
47	14	Pecans	0.050000	1.000	1.000	CFR 03
156	8	Peppers-chilli incl jalapeno	1.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 8 Fruiting Veg				
157	8	Peppers-other	1.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 8 Fruiting Veg				
155	8	Peppers-sweet(garden)	1.000000	1.000	1.000	CFR 03

		Full comment: CFR 03 Group 8 Fruiting Veg				
88	O	Persimmons	3.000000	1.000	1.000	CFR 03
158	8	Pimientos	1.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 8 Fruiting Veg				
67	12	Plums (damsons)	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
68	12	Plums-prunes (dried)	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
69	12	Plums/prune-juice	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
344	M	Pork-fat w/o bone	0.300000	1.000	1.000	CFR 03
345	M	Pork-kidney	0.300000	1.000	1.000	CFR 03
347	M	Pork-lean (fat free) w/o bone	0.300000	1.000	1.000	CFR 03
346	M	Pork-liver	0.300000	1.000	1.000	CFR 03
342	M	Pork-meat byproducts	0.300000	1.000	1.000	CFR 03
343	M	Pork-other organ meats	0.300000	1.000	1.000	CFR 03
210	1C	Potatoes/white-dry	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
209	1C	Potatoes/white-peeled	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
211	1C	Potatoes/white-peel only	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
208	1C	Potatoes/white-unspecified	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
207	1C	Potatoes/white-whole	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
362	P	Poultry-other-fat w/o bones	0.050000	1.000	1.000	CFR 03
361	P	Poultry-other-giblets(liver)	0.050000	1.000	1.000	CFR 03
360	P	Poultry-other-lean (fat free) w/	0.050000	1.000	1.000	CFR 03
149	9B	Pumpkin	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
58	11	Quinces	0.600000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 11				
407	1AB	Radishes-japanese (daiken)	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
212	1AB	Radishes-roots	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
213	2	Radishes-tops	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 2 leaves root & tuber				
185	4B	Rhubarb	6.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4b petioles				
408	15	Rice-bran	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
271	15	Rice-milled (white)	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
270	15	Rice-rough (brown)	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
409	15	Rice-wild	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
214	1AB	Rutabagas-roots	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
215	2	Rutabagas-tops	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 2 leaves root & tuber				
274	15	Rye-flour	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
273	15	Rye-germ	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
272	15	Rye-rough	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
295	O	Safflower-oil	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg				
294	O	Safflower-seed	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg				
216	1AB	Salsify(oyster plant)	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
473	O	Sapodilla	1.000000	1.000	1.000	CFR 03
338	M	Sheep-fat w/o bone	0.300000	1.000	1.000	CFR 03

339	M	Sheep-kidney	0.300000	1.000	1.000	CFR 03
341	M	Sheep-lean (fat free) w/o bone	0.300000	1.000	1.000	CFR 03
340	M	Sheep-liver	0.300000	1.000	1.000	CFR 03
336	M	Sheep-meat byproducts	0.300000	1.000	1.000	CFR 03
337	M	Sheep-other organ meats	0.300000	1.000	1.000	CFR 03
413	6A	Snowpeas	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
275	15	Sorghum (including milo)	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03				
303	6A	Soybean-other	1.000000	1.000	1.000	Emerg.
		Full comment: Emerg. expires 12 31 2006 group 6				
307	6A	Soybeans-flour (defatted)	0.500000	1.000	1.000	Region
		Full comment: Regional; no expir date group 6				
306	6A	Soybeans-flour (low fat)	0.500000	1.000	1.000	Region
		Full comment: Regional; no expir date group 6				
305	6A	Soybeans-flour (full fat)	0.500000	1.000	1.000	Region
		Full comment: Regional; no expir date group 6				
304	6A	Soybeans-mature seeds dry	1.000000	1.000	1.000	Emerg.
		Full comment: Emerg. expires 12 31 2006 group 6				
297	6A	Soybeans-oil	1.000000	1.000	1.000	Emerg.
		Full comment: Emerg. expires 12 31 2006 group 6				
482	O	Soybeans-protein isolate	0.300000	1.000	1.000	
255	6A	Soybeans-sprouted seeds	1.000000	1.000	1.000	Emerg.
		Full comment: Emerg. expires 12 31 2006 group 6				
186	4A	Spinach	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
150	9B	Squash-summer	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
415	9B	Squash-spaghetti	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
151	9B	Squash-winter	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
17	O	Strawberries	0.050000	1.000	1.000	CFR 03
416	O	Strawberries-juice	0.050000	1.000	1.000	CFR 03
282	1A	Sugar-beet	0.050000	1.000	1.000	CFR 03
379	1A	Sugar-beet-molasses	0.300000	1.000	1.000	CFR 03
218	1CD	Sweet potatoes (incl yams)	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root&tuber				
418	2	Sweet potatos-leaves	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 2 leaves root & tuber				
187	4B	Swiss chard	6.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4b petioles				
37	10	Tangelos	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
38	10	Tangerines	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
39	10	Tangerines-juice	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
420	10	Tangerines-juice-concentrate	0.023000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 10				
201	1CD	Taro-root	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root&tuber				
190	2	Taro-greens	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 2 leaves root & tuber				
163	8	Tomatoes-catsup	3.000000	1.000	1.000	CFR 03
423	8	Tomatoes-dried	3.000000	1.000	1.000	CFR 03
160	8	Tomatoes-juice	3.000000	1.000	1.000	CFR 03
162	8	Tomatoes-paste	6.000000	1.000	1.000	CFR 03
161	8	Tomatoes-puree	3.000000	1.000	1.000	CFR 03
159	8	Tomatoes-whole	1.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 8 Fruiting Veg				
355	P	Turkey-byproducts	0.050000	1.000	1.000	CFR 03
357	P	Turkey--fat w/o bones	0.050000	1.000	1.000	CFR 03
356	P	Turkey-giblets (liver)	0.050000	1.000	1.000	CFR 03
358	P	Turkey- lean/fat free w/o bones	0.050000	1.000	1.000	CFR 03
449	P	Turkey-other organ meats	0.050000	1.000	1.000	CFR 03
137	1CD	Turmeric	0.400000	1.000	1.000	CFR 03

		Full comment: CFR 03 Group 1 root&tuber				
219	1AB	Turnips-roots	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root&tuber				
188	2	Turnips-tops	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 2 leaves root & tuber				
429	M	Veal-dried	0.300000	1.000	1.000	CFR 03
424	M	Veal-fat w/o bones	0.300000	1.000	1.000	CFR 03
426	M	Veal-kidney	0.300000	1.000	1.000	CFR 03
425	M	Veal-lean (fat free) w/o bones	0.300000	1.000	1.000	CFR 03
427	M	Veal-liver	0.300000	1.000	1.000	CFR 03
430	M	Veal-meat byproducts	0.300000	1.000	1.000	CFR 03
428	M	Veal-other organ meats	0.300000	1.000	1.000	CFR 03
189	O	Watercress	3.500000	1.000	1.000	
147	9A	Watermelon	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
436	9A	Watermelon-juice	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
278	15	Wheat-bran	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03				
279	15	Wheat-flour	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03				
277	15	Wheat-germ	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03				
437	15	Wheat-germ oil	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03				
276	15	Wheat-rough	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03				
439	9B	Wintermelon	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
221	1CD	Yambean tuber (jicama)	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root&tuber				
224	1CD	Yautia (tannier)	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root&tuber				

## I.2. Tier 1 Dietary Exposure and Risk Estimates

California Department of Pesticide Regulation Ver. 7.87  
DEEM ACUTE Analysis for (1994-98 data)  
Residue file: Tier 1 Residues+Adj F1.RS7 Adjustment factor #2 NOT used.  
Analysis Date: 07-13-2004/17:36:25 Residue file dated: 07-13-2004/17:29:00/14  
NOEL (Acute) = 9.000000 mg/kg body-wt/day  
Daily totals for food and foodform consumption used.  
Run Comment: ""

U.S. Population	Daily Exposure Analysis /a	
-----	(mg/kg body-weight/day)	
	per Capita	per User
	-----	-----
Mean	0.010629	0.010651
Standard Deviation	0.010908	0.010909
Standard Error of mean	0.000054	0.000054
Margin of Exposure 2/	846	844
Percent of aRfD	11.81	11.83

Percent of Person-Days that are User-Days = 99.80%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
-----	-----	-----	-----	-----	-----	-----	-----
10.00	0.002068	2.30	4,352	90.00	0.021808	24.23	412
20.00	0.003379	3.75	2,663	95.00	0.029714	33.02	302
30.00	0.004676	5.20	1,924	97.50	0.038805	43.12	231
40.00	0.006071	6.75	1,482	99.00	0.053729	59.70	167
50.00	0.007658	8.51	1,175	99.50	0.066137	73.49	136
60.00	0.009534	10.59	944	99.75	0.080544	89.49	111



70.00	0.011958	13.29	752	99.90	0.104662	116.29	85
80.00	0.015461	17.18	582				

Western region

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Daily Exposure Analysis  
(mg/kg body-weight/day)  
per Capita      per User

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Mean	0.011326	0.011362
Standard Deviation	0.011044	0.011043
Standard Error of mean	0.000112	0.000112
Margin of Exposure	794	792
Percent of aRfD	12.58	12.62

Percent of Person-Days that are User-Days = 99.68%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.002326	2.58	3,868	90.00	0.023407	26.01	384
20.00	0.003772	4.19	2,386	95.00	0.031188	34.65	288
30.00	0.005133	5.70	1,753	97.50	0.039028	43.36	230
40.00	0.006736	7.48	1,336	99.00	0.053863	59.85	167
50.00	0.008385	9.32	1,073	99.50	0.065352	72.61	137
60.00	0.010323	11.47	871	99.75	0.079283	88.09	113
70.00	0.013104	14.56	686	99.90	0.101485	112.76	88
80.00	0.016486	18.32	545				

Hispanics

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Daily Exposure Analysis  
(mg/kg body-weight/day)  
per Capita      per User

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Mean	0.011430	0.011455
Standard Deviation	0.011711	0.011712
Standard Error of mean	0.000158	0.000159
Margin of Exposure	787	785
Percent of aRfD	12.70	12.73

Percent of Person-Days that are User-Days = 99.78%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.002170	2.41	4,147	90.00	0.023848	26.50	377
20.00	0.003559	3.95	2,528	95.00	0.032785	36.43	274
30.00	0.004939	5.49	1,822	97.50	0.043537	48.37	206
40.00	0.006541	7.27	1,375	99.00	0.057050	63.39	157
50.00	0.008043	8.94	1,118	99.50	0.069085	76.76	130
60.00	0.010179	11.31	884	99.75	0.083297	92.55	108
70.00	0.012876	14.31	698	99.90	0.105874	117.64	85
80.00	0.016817	18.69	535				

Non-hispanic whites

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Daily Exposure Analysis  
(mg/kg body-weight/day)  
per Capita      per User

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Mean	0.010342	0.010363
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Standard Deviation	0.010378	0.010378
Standard Error of mean	0.000062	0.000062
Margin of Exposure	870	868
Percent of aRfD	11.49	11.51

Percent of Person-Days that are User-Days = 99.80%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.002139	2.38	4,207	90.00	0.021020	23.36	428
20.00	0.003410	3.79	2,639	95.00	0.028221	31.36	318
30.00	0.004666	5.18	1,928	97.50	0.037301	41.45	241
40.00	0.006006	6.67	1,498	99.00	0.051402	57.11	175
50.00	0.007573	8.41	1,188	99.50	0.062909	69.90	143
60.00	0.009379	10.42	959	99.75	0.076242	84.71	118
70.00	0.011659	12.95	771	99.90	0.097250	108.06	92
80.00	0.015038	16.71	598				

Non-hispanic blacks		Daily Exposure Analysis (mg/kg body-weight/day)	
-----		per Capita	per User
Mean		0.010732	0.010753
Standard Deviation		0.012593	0.012596
Standard Error of mean		0.000172	0.000173
Margin of Exposure		838	836
Percent of aRfD		11.92	11.95

Percent of Person-Days that are User-Days = 99.81%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.001378	1.53	6,531	90.00	0.022569	25.08	398
20.00	0.002777	3.09	3,240	95.00	0.032677	36.31	275
30.00	0.004083	4.54	2,204	97.50	0.044290	49.21	203
40.00	0.005608	6.23	1,604	99.00	0.061903	68.78	145
50.00	0.007291	8.10	1,234	99.50	0.078354	87.06	114
60.00	0.009305	10.34	967	99.75	0.101643	112.94	88
70.00	0.011716	13.02	768	99.90	0.122781	136.42	73
80.00	0.015317	17.02	587				

Non-hisp/non-white/non-black		Daily Exposure Analysis (mg/kg body-weight/day)	
-----		per Capita	per User
Mean		0.013132	0.013164
Standard Deviation		0.011790	0.011786
Standard Error of mean		0.000265	0.000267
Margin of Exposure		685	683
Percent of aRfD		14.59	14.63

Percent of Person-Days that are User-Days = 99.76%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.002538	2.82	3,546	90.00	0.027670	30.74	325
20.00	0.004466	4.96	2,015	95.00	0.035015	38.91	257
30.00	0.006357	7.06	1,415	97.50	0.041831	46.48	215
40.00	0.008140	9.04	1,105	99.00	0.055349	61.50	162
50.00	0.009984	11.09	901	99.50	0.065040	72.27	138
60.00	0.012624	14.03	712	99.75	0.076904	85.45	117
70.00	0.015336	17.04	586	99.90	0.092380	102.65	97
80.00	0.019914	22.13	451				

All infants  
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Daily Exposure Analysis  
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.017456	0.019336
Standard Deviation	0.021325	0.021619
Standard Error of mean	0.000391	0.000416
Margin of Exposure	515	465
Percent of aRfD	19.40	21.48

Percent of Person-Days that are User-Days = 90.28%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.002843	3.16	3,165	90.00	0.050081	55.65	179
20.00	0.004094	4.55	2,198	95.00	0.064531	71.70	139
30.00	0.005468	6.08	1,645	97.50	0.076496	85.00	117
40.00	0.007421	8.25	1,212	99.00	0.097824	108.69	92
50.00	0.010464	11.63	860	99.50	0.115349	128.17	78
60.00	0.015101	16.78	595	99.75	0.126785	140.87	70
70.00	0.021510	23.90	418	99.90	0.147432	163.81	61
80.00	0.033016	36.68	272				

Nursing infants (<1 yr old)  
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Daily Exposure Analysis  
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.009598	0.014829
Standard Deviation	0.017008	0.019219
Standard Error of mean	0.000586	0.000806
Margin of Exposure	937	606
Percent of aRfD	10.66	16.48

Percent of Person-Days that are User-Days = 64.72%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000511	0.57	17,595	90.00	0.046113	51.24	195
20.00	0.001369	1.52	6,573	95.00	0.059802	66.45	150
30.00	0.002487	2.76	3,618	97.50	0.068860	76.51	130
40.00	0.003920	4.36	2,295	99.00	0.079920	88.80	112
50.00	0.006291	6.99	1,430	99.50	0.086785	96.43	103
60.00	0.010057	11.17	894	99.75	0.105368	117.08	85
70.00	0.017293	19.21	520	99.90	0.106167	117.96	84
80.00	0.026714	29.68	336				

Non-nursing infants (<1 yr old)		Daily Exposure Analysis (mg/kg body-weight/day)	
-----		per Capita	per User
Mean		0.020439	0.020444
Standard Deviation		0.022027	0.022028
Standard Error of mean		0.000477	0.000477
Margin of Exposure		440	440
Percent of aRfD		22.71	22.72

Percent of Person-Days that are User-Days = 99.98%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.003661	4.07	2,458	90.00	0.051025	56.69	176
20.00	0.004664	5.18	1,929	95.00	0.065398	72.66	137
30.00	0.006063	6.74	1,484	97.50	0.077934	86.59	115
40.00	0.008128	9.03	1,107	99.00	0.101259	112.51	88
50.00	0.011274	12.53	798	99.50	0.119198	132.44	75
60.00	0.016105	17.89	558	99.75	0.131385	145.98	68
70.00	0.023187	25.76	388	99.90	0.146978	163.31	61
80.00	0.034616	38.46	259				

Children 1-2 yrs		Daily Exposure Analysis (mg/kg body-weight/day)	
-----		per Capita	per User
Mean		0.030238	0.030238
Standard Deviation		0.023322	0.023322
Standard Error of mean		0.000360	0.000360
Margin of Exposure		297	297
Percent of aRfD		33.60	33.60

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.008407	9.34	1,070	90.00	0.059278	65.86	151
20.00	0.012451	13.83	722	95.00	0.073497	81.66	122
30.00	0.015867	17.63	567	97.50	0.089668	99.63	100
40.00	0.020049	22.28	448	99.00	0.114523	127.25	78
50.00	0.024602	27.34	365	99.50	0.132060	146.73	68
60.00	0.029596	32.88	304	99.75	0.157755	175.28	57
70.00	0.035429	39.37	254	99.90	0.188044	208.94	47
80.00	0.043801	48.67	205				

Children 3-5 yrs		Daily Exposure Analysis (mg/kg body-weight/day)	
-----		per Capita	per User
Mean		0.022993	0.022993
Standard Deviation		0.017690	0.017690
Standard Error of mean		0.000189	0.000189
Margin of Exposure		391	391
Percent of aRfD		25.55	25.55

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.006604	7.34	1,362	90.00	0.045356	50.40	198
20.00	0.009457	10.51	951	95.00	0.056589	62.88	159
30.00	0.012156	13.51	740	97.50	0.068237	75.82	131
40.00	0.015056	16.73	597	99.00	0.086841	96.49	103
50.00	0.018212	20.24	494	99.50	0.105207	116.90	85
60.00	0.021891	24.32	411	99.75	0.117325	130.36	76
70.00	0.026988	29.99	333	99.90	0.136787	151.99	65
80.00	0.033762	37.51	266				

Children 6-12 yrs

Daily Exposure Analysis  
(mg/kg body-weight/day)  
per Capita per User

Mean	0.014139	0.014139
Standard Deviation	0.011976	0.011976
Standard Error of mean	0.000185	0.000185
Margin of Exposure	636	636
Percent of aRfD	15.71	15.71

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.003976	4.42	2,263	90.00	0.027768	30.85	324
20.00	0.005622	6.25	1,600	95.00	0.036092	40.10	249
30.00	0.007153	7.95	1,258	97.50	0.045453	50.50	198
40.00	0.008697	9.66	1,034	99.00	0.056592	62.88	159
50.00	0.010704	11.89	840	99.50	0.066304	73.67	135
60.00	0.013334	14.82	674	99.75	0.079778	88.64	112
70.00	0.016436	18.26	547	99.90	0.113609	126.23	79
80.00	0.020491	22.77	439				

Youth 13-19 yrs

Daily Exposure Analysis  
(mg/kg body-weight/day)  
per Capita per User

Mean	0.008614	0.008622
Standard Deviation	0.007877	0.007876
Standard Error of mean	0.000159	0.000159
Margin of Exposure	1,044	1,043
Percent of aRfD	9.57	9.58

Percent of Person-Days that are User-Days = 99.90%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.001954	2.17	4,605	90.00	0.017415	19.35	516
20.00	0.003086	3.43	2,916	95.00	0.022813	25.35	394
30.00	0.004125	4.58	2,181	97.50	0.029013	32.24	310
40.00	0.005283	5.87	1,703	99.00	0.035386	39.32	254

50.00	0.006553	7.28	1,373	99.50	0.039301	43.67	229
60.00	0.008051	8.95	1,117	99.75	0.045595	50.66	197
70.00	0.010035	11.15	896	99.90	0.062646	69.61	143
80.00	0.012564	13.96	716				

Adults 20-49 yrs	Daily Exposure Analysis	
-----	(mg/kg body-weight/day)	
	per Capita	per User
	-----	-----
Mean	0.008479	0.008487
Standard Deviation	0.007056	0.007055
Standard Error of mean	0.000073	0.000073
Margin of Exposure	1,061	1,060
Percent of aRfD	9.42	9.43

Percent of Person-Days that are User-Days = 99.90%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
-----	-----	-----	-----	-----	-----	-----	-----
10.00	0.001836	2.04	4,900	90.00	0.017494	19.44	514
20.00	0.002870	3.19	3,135	95.00	0.021992	24.44	409
30.00	0.003967	4.41	2,268	97.50	0.026701	29.67	337
40.00	0.005197	5.77	1,731	99.00	0.032499	36.11	276
50.00	0.006678	7.42	1,347	99.50	0.038319	42.58	234
60.00	0.008268	9.19	1,088	99.75	0.043799	48.67	205
70.00	0.010311	11.46	872	99.90	0.048849	54.28	184
80.00	0.013106	14.56	686				

Adults 50+ yrs	Daily Exposure Analysis	
-----	(mg/kg body-weight/day)	
	per Capita	per User
	-----	-----
Mean	0.008690	0.008693
Standard Deviation	0.006997	0.006997
Standard Error of mean	0.000073	0.000073
Margin of Exposure	1,035	1,035
Percent of aRfD	9.66	9.66

Percent of Person-Days that are User-Days = 99.97%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
-----	-----	-----	-----	-----	-----	-----	-----
10.00	0.001830	2.03	4,916	90.00	0.017578	19.53	512
20.00	0.003124	3.47	2,881	95.00	0.021635	24.04	415
30.00	0.004389	4.88	2,050	97.50	0.026676	29.64	337
40.00	0.005644	6.27	1,594	99.00	0.033520	37.24	268
50.00	0.006984	7.76	1,288	99.50	0.038836	43.15	231
60.00	0.008555	9.51	1,052	99.75	0.043520	48.36	206
70.00	0.010454	11.62	860	99.90	0.053404	59.34	168
80.00	0.013178	14.64	682				

Females 13-49 yrs	Daily Exposure Analysis	
-----	(mg/kg body-weight/day)	
	per Capita	per User
	-----	-----

Mean	0.008284	0.008295
Standard Deviation	0.007107	0.007105
Standard Error of mean	0.000093	0.000093
Margin of Exposure	1,086	1,085
Percent of aRfD	9.20	9.22

Percent of Person-Days that are User-Days = 99.87%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.001696	1.88	5,305	90.00	0.017135	19.04	525
20.00	0.002748	3.05	3,274	95.00	0.021566	23.96	417
30.00	0.003848	4.28	2,338	97.50	0.026140	29.04	344
40.00	0.005033	5.59	1,788	99.00	0.032025	35.58	281
50.00	0.006472	7.19	1,390	99.50	0.037233	41.37	241
60.00	0.008107	9.01	1,110	99.75	0.042561	47.29	211
70.00	0.010073	11.19	893	99.90	0.049975	55.53	180
80.00	0.012785	14.21	703				

### I.3. Tier 2 Residue Data Files

Filename: H:\svetlana\Imidacloprid\DEEM\ImI Tier 2a\Tier 2\_a\_Residues.RS7

Chemical:

RfD(Chronic): 0 mg/kg bw/day NOEL(Chronic): 0 mg/kg bw/day

RfD(Acute): 0 mg/kg bw/day NOEL(Acute): 0 mg/kg bw/day

Date created/last modified: 09-09-2004/10:25:51/14

Program ver. 7.87

Food Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	Adj.Factors #2	Comment
98	0	Acerola	1.000000	1.000	1.000	CFR 03
40	14	Almonds	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03; Nov26 03 Sec 18 CA exp June 22 04				
498	4A	Amaranth	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
52	11	Apples	0.500000	1.000	1.000	CFR 03
53	11	Apples-dried	0.500000	1.000	1.000	CFR 03
54	11	Apples-juice/cider	0.500000	1.000	1.000	CFR 03
377	11	Apples-juice-concentrate	0.500000	1.000	1.000	CFR 03
410	12	Apricot juice	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
59	12	Apricots	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
60	12	Apricots-dried	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
181	0	Artichokes-globe	2.500000	1.000	1.000	CFR 03
203	1CD	Artichokes-jerusalem	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
70	0	Avocados	1.000000	1.000	1.000	CFR 03
497	9B	Balsam pear	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
72	0	Bananas	0.020000	1.000	1.000	CFR 03
		Full comment: CFR 03 imported tolearnce				
73	0	Bananas-dried	0.020000	1.000	1.000	CFR 03
		Full comment: CFR 03 imported tolearnce				
378	0	Bananas-juice	0.020000	1.000	1.000	CFR 03
		Full comment: CFR 03 imported tolearnce				
265	15	Barley	0.050000	1.000	1.000	CFR 03
258	6C	Beans-dry-blackeye peas/cowpea	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
249	6C	Beans-dry-broadbeans	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
259	6C	Beans-dry-garbanzo/chick pea	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
227	6C	Beans-dry-great northern	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
228	6C	Beans-dry-kidney	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
229	6C	Beans-dry-lima	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
230	6C	Beans-dry-navy (pea)	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
231	6C	Beans-dry-other	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
251	6C	Beans-dry-pigeon beans	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
232	6C	Beans-dry-pinto	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
250	6B	Beans-succulent-broadbeans	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
234	6A	Beans-succulent-green	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
233	6B	Beans-succulent-lima	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				



235	6A	Beans-succulent-other	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
236	6A	Beans-succulent-yellow/wax	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
253	6	Beans-unspecified	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
323	M	Beef-dried	0.300000	1.000	1.000	CFR 03
324	M	Beef-fat w/o bones	0.300000	1.000	1.000	CFR 03
325	M	Beef-kidney	0.300000	1.000	1.000	CFR 03
327	M	Beef-lean (fat/free) w/o bones	0.300000	1.000	1.000	CFR 03
326	M	Beef-liver	0.300000	1.000	1.000	CFR 03
321	M	Beef-meat byproducts	0.300000	1.000	1.000	CFR 03
322	M	Beef-other organ meats	0.300000	1.000	1.000	CFR 03
197	1AB	Beets-garden-roots	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
165	2	Beets-garden-tops(greens)	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 2 leaves root & tuber				
152	9B	Bitter melon	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
7	13B	Blueberries	3.500000	1.000	1.000	FR May
		Full comment: FR May 26 04				
452	5B	Bok choy	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
168	5A	Broccoli	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
451	5A	Broccoli-chinese	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
169	5A	Brussels sprouts	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
286	15	Buckwheat	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
382	1AB	Burdock	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
170	5A	Cabbage-green and red	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
383	5B	Cabbage-savoy	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
301	O	Canola oil (rape seed oil)	0.050000	1.000	1.000	CFR 03
106	O	Carambola (starfruit)	1.000000	1.000	1.000	CFR 03
198	1AB	Carrots	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
143	9A	Casabas	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
222	1CD	Cassava (yuca blanca)	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
171	5A	Cauliflower	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
199	1AB	Celeriac	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
166	4B	Celery	6.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4b petioles				
384	4B	Celery juice	6.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4b petioles				
61	12	Cherries	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
62	12	Cherries-dried	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
63	12	Cherries-juice	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
447	4A	Chervil	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
366	P	Chicken-byproducts	0.050000	1.000	1.000	CFR 03
368	P	Chicken-fat w/o bones	0.050000	1.000	1.000	CFR 03
367	P	Chicken-giblets(liver)	0.050000	1.000	1.000	CFR 03
385	P	Chicken-giblets (excl. liver)	0.050000	1.000	1.000	CFR 03
369	P	Chicken-lean/fat free w/o bones	0.050000	1.000	1.000	CFR 03

114	1AB	Chicory	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
167	4A	Chicory(french/belgian endive)	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
386	9B	Christophine	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
495	O	Cilantro	3.500000	1.000	1.000	CFR 02
20	10	Citrus citron	0.120000	1.000	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
172	5B	Collards	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
121	19B	Coriander	3.500000	1.000	1.000	CFR 03
267	15	Corn grain-bran	0.050000	1.000	1.000	CFR 03
266	15	Corn grain-endosperm	0.050000	1.000	1.000	CFR 03
289	15	Corn grain-oil	0.050000	1.000	1.000	CFR 03
268	15	Corn grain/sugar/hfcs	0.050000	1.000	1.000	CFR 03
388	15	Corn grain/sugar-molasses	0.050000	1.000	1.000	CFR 03
237	15	Corn/pop	0.050000	1.000	1.000	CFR 03
238	15	Corn/sweet	0.050000	1.000	1.000	CFR 03
291	O	Cottonseed-meal	8.000000	1.000	1.000	CFR 03
290	O	Cottonseed-oil	6.000000	1.000	1.000	CFR 03
55	11	Crabapples	0.600000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 11				
8	O	Cranberries	0.050000	1.000	1.000	June 1
		Full comment: June 13 03				
9	O	Cranberries-juice	0.050000	1.000	1.000	June 1
		Full comment: June 13 03				
389	O	Cranberries-juice-concentrate	0.050000	1.000	1.000	June 1
		Full comment: June 13 03				
144	9A	Crenshaws	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
180	4A	Cress-garden/field	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
191	4A	Cress-upland	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
148	9B	Cucumbers	0.400000	1.000	1.000	DPR 02
		Full comment: DPR 02; 15 samples ND LOD 0.4				
10	13B	Currants	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 13B				
177	4A	Dandelion-greens	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
154	8	Eggplant	1.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 8 Fruiting Veg				
364	P	Eggs-white only	0.020000	1.000	1.000	CFR 03
363	P	Eggs-whole	0.020000	1.000	1.000	CFR 03
365	P	Eggs-yolk only	0.020000	1.000	1.000	CFR 03
11	13B	Elderberries	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 13B				
178	4A	Endive-curley and escarole	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
124	1CD	Ginger	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
450	1AB	Ginseng	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
330	M	Goat-fat w/o bone	0.300000	1.000	1.000	CFR 03
331	M	Goat-kidney	0.300000	1.000	1.000	CFR 03
333	M	Goat-lean (fat/free) w/o bone	0.300000	1.000	1.000	CFR 03
332	M	Goat-liver	0.300000	1.000	1.000	CFR 03
328	M	Goat-meat byproducts	0.300000	1.000	1.000	CFR 03
329	M	Goat-other organ meats	0.300000	1.000	1.000	CFR 03
12	13B	Gooseberries	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 13B				
23	10	Grapefruit-juice	0.120000	2.100	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
441	10	Grapefruit-juice-concentrate	0.120000	8.260	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
448	10	Grapefruit peel	0.120000	1.000	1.000	PDP 00

		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
22	10	Grapefruit-peeled fruit	0.120000	1.000	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
13	O	Grapes	0.400000	1.200	1.000	DPR 02
		Full comment: DPR 02 #34 ND LOD=0.4				
15	O	Grapes-juice	0.400000	1.000	1.000	DPR 02
		Full comment: DPR 02 #34 ND LOD=0.4				
392	O	Grapes-juice-concentrate	0.400000	3.600	1.000	DPR 02
		Full comment: DPR 02 #34 ND LOD=0.4				
195	O	Grapes-leaves	0.400000	1.000	1.000	DPR 02
		Full comment: DPR 02 #34 ND LOD=0.4				
14	O	Grapes-raisins	0.400000	4.300	1.000	DPR 02
		Full comment: DPR 02 #34 ND LOD=0.4				
315	O	Grapes-wine and sherry	0.400000	1.000	1.000	DPR 02
		Full comment: DPR 02 #34 ND LOD=0.4				
164	8	Groundcherries	1.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 8 Fruiting Veg				
287	6C	Guar beans	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
393	O	Guava-juice	1.000000	1.000	1.000	CFR 03
79	O	Guava	1.000000	1.000	1.000	CFR 03
125	O	Hops	6.000000	1.000	1.000	CFR 03
334	M	Horsemeat	0.300000	1.000	1.000	CFR 03
126	1AB	Horseradish	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
16	13B	Huckleberries	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 13B				
18	O	Juneberry	3.500000	1.000	1.000	CFR 03
174	5B	Kale	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
175	5A	Kohlrabi	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
24	10	Kumquats	0.120000	1.000	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
28	10	Lemons-juice	0.120000	2.000	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
442	10	Lemons-juice-concentrate	0.120000	11.400	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
27	10	Lemons-peel	0.120000	1.000	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
26	10	Lemons-peeled fruit	0.120000	1.000	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
243	6C	Lentils	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
182	4A	Lettuce-unspecified	0.400000	1.000	1.000	DPR 02
		Full comment: DPR 02 #14 ND LOD 0.4				
176	4A	Lettuce-leafy varieties	0.400000	1.000	1.000	DPR 02
		Full comment: DPR 02 #14 ND LOD 0.4				
192	4A	Lettuce-head varieties	0.400000	1.000	1.000	DPR 02
		Full comment: DPR 02 #14 ND LOD 0.4				
32	10	Limes-juice	0.120000	2.000	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
443	10	Limes-juice-concentrate	0.120000	6.000	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
31	10	Limes-peel	0.120000	1.000	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
30	10	Limes-peeled fruit	0.120000	1.000	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
108	O	Longan fruit	3.000000	1.000	1.000	CFR 03
81	11	Loquats	0.600000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 11				
96	O	Lychee-dried	3.000000	1.000	1.000	CFR 03
95	O	Lychees (litchi)/fresh	3.000000	1.000	1.000	CFR 03
80	O	Mangoes	1.000000	1.000	1.000	CFR 03
141	9A	Melons-cantaloupes-juice	0.400000	1.000	1.000	DPR 02
		Full comment: DPR 02; 18 samples ND LOD 0.4				
142	9A	Melons-cantaloupes-pulp	0.400000	1.000	1.000	DPR 02

		Full comment: DPR 02; 18 samples ND LOD 0.4				
145	9A	Melons-honeydew	0.400000	1.000	1.000	DPR 02
		Full comment: DPR 02; 18 samples ND LOD 0.4				
146	9A	Melons-persian	0.400000	1.000	1.000	DPR 02
		Full comment: DPR 02; 18 samples ND LOD 0.4				
398	D	Milk-based water	0.100000	1.000	1.000	CFR 03
319	D	Milk-fat solids	0.100000	1.000	1.000	CFR 03
318	D	Milk-nonfat solids	0.100000	1.000	1.000	CFR 03
320	D	Milk sugar (lactose)	0.100000	1.000	1.000	CFR 03
280	15	Millet	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
244	6C	Mung beans (sprouts)	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 6 Leg Veg				
183	5B	Mustard greens	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 5 Brassica				
130	19B	Mustard seed	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03				
64	12	Nectarines	0.010000	1.000	1.000	PDP 00
		Full comment: PDP 00-01 #508 ND LOD 0.01				
399	15	Oats-bran	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
269	15	Oats	0.008000	1.000	1.000	PDP 99
		Full comment: PDP 99 #332 ND LOD 0.008				
245	O	Okra	1.000000	1.000	1.000	CFR 03
397	9B	Okra/chinese (luffa)	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
36	10	Oranges-juice	0.120000	1.800	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
33	10	Oranges-juice-concentrate	0.120000	6.700	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
35	10	Oranges-peel	0.120000	1.000	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
34	10	Oranges-peeled fruit	0.120000	1.000	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
85	O	Papayas-dried	1.000000	1.000	1.000	CFR 03
86	O	Papayas-juice	1.000000	1.000	1.000	CFR 03
84	O	Papayas-pulp	1.000000	1.000	1.000	CFR 03
139	8	Paprika	1.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 8 Fruiting Veg				
184	4A	Parsley	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
225	1AB	Parsley roots	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
220	1AB	Parsnips	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
401	O	Passion fruit-juice	1.000000	1.000	1.000	CFR 03
92	O	Passion fruit (granadilla)	1.000000	1.000	1.000	CFR 03
65	12	Peaches	0.010000	1.000	1.000	PDP 00
		Full comment: PDP 00-01 #508 ND LOD 0.01				
66	12	Peaches-dried	0.010000	7.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
402	12	Peaches-juice	0.010000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
56	11	Pears	0.600000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 11				
57	11	Pears-dried	0.600000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 11				
404	11	Pears-juice	0.600000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 11				
240	6C	Peas (garden)-dry	0.010000	1.000	1.000	PDP 01
		Full comment: PDP 01-02 #630 ND LOD 0.01				
241	6AB	Peas (garden)-green	0.010000	1.000	1.000	PDP 01
		Full comment: PDP 01-02 #630 ND LOD 0.01				
405	6B	Peas-succulent/blackeye/cowpea	0.010000	1.000	1.000	PDP 01
		Full comment: PDP 01-02 #630 ND LOD 0.01				
47	14	Pecans	0.050000	1.000	1.000	CFR 03
156	8	Peppers-chilli incl jalapeno	0.400000	1.000	1.000	PDP 02

		Full comment: PDP 02 #24 ND LOD 0.4				
157	8	Peppers-other	0.400000	1.000	1.000	PDP 02
		Full comment: PDP 02 #13 ND LOD 0.4				
155	8	Peppers-sweet(garden)	0.400000	1.000	1.000	PDP 02
		Full comment: PDP 02 #13 ND LOD 0.4				
88	0	Persimmons	3.000000	1.000	1.000	CFR 03
158	8	Pimientos	0.400000	1.000	1.000	PDP 02
		Full comment: PDP 02 #13 ND LOD 0.4				
67	12	Plums (damsons)	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
68	12	Plums-prunes (dried)	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
69	12	Plums/prune-juice	3.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 12 stone fruit				
344	M	Pork-fat w/o bone	0.300000	1.000	1.000	CFR 03
345	M	Pork-kidney	0.300000	1.000	1.000	CFR 03
347	M	Pork-lean (fat free) w/o bone	0.300000	1.000	1.000	CFR 03
346	M	Pork-liver	0.300000	1.000	1.000	CFR 03
342	M	Pork-meat byproducts	0.300000	1.000	1.000	CFR 03
343	M	Pork-other organ meats	0.300000	1.000	1.000	CFR 03
210	1C	Potatoes/white-dry	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
209	1C	Potatoes/white-peeled	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
211	1C	Potatoes/white-peel only	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
208	1C	Potatoes/white-unspecified	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
207	1C	Potatoes/white-whole	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
362	P	Poultry-other-fat w/o bones	0.050000	1.000	1.000	CFR 03
361	P	Poultry-other-giblets(liver)	0.050000	1.000	1.000	CFR 03
360	P	Poultry-other-lean (fat free) w/	0.050000	1.000	1.000	CFR 03
149	9B	Pumpkin	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
58	11	Quinces	0.600000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 11				
407	1AB	Radishes-japanese (daiken)	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
212	1AB	Radishes-roots	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
213	2	Radishes-tops	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 2 leaves root & tuber				
185	4B	Rhubarb	6.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4b petioles				
408	15	Rice-bran	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
271	15	Rice-milled (white)	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
270	15	Rice-rough (brown)	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
409	15	Rice-wild	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
214	1AB	Rutabagas-roots	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
215	2	Rutabagas-tops	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 2 leaves root & tuber				
274	15	Rye-flour	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
273	15	Rye-germ	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
272	15	Rye-rough	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg group 15				
295	0	Safflower-oil	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg				
294	0	Safflower-seed	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03 regional reg				

216	1AB	Salsify(oyster plant)	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root & tuber				
473	O	Sapodilla	1.000000	1.000	1.000	CFR 03
338	M	Sheep-fat w/o bone	0.300000	1.000	1.000	CFR 03
339	M	Sheep-kidney	0.300000	1.000	1.000	CFR 03
341	M	Sheep-lean (fat free) w/o bone	0.300000	1.000	1.000	CFR 03
340	M	Sheep-liver	0.300000	1.000	1.000	CFR 03
336	M	Sheep-meat byproducts	0.300000	1.000	1.000	CFR 03
337	M	Sheep-other organ meats	0.300000	1.000	1.000	CFR 03
413	6A	Snowpeas	0.010000	1.000	1.000	PDP 01
		Full comment: PDP 01-02 #630 ND LOD 0.01				
275	15	Sorghum (including milo)	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03				
303	6A	Soybean-other	1.000000	1.000	1.000	Emerg.
		Full comment: Emerg. expires 12 31 2006 group 6				
307	6A	Soybeans-flour (defatted)	0.500000	1.000	1.000	Region
		Full comment: Regional; no expir date group 6				
306	6A	Soybeans-flour (low fat)	0.500000	1.000	1.000	Region
		Full comment: Regional; no expir date group 6				
305	6A	Soybeans-flour (full fat)	0.500000	1.000	1.000	Region
		Full comment: Regional; no expir date group 6				
304	6A	Soybeans-mature seeds dry	1.000000	1.000	1.000	Emerg.
		Full comment: Emerg. expires 12 31 2006 group 6				
297	6A	Soybeans-oil	1.000000	1.000	1.000	Emerg.
		Full comment: Emerg. expires 12 31 2006 group 6				
482	O	Soybeans-protein isolate	0.300000	1.000	1.000	
255	6A	Soybeans-sprouted seeds	1.000000	1.000	1.000	Emerg.
		Full comment: Emerg. expires 12 31 2006 group 6				
186	4A	Spinach	3.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens				
150	9B	Squash-summer	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
415	9B	Squash-spaghetti	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
151	9B	Squash-winter	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
17	O	Strawberries	0.400000	1.000	1.000	DPR 02
		Full comment: DPR 02 samples 14 ND LOD=0.4				
416	O	Strawberries-juice	0.400000	1.000	1.000	DPR 02
		Full comment: DPR 02 samples 14 ND LOD=0.4				
282	1A	Sugar-beet	0.400000	1.000	1.000	CFR 03
379	1A	Sugar-beet-molasses	0.300000	1.000	1.000	CFR 03
218	1CD	Sweet potatoes (incl yams)	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root&tuber				
418	2	Sweet potatos-leaves	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 2 leaves root & tuber				
187	4B	Swiss chard	6.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 subgroup 4b petioles				
37	10	Tangelos	0.120000	1.000	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
38	10	Tangerines	0.120000	1.000	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
39	10	Tangerines-juice	0.120000	2.300	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
420	10	Tangerines-juice-concentrate	0.120000	7.350	1.000	PDP 00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01				
201	1CD	Taro-root	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root&tuber				
190	2	Taro-greens	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 2 leaves root & tuber				
163	8	Tomatoes-catsup	0.025000	2.500	1.000	PDP 01
		Full comment: PDP 01 #369 paste ND LOD 0.025				
423	8	Tomatoes-dried	3.000000	1.000	1.000	CFR 03
160	8	Tomatoes-juice	3.000000	1.000	1.000	CFR 03
162	8	Tomatoes-paste	0.025000	5.400	1.000	PDP 01
		Full comment: PDP 01 #369 paste ND LOD 0.025				
161	8	Tomatoes-puree	0.025000	3.300	1.000	PDP 01

		Full comment: PDP 01 #369 paste ND LOD 0.025				
159	8	Tomatoes-whole	1.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 8 Fruiting Veg				
355	P	Turkey-byproducts	0.050000	1.000	1.000	CFR 03
357	P	Turkey--fat w/o bones	0.050000	1.000	1.000	CFR 03
356	P	Turkey-giblets (liver)	0.050000	1.000	1.000	CFR 03
358	P	Turkey- lean/fat free w/o bones	0.050000	1.000	1.000	CFR 03
449	P	Turkey-other organ meats	0.050000	1.000	1.000	CFR 03
137	1CD	Turmeric	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root&tuber				
219	1AB	Turnips-roots	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root&tuber				
188	2	Turnips-tops	4.000000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 2 leaves root & tuber				
429	M	Veal-dried	0.300000	1.000	1.000	CFR 03
424	M	Veal-fat w/o bones	0.300000	1.000	1.000	CFR 03
426	M	Veal-kidney	0.300000	1.000	1.000	CFR 03
425	M	Veal-lean (fat free) w/o bones	0.300000	1.000	1.000	CFR 03
427	M	Veal-liver	0.300000	1.000	1.000	CFR 03
430	M	Veal-meat byproducts	0.300000	1.000	1.000	CFR 03
428	M	Veal-other organ meats	0.300000	1.000	1.000	CFR 03
189	O	Watercress	3.500000	1.000	1.000	
147	9A	Watermelon	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
436	9A	Watermelon-juice	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
278	15	Wheat-bran	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03				
279	15	Wheat-flour	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03				
277	15	Wheat-germ	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03				
437	15	Wheat-germ oil	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03				
276	15	Wheat-rough	0.050000	1.000	1.000	CFR 03
		Full comment: CFR 03				
439	9B	Wintermelon	0.500000	1.000	1.000	CFR 03
		Full comment: CFR 03 group 9 cucurbit				
221	1CD	Yambean tuber (jicama)	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root&tuber				
224	1CD	Yautia (tannier)	0.400000	1.000	1.000	CFR 03
		Full comment: CFR 03 Group 1 root&tuber				

## I.4. Tier 2 Dietary Exposure and Risk Estimates

California Department of Pesticide Regulation Ver. 7.87  
 DEEM ACUTE Analysis for (1994-98 data)  
 Residue file: Tier 2\_a\_Residues.RS7 Adjustment factor #2 NOT used.  
 Analysis Date: 09-09-2004/11:08:38 Residue file dated: 09-09-2004/10:25:51/14  
 NOEL (Acute) = 9.000000 mg/kg body-wt/day  
 Daily totals for food and foodform consumption used.  
 Run Comment: "Tier 2 Acute - most foods at tolerance (no Adj F 1); a few foods  
 with PDP and DPR +Adj F1"

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U.S. Population          Daily Exposure Analysis /a
-----                (mg/kg body-weight/day)
                        per Capita   per User
                        -----
Mean                    0.007417   0.007432
Standard Deviation      0.007623   0.007623
Standard Error of mean  0.000038   0.000038
Margin of Exposure 2/   1,213     1,210
Percent of aRfD         8.24      8.26
  
```

Percent of Person-Days that are User-Days = 99.80%

Estimated percentile of user-days falling below calculated exposure  
 in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.001668	1.85	5,395	90.00	0.015538	17.26	579
20.00	0.002482	2.76	3,626	95.00	0.020939	23.27	429
30.00	0.003274	3.64	2,748	97.50	0.027635	30.71	325
40.00	0.004147	4.61	2,170	99.00	0.037856	42.06	237
50.00	0.005161	5.73	1,743	99.50	0.046543	51.71	193
60.00	0.006459	7.18	1,393	99.75	0.054845	60.94	164
70.00	0.008218	9.13	1,095	99.90	0.066918	74.35	134
80.00	0.010694	11.88	841				

```

Western region          Daily Exposure Analysis
-----                (mg/kg body-weight/day)
                        per Capita   per User
                        -----
Mean                    0.007949   0.007975
Standard Deviation      0.007900   0.007900
Standard Error of mean  0.000080   0.000080
Margin of Exposure      1,132     1,128
Percent of aRfD         8.83      8.86
  
```

Percent of Person-Days that are User-Days = 99.68%

Estimated percentile of user-days falling below calculated exposure  
 in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.001838	2.04	4,895	90.00	0.016476	18.31	546
20.00	0.002730	3.03	3,297	95.00	0.022523	25.03	399
30.00	0.003622	4.02	2,484	97.50	0.029101	32.33	309
40.00	0.004538	5.04	1,983	99.00	0.039036	43.37	230
50.00	0.005615	6.24	1,602	99.50	0.047027	52.25	191
60.00	0.006998	7.78	1,286	99.75	0.056888	63.21	158
70.00	0.008895	9.88	1,011	99.90	0.065982	73.31	136
80.00	0.011582	12.87	777				



Hispanics

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Daily Exposure Analysis  
(mg/kg body-weight/day)  
per Capita per User

-----

Mean	0.008401	0.008420
Standard Deviation	0.008538	0.008539
Standard Error of mean	0.000115	0.000116
Margin of Exposure	1,071	1,068
Percent of aRfD	9.33	9.36

Percent of Person-Days that are User-Days = 99.78%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.001870	2.08	4,811	90.00	0.017402	19.34	517
20.00	0.002815	3.13	3,197	95.00	0.023978	26.64	375
30.00	0.003776	4.20	2,383	97.50	0.032078	35.64	280
40.00	0.004764	5.29	1,889	99.00	0.043499	48.33	206
50.00	0.005837	6.49	1,541	99.50	0.051603	57.34	174
60.00	0.007306	8.12	1,231	99.75	0.061138	67.93	147
70.00	0.009319	10.35	965	99.90	0.073483	81.65	122
80.00	0.011981	13.31	751				

Non-hispanic whites

-----

Daily Exposure Analysis  
(mg/kg body-weight/day)  
per Capita per User

-----

Mean	0.007050	0.007064
Standard Deviation	0.007097	0.007097
Standard Error of mean	0.000042	0.000042
Margin of Exposure	1,276	1,274
Percent of aRfD	7.83	7.85

Percent of Person-Days that are User-Days = 99.80%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.001686	1.87	5,337	90.00	0.014547	16.16	618
20.00	0.002452	2.72	3,671	95.00	0.019477	21.64	462
30.00	0.003214	3.57	2,800	97.50	0.025533	28.37	352
40.00	0.004028	4.48	2,234	99.00	0.035881	39.87	250
50.00	0.004966	5.52	1,812	99.50	0.043798	48.66	205
60.00	0.006185	6.87	1,455	99.75	0.052217	58.02	172
70.00	0.007803	8.67	1,153	99.90	0.063241	70.27	142
80.00	0.010132	11.26	888				

Non-hispanic blacks

-----

Daily Exposure Analysis  
(mg/kg body-weight/day)  
per Capita per User

-----

Mean	0.007760	0.007775
Standard Deviation	0.008615	0.008617
Standard Error of mean	0.000118	0.000118
Margin of Exposure	1,159	1,157
Percent of aRfD	8.62	8.64

Percent of Person-Days that are User-Days = 99.81%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.001333	1.48	6,749	90.00	0.016933	18.81	531
20.00	0.002167	2.41	4,153	95.00	0.023456	26.06	383
30.00	0.003005	3.34	2,994	97.50	0.030391	33.77	296
40.00	0.003921	4.36	2,295	99.00	0.040712	45.24	221
50.00	0.005050	5.61	1,782	99.50	0.051284	56.98	175
60.00	0.006615	7.35	1,360	99.75	0.061158	67.95	147
70.00	0.008577	9.53	1,049	99.90	0.088375	98.19	101
80.00	0.011470	12.74	784				

Non-hisp/non-white/non-black		Daily Exposure Analysis (mg/kg body-weight/day)	
-----		per Capita	per User
		-----	-----
Mean		0.010113	0.010137
Standard Deviation		0.009573	0.009571
Standard Error of mean		0.000215	0.000217
Margin of Exposure		889	887
Percent of aRfD		11.24	11.26

Percent of Person-Days that are User-Days = 99.76%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.002221	2.47	4,052	90.00	0.021992	24.44	409
20.00	0.003282	3.65	2,742	95.00	0.027475	30.53	327
30.00	0.004351	4.83	2,068	97.50	0.033710	37.46	266
40.00	0.005890	6.54	1,527	99.00	0.042761	47.51	210
50.00	0.007683	8.54	1,171	99.50	0.052316	58.13	172
60.00	0.009258	10.29	972	99.75	0.058743	65.27	153
70.00	0.011781	13.09	763	99.90	0.071788	79.76	125
80.00	0.015418	17.13	583				

All infants		Daily Exposure Analysis (mg/kg body-weight/day)	
-----		per Capita	per User
		-----	-----
Mean		0.012695	0.014063
Standard Deviation		0.014599	0.014726
Standard Error of mean		0.000268	0.000284
Margin of Exposure		708	639
Percent of aRfD		14.11	15.63

Percent of Person-Days that are User-Days = 90.28%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.002870	3.19	3,136	90.00	0.033299	37.00	270
20.00	0.004269	4.74	2,108	95.00	0.045329	50.37	198
30.00	0.005367	5.96	1,676	97.50	0.057581	63.98	156
40.00	0.006766	7.52	1,330	99.00	0.070046	77.83	128

50.00	0.008533	9.48	1,054	99.50	0.077904	86.56	115
60.00	0.011288	12.54	797	99.75	0.086405	96.01	104
70.00	0.015115	16.79	595	99.90	0.098301	109.22	91
80.00	0.021238	23.60	423				

Nursing infants (<1 yr old)

-----

	Daily Exposure Analysis (mg/kg body-weight/day)	
	per Capita	per User
Mean	0.006715	0.010375
Standard Deviation	0.012227	0.013892
Standard Error of mean	0.000421	0.000583
Margin of Exposure	1,340	867
Percent of aRfD	7.46	11.53

Percent of Person-Days that are User-Days = 64.72%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000502	0.56	17,917	90.00	0.028691	31.88	313
20.00	0.001336	1.48	6,738	95.00	0.035900	39.89	250
30.00	0.002479	2.75	3,629	97.50	0.052525	58.36	171
40.00	0.003757	4.17	2,395	99.00	0.065200	72.44	138
50.00	0.004748	5.28	1,895	99.50	0.071247	79.16	126
60.00	0.007286	8.10	1,235	99.75	0.078182	86.87	115
70.00	0.011083	12.31	812	99.90	0.083682	92.98	107
80.00	0.016254	18.06	553				

Non-nursing infants (<1 yr old)

-----

	Daily Exposure Analysis (mg/kg body-weight/day)	
	per Capita	per User
Mean	0.014966	0.014969
Standard Deviation	0.014784	0.014784
Standard Error of mean	0.000320	0.000320
Margin of Exposure	601	601
Percent of aRfD	16.63	16.63

Percent of Person-Days that are User-Days = 99.98%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.003830	4.26	2,350	90.00	0.034405	38.23	261
20.00	0.004905	5.45	1,834	95.00	0.046066	51.18	195
30.00	0.005958	6.62	1,510	97.50	0.057810	64.23	155
40.00	0.007408	8.23	1,214	99.00	0.070778	78.64	127
50.00	0.009337	10.37	963	99.50	0.078628	87.36	114
60.00	0.012081	13.42	744	99.75	0.091726	101.92	98
70.00	0.016106	17.90	558	99.90	0.097759	108.62	92
80.00	0.022328	24.81	403				

Children 1-2 yrs

-----

	Daily Exposure Analysis (mg/kg body-weight/day)	
	per Capita	per User
Mean	0.022297	0.022297

Standard Deviation	0.015718	0.015718
Standard Error of mean	0.000243	0.000243
Margin of Exposure	403	403
Percent of aRfD	24.77	24.77

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.007534	8.37	1,194	90.00	0.041315	45.91	217
20.00	0.010499	11.67	857	95.00	0.051266	56.96	175
30.00	0.013074	14.53	688	97.50	0.059544	66.16	151
40.00	0.015658	17.40	574	99.00	0.078200	86.89	115
50.00	0.018523	20.58	485	99.50	0.093639	104.04	96
60.00	0.021854	24.28	411	99.75	0.099769	110.85	90
70.00	0.025931	28.81	347	99.90	0.125696	139.66	71
80.00	0.031613	35.13	284				

Children 3-5 yrs	Daily Exposure Analysis	
-----	(mg/kg body-weight/day)	
	per Capita	per User
	-----	-----
Mean	0.016667	0.016667
Standard Deviation	0.011654	0.011654
Standard Error of mean	0.000124	0.000124
Margin of Exposure	540	540
Percent of aRfD	18.52	18.52

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.005965	6.63	1,508	90.00	0.030882	34.31	291
20.00	0.007882	8.76	1,141	95.00	0.038461	42.73	234
30.00	0.009771	10.86	921	97.50	0.047179	52.42	190
40.00	0.011600	12.89	775	99.00	0.057123	63.47	157
50.00	0.013597	15.11	661	99.50	0.064933	72.15	138
60.00	0.016104	17.89	558	99.75	0.077067	85.63	116
70.00	0.019227	21.36	468	99.90	0.091022	101.14	98
80.00	0.023568	26.19	381				

Children 6-12 yrs	Daily Exposure Analysis	
-----	(mg/kg body-weight/day)	
	per Capita	per User
	-----	-----
Mean	0.009972	0.009972
Standard Deviation	0.008101	0.008101
Standard Error of mean	0.000125	0.000125
Margin of Exposure	902	902
Percent of aRfD	11.08	11.08

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
-----	-----	-----	-----	-----	-----	-----	-----

10.00	0.003259	3.62	2,761	90.00	0.019287	21.43	466
20.00	0.004484	4.98	2,006	95.00	0.024302	27.00	370
30.00	0.005472	6.08	1,644	97.50	0.030865	34.29	291
40.00	0.006609	7.34	1,361	99.00	0.041668	46.30	215
50.00	0.007760	8.62	1,159	99.50	0.048275	53.64	186
60.00	0.009099	10.11	989	99.75	0.054466	60.52	165
70.00	0.011033	12.26	815	99.90	0.060194	66.88	149
80.00	0.014168	15.74	635				

Youth 13-19 yrs

-----

Daily Exposure Analysis  
(mg/kg body-weight/day)  
per Capita per User

Mean	0.005838	0.005843
Standard Deviation	0.005028	0.005027
Standard Error of mean	0.000102	0.000102
Margin of Exposure	1,541	1,540
Percent of aRfD	6.49	6.49

Percent of Person-Days that are User-Days = 99.90%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.001664	1.85	5,407	90.00	0.011601	12.89	775
20.00	0.002450	2.72	3,674	95.00	0.015631	17.37	575
30.00	0.003103	3.45	2,900	97.50	0.018935	21.04	475
40.00	0.003709	4.12	2,426	99.00	0.024271	26.97	370
50.00	0.004456	4.95	2,019	99.50	0.029274	32.53	307
60.00	0.005325	5.92	1,690	99.75	0.033710	37.46	266
70.00	0.006564	7.29	1,371	99.90	0.043263	48.07	208
80.00	0.008235	9.15	1,092				

Adults 20-49 yrs

-----

Daily Exposure Analysis  
(mg/kg body-weight/day)  
per Capita per User

Mean	0.005662	0.005667
Standard Deviation	0.004843	0.004842
Standard Error of mean	0.000050	0.000050
Margin of Exposure	1,589	1,588
Percent of aRfD	6.29	6.30

Percent of Person-Days that are User-Days = 99.90%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.001453	1.61	6,193	90.00	0.011756	13.06	765
20.00	0.002124	2.36	4,236	95.00	0.015022	16.69	599
30.00	0.002734	3.04	3,291	97.50	0.018290	20.32	492
40.00	0.003412	3.79	2,637	99.00	0.023067	25.63	390
50.00	0.004201	4.67	2,142	99.50	0.027620	30.69	325
60.00	0.005215	5.79	1,725	99.75	0.032385	35.98	277
70.00	0.006497	7.22	1,385	99.90	0.039230	43.59	229
80.00	0.008506	9.45	1,058				

Adults 50+ yrs

Daily Exposure Analysis

	(mg/kg body-weight/day)	
	per Capita	per User
Mean	0.006246	0.006248
Standard Deviation	0.005221	0.005220
Standard Error of mean	0.000054	0.000054
Margin of Exposure	1,440	1,440
Percent of aRfD	6.94	6.94

Percent of Person-Days that are User-Days = 99.97%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.001554	1.73	5,789	90.00	0.012676	14.08	709
20.00	0.002314	2.57	3,888	95.00	0.016225	18.03	554
30.00	0.003049	3.39	2,951	97.50	0.020037	22.26	449
40.00	0.003841	4.27	2,342	99.00	0.025037	27.82	359
50.00	0.004790	5.32	1,878	99.50	0.029838	33.15	301
60.00	0.005866	6.52	1,534	99.75	0.034382	38.20	261
70.00	0.007293	8.10	1,234	99.90	0.039963	44.40	225
80.00	0.009363	10.40	961				

Females 13-49 yrs		Daily Exposure Analysis	
-----		(mg/kg body-weight/day)	
		per Capita	per User
		-----	-----
Mean		0.005530	0.005537
Standard Deviation		0.004771	0.004770
Standard Error of mean		0.000062	0.000062
Margin of Exposure		1,627	1,625
Percent of aRfD		6.14	6.15

Percent of Person-Days that are User-Days = 99.87%

Estimated percentile of user-days falling below calculated exposure  
in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.001389	1.54	6,477	90.00	0.011534	12.82	780
20.00	0.002043	2.27	4,404	95.00	0.014635	16.26	614
30.00	0.002663	2.96	3,379	97.50	0.017991	19.99	500
40.00	0.003345	3.72	2,690	99.00	0.022799	25.33	394
50.00	0.004122	4.58	2,183	99.50	0.026947	29.94	333
60.00	0.005099	5.67	1,765	99.75	0.032119	35.69	280
70.00	0.006395	7.11	1,407	99.90	0.039186	43.54	229
80.00	0.008353	9.28	1,077				

# ATTACHMENT II: DEEM Chronic Dietary Exposure Assessment

## II.1. Chronic Residue Data Files

Filename: H:\svetlana\Imidacloprid\DEEM\IMI Chronic\Chronic 1.RS7 Chemical:  
 RfD(Chronic): 0 mg/kg bw/day NOEL(Chronic): 0 mg/kg bw/day  
 RfD(Acute): 0 mg/kg bw/day NOEL(Acute): 0 mg/kg bw/day  
 Date created/last modified: 09-07-2004/16:10:40/14 Program ver. 7.87

Food Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	Adj.Factors #2	RDL Pntr	Comment
98	0	Acerola	0.500000	1.000	1.000		CFR 03
		Full comment: CFR 03 chr					
40	14	Almonds	0.025000	1.000	1.000		CFR 03
		Full comment: CFR 03 112603;Sec18;exp 6'04;chr					
498	4A	Amaranth	1.750000	1.000	1.000		CFR 03
		Full comment: CFR 03 subgroup 4a leafy greens chr					
52	11	Apples	0.250000	1.000	0.340		CFR 03
		Full comment: CFR 03 chr					
53	11	Apples-dried	0.250000	1.000	1.000		CFR 03
		Full comment: CFR 03 chr					
54	11	Apples-juice/cider	0.250000	1.000	1.000		CFR 03
		Full comment: CFR 03 chr					
377	11	Apples-juice-concentrate	0.250000	1.000	1.000		CFR 03
		Full comment: CFR 03 chr					
410	12	Apricot juice	1.500000	1.000	1.000		CFR 03
		Full comment: CFR 03 Group 12 stone fruit chr					
59	12	Apricots	1.500000	1.000	1.000		CFR 03
		Full comment: CFR 03 Group 12 stone fruit chr					
60	12	Apricots-dried	1.500000	1.000	1.000		CFR 03
		Full comment: CFR 03 Group 12 stone fruit chr					
181	0	Artichokes-globe	1.250000	1.000	1.000		CFR 03
		Full comment: CFR 03 chr					
203	1CD	Artichokes-jerusalem	0.200000	1.000	1.000		CFR 03
		Full comment: CFR 03 Group 1 root & tuber chr					
70	0	Avocados	0.500000	1.000	1.000		CFR 03
		Full comment: CFR 03 chr					
497	9B	Balsam pear	0.250000	1.000	1.000		CFR 03
		Full comment: CFR 03 group 9 cucurbit chr					
72	0	Bananas	0.010000	1.000	1.000		CFR 03
		Full comment: CFR 03 imported tolearnce chr					
73	0	Bananas-dried	0.010000	1.000	1.000		CFR 03
		Full comment: CFR 03 imported tolearnce chr					
378	0	Bananas-juice	0.010000	1.000	1.000		CFR 03
		Full comment: CFR 03 imported tolearnce chr					
265	15	Barley	0.025000	1.000	1.000		CFR 03
		Full comment: CFR 03 chr					
258	6C	Beans-dry-blackeye peas/cowpea	2.000000	1.000	1.000		CFR 03
		Full comment: CFR 03 group 6 Leg Veg chr					
249	6C	Beans-dry-broadbeans	2.000000	1.000	1.000		CFR 03
		Full comment: CFR 03 group 6 Leg Veg chr					
259	6C	Beans-dry-garbanzo/chick pea	2.000000	1.000	1.000		CFR 03
		Full comment: CFR 03 group 6 Leg Veg chr					
227	6C	Beans-dry-great northern	2.000000	1.000	1.000		CFR 03
		Full comment: CFR 03 group 6 Leg Veg chr					
228	6C	Beans-dry-kidney	2.000000	1.000	1.000		CFR 03
		Full comment: CFR 03 group 6 Leg Veg chr					
229	6C	Beans-dry-lima	2.000000	1.000	1.000		CFR 03
		Full comment: CFR 03 group 6 Leg Veg chr					
230	6C	Beans-dry-navy (pea)	2.000000	1.000	0.060		CFR 03
		Full comment: CFR 03 group 6 Leg Veg chr					
231	6C	Beans-dry-other	2.000000	1.000	0.060		CFR 03
		Full comment: CFR 03 group 6 Leg Veg chr					
251	6C	Beans-dry-pigeon beans	2.000000	1.000	0.060		CFR 03
		Full comment: CFR 03 group 6 Leg Veg chr					
232	6C	Beans-dry-pinto	2.000000	1.000	0.060		CFR 03

	Full comment: CFR 03 group 6 Leg Veg chr					
250	6B Beans-succulent-broadbeans	2.000000	1.000	0.060		CFR 03
	Full comment: CFR 03 group 6 Leg Veg chr					
234	6A Beans-succulent-green	2.000000	1.000	0.060		CFR 03
	Full comment: CFR 03 group 6 Leg Veg chr					
233	6B Beans-succulent-lima	2.000000	1.000	0.060		CFR 03
	Full comment: CFR 03 group 6 Leg Veg chr					
235	6A Beans-succulent-other	2.000000	1.000	0.060		CFR 03
	Full comment: CFR 03 group 6 Leg Veg chr					
236	6A Beans-succulent-yellow/wax	2.000000	1.000	0.060		CFR 03
	Full comment: CFR 03 group 6 Leg Veg chr					
253	6 Beans-unspecified	2.000000	1.000	0.060		CFR 03
	Full comment: CFR 03 group 6 Leg Veg chr					
323	M Beef-dried	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
324	M Beef-fat w/o bones	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
325	M Beef-kidney	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
327	M Beef-lean (fat/free) w/o bones	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
326	M Beef-liver	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
321	M Beef-meat byproducts	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
322	M Beef-other organ meats	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
197	1AB Beets-garden-roots	0.200000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
165	2 Beets-garden-tops(greens)	2.000000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 2 leaves root & tuber chr					
152	9B Bitter melon	0.250000	1.000	1.000		CFR 03
	Full comment: CFR 03 group 9 cucurbit chr					
7	13B Blueberries	1.750000	1.000	1.000		FR May
	Full comment: FR May 26 04 chr					
452	5B Bok choy	1.750000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 5 Brassica chr					
168	5A Broccoli	1.750000	1.000	0.350		CFR 03
	Full comment: CFR 03 Group 5 Brassica chr					
451	5A Broccoli-chinese	1.750000	1.000	0.350		CFR 03
	Full comment: CFR 03 Group 5 Brassica chr					
169	5A Brussels sprouts	1.750000	1.000	0.560		CFR 03
	Full comment: CFR 03 Group 5 Brassica chr					
286	15 Buckwheat	0.025000	1.000	1.000		CFR 03
	Full comment: CFR 03 regional reg group 15 chr					
382	1AB Burdock	0.200000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
170	5A Cabbage-green and red	1.750000	1.000	0.200		CFR 03
	Full comment: CFR 03 Group 5 Brassica chr					
383	5B Cabbage-savoy	1.750000	1.000	0.200		CFR 03
	Full comment: CFR 03 Group 5 Brassica chr					
301	O Canola oil (rape seed oil)	0.025000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
106	O Carambola (starfruit)	0.500000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
198	1AB Carrots	0.200000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
143	9A Casabas	0.250000	1.000	1.000		CFR 03
	Full comment: CFR 03 group 9 cucurbit chr					
222	1CD Cassava (yuca blanca)	0.200000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
171	5A Cauliflower	1.750000	1.000	0.600		CFR 03
	Full comment: CFR 03 Group 5 Brassica chr					
199	1AB Celeriac	0.200000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
166	4B Celery	3.000000	1.000	1.000		CFR 03
	Full comment: CFR 03 subgroup 4b petioles chr					
384	4B Celery juice	3.000000	1.000	1.000		CFR 03
	Full comment: CFR 03 subgroup 4b petioles chr					
61	12 Cherries	1.500000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 12 stone fruit chr					



62 12	Cherries-dried	1.500000	1.000	1.000	CFR 03
	Full comment: CFR 03 Group 12 stone fruit chr				
63 12	Cherries-juice	1.500000	1.000	1.000	CFR 03
	Full comment: CFR 03 Group 12 stone fruit chr				
447 4A	Chervil	1.750000	1.000	1.000	CFR 03
	Full comment: CFR 03 subgroup 4a leafy greens chr				
366 P	Chicken-byproducts	0.025000	1.000	1.000	CFR 03
	Full comment: CFR 03 chr				
368 P	Chicken-fat w/o bones	0.025000	1.000	1.000	CFR 03
	Full comment: CFR 03 chr				
367 P	Chicken-giblets(liver)	0.025000	1.000	1.000	CFR 03
	Full comment: CFR 03 chr				
385 P	Chicken-giblets (excl. liver)	0.025000	1.000	1.000	CFR 03
	Full comment: CFR 03 chr				
369 P	Chicken-lean/fat free w/o bones	0.025000	1.000	1.000	CFR 03
	Full comment: CFR 03 chr				
114 1AB	Chicory	0.200000	1.000	1.000	CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr				
167 4A	Chicory(french/belgian endive)	1.750000	1.000	1.000	CFR 03
	Full comment: CFR 03 subgroup 4a leafy greens chr				
386 9B	Christophine	0.250000	1.000	1.000	CFR 03
	Full comment: CFR 03 group 9 cucurbit chr				
20 10	Citrus citron	0.038000	1.000	1.000	PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr				
172 5B	Collards	1.750000	1.000	0.100	CFR 03
	Full comment: CFR 03 Group 5 Brassica chr				
121 19B	Coriander	1.750000	1.000	1.000	CFR 03
	Full comment: CFR 03 chr				
267 15	Corn grain-bran	0.025000	1.000	1.000	CFR 03
	Full comment: CFR 03 chr				
266 15	Corn grain-endosperm	0.025000	1.000	1.000	CFR 03
	Full comment: CFR 03 chr				
289 15	Corn grain-oil	0.025000	1.000	1.000	CFR 03
	Full comment: CFR 03 chr				
268 15	Corn grain/sugar/hfcs	0.025000	1.000	1.000	CFR 03
	Full comment: CFR 03 chr				
388 15	Corn grain/sugar-molasses	0.025000	1.000	1.000	CFR 03
	Full comment: CFR 03 chr				
237 15	Corn/pop	0.025000	1.000	1.000	CFR 03
	Full comment: CFR 03 chr				
238 15	Corn/sweet	0.025000	1.000	1.000	CFR 03
	Full comment: CFR 03 chr				
291 0	Cottonseed-meal	4.000000	1.000	0.030	CFR 03
	Full comment: CFR 03 chr				
290 0	Cottonseed-oil	3.000000	1.000	0.030	CFR 03
	Full comment: CFR 03 chr				
55 11	Crabapples	0.300000	1.000	1.000	CFR 03
	Full comment: CFR 03 group 11 chr				
8 0	Cranberries	0.025000	1.000	1.000	June 1
	Full comment: June 13 03 chr				
9 0	Cranberries-juice	0.050000	1.000	1.000	June 1
	Full comment: June 13 03 chr				
389 0	Cranberries-juice-concentrate	0.050000	1.000	1.000	June 1
	Full comment: June 13 03 chr				
144 9A	Crenshaws	0.250000	1.000	1.000	CFR 03
	Full comment: CFR 03 group 9 cucurbit chr				
180 4A	Cress-garden/field	1.750000	1.000	1.000	CFR 03
	Full comment: CFR 03 subgroup 4a leafy greens chr				
191 4A	Cress-upland	1.750000	1.000	1.000	CFR 03
	Full comment: CFR 03 subgroup 4a leafy greens chr				
148 9B	Cucumbers	0.200000	1.000	1.000	1 DPR 02
	Full comment: DPR 02; 15 samples ND LOD 0.4 chr				
10 13B	Currants	1.750000	1.000	1.000	CFR 03
	Full comment: CFR 03 Group 13B chr				
177 4A	Dandelion-greens	1.750000	1.000	1.000	CFR 03
	Full comment: CFR 03 subgroup 4a leafy greens chr				
154 8	Eggplant	0.500000	1.000	0.360	CFR 03
	Full comment: CFR 03 Group 8 Fruiting Veg chr				
364 P	Eggs-white only	0.010000	1.000	1.000	CFR 03
	Full comment: CFR 03 chr				
363 P	Eggs-whole	0.010000	1.000	1.000	CFR 03

	Full comment: CFR 03 chr					
365 P	Eggs-yolk only	0.010000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
11 13B	Elderberries	1.750000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 13B chr					
178 4A	Endive-curley and escarole	1.750000	1.000	1.000		CFR 03
	Full comment: CFR 03 subgroup 4a leafy greens chr					
124 1CD	Ginger	0.200000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
450 1AB	Ginseng	0.200000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
330 M	Goat-fat w/o bone	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
331 M	Goat-kidney	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
333 M	Goat-lean (fat/free) w/o bone	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
332 M	Goat-liver	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
328 M	Goat-meat byproducts	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
329 M	Goat-other organ meats	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
12 13B	Gooseberries	1.750000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 13B chr					
23 10	Grapefruit-juice	0.038000	2.100	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
441 10	Grapefruit-juice-concentrate	0.038000	8.260	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
448 10	Grapefruit peel	0.038000	1.000	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
22 10	Grapefruit-peeled fruit	0.038000	1.000	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
13 O	Grapes	0.200000	1.000	0.500	2	DPR 02
	Full comment: DPR 02 #34 ND LOD=0.4 chr					
15 O	Grapes-juice	0.200000	1.200	0.500	2	DPR 02
	Full comment: DPR 02 #34 ND LOD=0.4 chr					
392 O	Grapes-juice-concentrate	0.200000	3.600	0.500	2	DPR 02
	Full comment: DPR 02 #34 ND LOD=0.4 chr					
195 O	Grapes-leaves	0.200000	1.000	0.500	2	DPR 02
	Full comment: DPR 02 #34 ND LOD=0.4 chr					
14 O	Grapes-raisins	0.200000	4.300	0.500	2	DPR 02
	Full comment: DPR 02 #34 ND LOD=0.4 chr					
315 O	Grapes-wine and sherry	0.200000	1.000	0.500	2	DPR 02
	Full comment: DPR 02 #34 ND LOD=0.4 chr					
164 8	Groundcherries	0.200000	1.000	1.000		DPR 02
	Full comment: DPR 02 #7 ND LOD=0.4 chr					
287 6C	Guar beans	2.000000	1.000	0.060		CFR 03
	Full comment: CFR 03 group 6 Leg Veg chr					
393 O	Guava-juice	0.500000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
79 O	Guava	0.500000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
125 O	Hops	3.000000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
334 M	Horsemeat	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
126 1AB	Horseradish	0.200000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
16 13B	Huckleberries	1.750000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 13B chr					
18 O	Juneberry	1.750000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
174 5B	Kale	1.750000	1.000	0.300		CFR 03
	Full comment: CFR 03 Group 5 Brassica chr					
175 5A	Kohlrabi	1.750000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 5 Brassica chr					
24 10	Kumquats	0.038000	1.000	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
28 10	Lemons-juice	0.038000	2.000	1.000		PDP 00

	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
442 10	Lemons-juice-concentrate	0.038000	11.400	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
27 10	Lemons-peel	0.038000	1.000	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
26 10	Lemons-peeled fruit	0.038000	1.000	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
243 6C	Lentils	2.000000	1.000	1.000		CFR 03
	Full comment: CFR 03 group 6 Leg Veg chr					
182 4A	Lettuce-unspecified	0.200000	1.000	0.850		DPR 02
	Full comment: DPR 02 #14 ND LOD 0.4 chr					
176 4A	Lettuce-leafy varieties	0.200000	1.000	0.850		DPR 02
	Full comment: DPR 02 #14 ND LOD 0.4 chr					
192 4A	Lettuce-head varieties	0.200000	1.000	0.850		DPR 02
	Full comment: DPR 02 #14 ND LOD 0.4 chr					
32 10	Limes-juice	0.038000	2.000	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
443 10	Limes-juice-concentrate	0.038000	6.000	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
31 10	Limes-peel	0.038000	1.000	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
30 10	Limes-peeled fruit	0.038000	1.000	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
108 O	Longan fruit	1.500000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
81 11	Loquats	0.300000	1.000	1.000		CFR 03
	Full comment: CFR 03 group 11 chr					
96 O	Lychee-dried	1.500000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
95 O	Lychees (litchi)/fresh	1.500000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
80 O	Mangoes	0.500000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
141 9A	Melons-cantaloupes-juice	0.200000	1.000	0.450		DPR 02
	Full comment: DPR 02; 18 samples ND LOD 0.4 chr					
142 9A	Melons-cantaloupes-pulp	0.200000	1.000	0.450		DPR 02
	Full comment: DPR 02; 18 samples ND LOD 0.4 chr					
145 9A	Melons-honeydew	0.200000	1.000	0.450		DPR 02
	Full comment: DPR 02; 18 samples ND LOD 0.4 chr					
146 9A	Melons-persian	0.200000	1.000	0.450		DPR 02
	Full comment: DPR 02; 18 samples ND LOD 0.4 chr					
398 D	Milk-based water	0.050000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
319 D	Milk-fat solids	0.050000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
318 D	Milk-nonfat solids	0.050000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
320 D	Milk sugar (lactose)	0.050000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
280 15	Millet	0.025000	1.000	1.000		CFR 03
	Full comment: CFR 03 regional reg group 15 chr					
244 6C	Mung beans (sprouts)	2.000000	1.000	1.000		CFR 03
	Full comment: CFR 03 group 6 Leg Veg chr					
183 5B	Mustard greens	1.750000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 5 Brassica chr					
130 19B	Mustard seed	0.025000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
64 12	Nectarines	0.005000	1.000	0.010	3	PDP 00
	Full comment: PDP 00-01 #508 ND LOD 0.01 chr					
399 15	Oats-bran	0.025000	1.000	1.000		CFR 03
	Full comment: CFR 03 regional reg group 15 chr					
269 15	Oats	0.004000	1.000	1.000	4	PDP 99
	Full comment: PDP 99 #332 ND LOD 0.008 chr					
245 O	Okra	0.500000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
397 9B	Okra/chinese (luffa)	0.250000	1.000	1.000		CFR 03
	Full comment: CFR 03 group 9 cucurbit chr					
36 10	Oranges-juice	0.038000	1.800	0.010	5	PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
33 10	Oranges-juice-concentrate	0.038000	6.700	0.010	5	PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					

35	10	Oranges-peel	0.038000	1.000	0.010	5	PDP	00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr						
34	10	Oranges-peeled fruit	0.038000	1.000	0.010	5	PDP	00
		Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr						
85	O	Papayas-dried	0.500000	1.000	1.000		CFR	03
		Full comment: CFR 03 chr						
86	O	Papayas-juice	0.500000	1.000	1.000		CFR	03
		Full comment: CFR 03 chr						
84	O	Papayas-pulp	0.500000	1.000	1.000		CFR	03
		Full comment: CFR 03 chr						
139	8	Paprika	0.500000	1.000	1.000		CFR	03
		Full comment: CFR 03 Group 8 Fruiting Veg chr						
184	4A	Parsley	1.750000	1.000	1.000		CFR	03
		Full comment: CFR 03 subgroup 4a leafy greens chr						
225	1AB	Parsley roots	0.200000	1.000	1.000		CFR	03
		Full comment: CFR 03 Group 1 root & tuber chr						
220	1AB	Parsnips	0.200000	1.000	1.000		CFR	03
		Full comment: CFR 03 Group 1 root & tuber chr						
401	O	Passion fruit-juice	0.500000	1.000	1.000		CFR	03
		Full comment: CFR 03 chr						
92	O	Passion fruit (granadilla)	0.500000	1.000	1.000		CFR	03
		Full comment: CFR 03 chr						
65	12	Peaches	0.005000	1.000	0.010	3	PDP	00
		Full comment: PDP 00-01 #508 ND LOD 0.01 chr						
66	12	Peaches-dried	0.005000	7.000	0.010	3	PDP	00
		Full comment: PDP 00-01 #508 ND LOD 0.01 chr						
402	12	Peaches-juice	0.005000	1.000	0.010	3	PDP	00
		Full comment: PDP 00-01 #508 ND LOD 0.01 chr						
56	11	Pears	0.300000	1.000	0.200		CFR	03
		Full comment: CFR 03 group 11 chr						
57	11	Pears-dried	0.300000	1.000	0.200		CFR	03
		Full comment: CFR 03 group 11 chr						
404	11	Pears-juice	0.300000	1.000	0.200		CFR	03
		Full comment: CFR 03 group 11 chr						
240	6C	Peas (garden)-dry	0.005000	1.000	0.010	6	PDP	01
		Full comment: PDP 01-02 #630 ND LOD 0.01 chr						
241	6AB	Peas (garden)-green	0.005000	1.000	0.010	6	PDP	01
		Full comment: PDP 01-02 #630 ND LOD 0.01 chr						
405	6B	Peas-succulent/blackeye/cowpea	0.005000	1.000	0.010	6	PDP	01
		Full comment: PDP 01-02 #630 ND LOD 0.01 chr						
47	14	Pecans	0.025000	1.000	1.000		CFR	03
		Full comment: CFR 03 chr						
156	8	Peppers-chilli incl jalapeno	0.200000	1.000	0.620	7	PDP	02
		Full comment: PDP 02 #24 ND LOD 0.4 chr						
157	8	Peppers-other	0.200000	1.000	0.620	7	PDP	02
		Full comment: PDP 02 #24 ND LOD 0.4 chr						
155	8	Peppers-sweet(garden)	0.200000	1.000	0.620	7	PDP	02
		Full comment: PDP 02 #24 ND LOD 0.4 chr						
88	O	Persimmons	1.500000	1.000	1.000		CFR	03
		Full comment: CFR 03 chr						
158	8	Pimientos	0.200000	1.000	0.620		PDP	02
		Full comment: PDP 02 #24 ND LOD 0.4 chr						
67	12	Plums (damsons)	1.500000	1.000	1.000		CFR	03
		Full comment: CFR 03 Group 12 stone fruit chr						
68	12	Plums-prunes (dried)	1.500000	1.000	1.000		CFR	03
		Full comment: CFR 03 Group 12 stone fruit chr						
69	12	Plums/prune-juice	1.500000	1.000	1.000		CFR	03
		Full comment: CFR 03 Group 12 stone fruit chr						
344	M	Pork-fat w/o bone	0.150000	1.000	1.000		CFR	03
		Full comment: CFR 03 chr						
345	M	Pork-kidney	0.150000	1.000	1.000		CFR	03
		Full comment: CFR 03 chr						
347	M	Pork-lean (fat free) w/o bone	0.150000	1.000	1.000		CFR	03
		Full comment: CFR 03 chr						
346	M	Pork-liver	0.150000	1.000	1.000		CFR	03
		Full comment: CFR 03 chr						
342	M	Pork-meat byproducts	0.150000	1.000	1.000		CFR	03
		Full comment: CFR 03 chr						
343	M	Pork-other organ meats	0.150000	1.000	1.000		CFR	03
		Full comment: CFR 03 chr						
210	1C	Potatoes/white-dry	0.200000	1.000	0.460		CFR	03

	Full comment: CFR 03 Group 1 root & tuber chr					
209	1C Potatoes/white-peeled	0.200000	1.000	0.460		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
211	1C Potatoes/white-peel only	0.200000	1.000	0.460		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
208	1C Potatoes/white-unspecified	0.200000	1.000	0.460		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
207	1C Potatoes/white-whole	0.200000	1.000	0.460		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
362	P Poultry-other-fat w/o bones	0.002500	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
361	P Poultry-other-giblets(liver)	0.002500	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
360	P Poultry-other-lean (fat free) w/	0.002500	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
149	9B Pumpkin	0.250000	1.000	0.700		CFR 03
	Full comment: CFR 03 group 9 cucurbit chr					
58	11 Quinces	0.300000	1.000	1.000		CFR 03
	Full comment: CFR 03 group 11 chr					
407	1AB Radishes-japanese (daiken)	0.200000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
212	1AB Radishes-roots	0.200000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
213	2 Radishes-tops	2.000000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 2 leaves root & tuber chr					
185	4B Rhubarb	3.000000	1.000	1.000		CFR 03
	Full comment: CFR 03 subgroup 4b petioles chr					
408	15 Rice-bran	0.025000	1.000	1.000		CFR 03
	Full comment: CFR 03 regional reg group 15 chr					
271	15 Rice-milled (white)	0.025000	1.000	1.000		CFR 03
	Full comment: CFR 03 regional reg group 15 chr					
270	15 Rice-rough (brown)	0.025000	1.000	1.000		CFR 03
	Full comment: CFR 03 regional reg group 15 chr					
409	15 Rice-wild	0.025000	1.000	1.000		CFR 03
	Full comment: CFR 03 regional reg group 15 chr					
214	1AB Rutabagas-roots	0.200000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
215	2 Rutabagas-tops	2.000000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 2 leaves root & tuber chr					
274	15 Rye-flour	0.025000	1.000	1.000		CFR 03
	Full comment: CFR 03 regional reg group 15 chr					
273	15 Rye-germ	0.025000	1.000	1.000		CFR 03
	Full comment: CFR 03 regional reg group 15 chr					
272	15 Rye-rough	0.025000	1.000	1.000		CFR 03
	Full comment: CFR 03 regional reg group 15 chr					
295	O Safflower-oil	0.250000	1.000	1.000		CFR 03
	Full comment: CFR 03 regional reg chr					
294	O Safflower-seed	0.003000	1.000	1.000		CFR 03
	Full comment: CFR 03 regional reg chr					
216	1AB Salsify(oyster plant)	0.200000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 1 root & tuber chr					
473	O Sapodilla	0.500000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
338	M Sheep-fat w/o bone	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
339	M Sheep-kidney	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
341	M Sheep-lean (fat free) w/o bone	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
340	M Sheep-liver	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
336	M Sheep-meat byproducts	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
337	M Sheep-other organ meats	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
413	6A Snowpeas	2.000000	1.000	1.000		CFR 03
	Full comment: CFR 03 group 6 Leg Veg chr					
275	15 Sorghum (including milo)	0.025000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
303	6A Soybean-other	0.500000	1.000	1.000		Emerg.
	Full comment: Emerg. expires 12 31 2006 group 6 chr					

307 6A	Soybeans-flour (defatted)	0.250000	1.000	1.000		Region
	Full comment: Regional; no expir date group 6 chr					
306 6A	Soybeans-flour (low fat)	0.250000	1.000	1.000		Region
	Full comment: Regional; no expir date group 6 chr					
305 6A	Soybeans-flour (full fat)	0.250000	1.000	1.000		Region
	Full comment: Regional; no expir date group 6 chr					
304 6A	Soybeans-mature seeds dry	0.500000	1.000	1.000		Emerg.
	Full comment: Emerg. expires 12 31 2006 group 6 chr					
297 6A	Soybeans-oil	0.500000	1.000	1.000		Emerg.
	Full comment: Emerg. expires 12 31 2006 group 6 chr					
482 O	Soybeans-protein isolate	0.250000	1.000	1.000		Region
	Full comment: Regional; no expir date group 6 chr					
255 6A	Soybeans-sprouted seeds	0.500000	1.000	1.000		Emerg.
	Full comment: Emerg. expires 12 31 2006 group 6 chr					
186 4A	Spinach	1.750000	1.000	1.000		CFR 03
	Full comment: CFR 03 subgroup 4a leafy greens chr					
150 9B	Squash-summer	0.250000	1.000	0.100		CFR 03
	Full comment: CFR 03 group 9 cucurbit chr					
415 9B	Squash-spaghetti	0.250000	1.000	0.100		CFR 03
	Full comment: CFR 03 group 9 cucurbit chr					
151 9B	Squash-winter	0.250000	1.000	0.100		CFR 03
	Full comment: CFR 03 group 9 cucurbit chr					
17 O	Strawberries	0.200000	1.000	1.000		DPR 02
	Full comment: DPR 02 samples 14 ND LOD=0.4 chr					
416 O	Strawberries-juice	0.200000	1.000	1.000		DPR 02
	Full comment: DPR 02 samples 14 ND LOD=0.4 chr					
282 1A	Sugar-beet	0.025000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
379 1A	Sugar-beet-molasses	0.150000	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
218 1CD	Sweet potatoes (incl yams)	0.200000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 1 root&tuber chr					
418 2	Sweet potatos-leaves	2.000000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 2 leaves root & tuber chr					
187 4B	Swiss chard	3.000000	1.000	1.000		CFR 03
	Full comment: CFR 03 subgroup 4b petioles chr					
37 10	Tangelos	0.038000	1.000	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
38 10	Tangerines	0.038000	1.000	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
39 10	Tangerines-juice	0.038000	2.300	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
420 10	Tangerines-juice-concentrate	0.038000	7.350	1.000		PDP 00
	Full comment: PDP 00-01 oranges 13 det; LOD 0.01chr					
201 1CD	Taro-root	0.200000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 1 root&tuber chr					
190 2	Taro-greens	2.000000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 2 leaves root & tuber chr					
163 8	Tomatoes-catsup	0.012500	2.500	0.700	8	PDP 01
	Full comment: PDP 01 #369 paste ND LOD 0.025 chr					
423 8	Tomatoes-dried	0.500000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 8 Fruiting Veg chr					
160 8	Tomatoes-juice	0.500000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 8 Fruiting Veg chr					
162 8	Tomatoes-paste	0.012500	5.400	0.700	8	PDP 01
	Full comment: PDP 01 #369 paste ND LOD 0.025 chr					
161 8	Tomatoes-puree	0.012500	3.300	0.700	8	PDP 01
	Full comment: PDP 01 #369 paste ND LOD 0.025 chr					
159 8	Tomatoes-whole	0.500000	1.000	1.000		CFR 03
	Full comment: CFR 03 Group 8 Fruiting Veg chr					
355 P	Turkey-byproducts	0.002500	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
357 P	Turkey--fat w/o bones	0.002500	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
356 P	Turkey-gIBLETS (liver)	0.002500	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
358 P	Turkey- lean/fat free w/o bones	0.002500	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
449 P	Turkey-other organ meats	0.002500	1.000	1.000		CFR 03
	Full comment: CFR 03 chr					
137 1CD	Turmeric	0.200000	1.000	1.000		CFR 03

Full comment: CFR 03 Group 1 root&tuber chr					
219 1AB Turnips-roots	0.200000	1.000	1.000	CFR 03	
Full comment: CFR 03 Group 1 root&tuber chr					
188 2 Turnips-tops	2.000000	1.000	1.000	CFR 03	
Full comment: CFR 03 Group 2 leaves root & tuber chr					
429 M Veal-dried	0.150000	1.000	1.000	CFR 03	
Full comment: CFR 03 chr					
424 M Veal-fat w/o bones	0.150000	1.000	1.000	CFR 03	
Full comment: CFR 03 chr					
426 M Veal-kidney	0.150000	1.000	1.000	CFR 03	
Full comment: CFR 03 chr					
425 M Veal-lean (fat free) w/o bones	0.150000	1.000	1.000	CFR 03	
Full comment: CFR 03 chr					
427 M Veal-liver	0.150000	1.000	1.000	CFR 03	
Full comment: CFR 03 chr					
430 M Veal-meat byproducts	0.150000	1.000	1.000	CFR 03	
Full comment: CFR 03 chr					
428 M Veal-other organ meats	0.150000	1.000	1.000	CFR 03	
Full comment: CFR 03 chr					
189 O Watercress	1.750000	1.000	1.000	CFR 03	
Full comment: CFR 03 chr					
147 9A Watermelon	0.250000	1.000	0.600	CFR 03	
Full comment: CFR 03 group 9 cucurbit chr					
436 9A Watermelon-juice	0.250000	1.000	0.600	CFR 03	
Full comment: CFR 03 group 9 cucurbit chr					
278 15 Wheat-bran	0.025000	1.000	1.000	CFR 03	
Full comment: CFR 03 chr					
279 15 Wheat-flour	0.025000	1.000	1.000	CFR 03	
Full comment: CFR 03 chr					
277 15 Wheat-germ	0.025000	1.000	1.000	CFR 03	
Full comment: CFR 03 chr					
437 15 Wheat-germ oil	0.025000	1.000	1.000	CFR 03	
Full comment: CFR 03 chr					
276 15 Wheat-rough	0.025000	1.000	1.000	CFR 03	
Full comment: CFR 03 chr					
439 9B Wintermelon	0.250000	1.000	0.600	CFR 03	
Full comment: CFR 03 group 9 cucurbit chr					
221 1CD Yambean tuber (jicama)	0.200000	1.000	1.000	CFR 03	
Full comment: CFR 03 Group 1 root&tuber chr					
224 1CD Yautia (tannier)	0.200000	1.000	1.000	CFR 03	
Full comment: CFR 03 Group 1 root&tuber chr					

## **II.2. Chronic Dietary Exposure and Risk Estimates**

California Department of Pesticide Regulation Ver. 7.87  
DEEM Chronic analysis for (1994-98 data)  
Residue file name: H:\svetlana\Imidacloprid\DEEM\IMI Chronic\Chronic 1.RS7  
Adjustment factor #2 used.  
Analysis Date 03-22-2005/14:38:44 Residue file dated: 09-07-2004/16:10:40/14  
NOEL (Chronic) = 5.7 mg/kg bw/day

=====  
Total exposure by population subgroup  
=====

Population Subgroup	Total Exposure		
	mg/kg body wt/day	Percent of NOEL	Margin of Exposr 1/
U.S. Population (total)	0.002368	0.04%	2,407
Western region	0.002640	0.05%	2,159
Hispanics	0.002657	0.05%	2,145
Non-hispanic whites	0.002280	0.04%	2,500
Non-hispanic blacks	0.002265	0.04%	2,516
Non-hisp/non-white/non-black	0.003401	0.06%	1,676
All infants (< 1 year)	0.004348	0.08%	1,311
Nursing infants	0.001982	0.03%	2,875
Non-nursing infants	0.005246	0.09%	1,087
Children 1-2 yrs	0.007405	0.13%	770

Children 3-5 yrs	0.005474	0.10%	1,041
Children 6-12 yrs	0.003235	0.06%	1,762
Youth 13-19 yrs	0.001926	0.03%	2,960
Adults 20-49 yrs	0.001794	0.03%	3,177
Adults 50+ yrs	0.001890	0.03%	3,015
Females 13-49 yrs	0.001753	0.03%	3,251



# ATTACHMENT III: Benchmark Dose Modeling. Polynomial Model

## Imidacloprid Acute Oral Treatment of Female Rats (Sheets, 1994a) Decreases In Motor Activity

```
=====
Polynomial Model. Revision: 2.2 Date: 9/12/2002
Input Data File: C:\DOCUMENTS AND SETTINGS\SKOSHLUKOVA\DESKTOP\BMD DATA\SVETLANA
IMI\BMD_IMI_MOTOR_ACTIVITY.(d)
Gnuplot Plotting File: C:\DOCUMENTS AND SETTINGS\SKOSHLUKOVA\DESKTOP\BMD DATA\SVETLANA
IMI\BMD_IMI_MOTOR_ACTIVITY.plt
Thu Dec 01 13:47:04 2005
=====
```

BMDS MODEL RUN

The form of the response function is:

$$Y[\text{dose}] = \beta_0 + \beta_1 \cdot \text{dose} + \beta_2 \cdot \text{dose}^2 + \dots$$

Dependent variable = MEAN

Independent variable = COLUMN1

Signs of the polynomial coefficients are not restricted

The variance is to be modeled as  $\text{Var}(i) = \alpha \cdot \text{mean}(i)^\rho$

Total number of dose groups = 4

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to: 1e-008

Parameter Convergence has been set to: 1e-008

### Default Initial Parameter Values

```
alpha = 1
rho = 0
beta_0 = 479.728
beta_1 = -1.86631
beta_2 = 0.00204728
```

### Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
alpha	1.48863	2.79055	-3.98074	6.95801
rho	1.68617	0.331116	1.0372	2.33515
beta_0	489.201	53.574	384.198	594.204
beta_1	-2.11196	0.755313	-3.59235	-0.631578
beta_2	0.00278779	0.00206514	-0.00125981	0.00683538

### Asymptotic Correlation Matrix of Parameter Estimates

	alpha	rho	beta_0	beta_1	beta_2
alpha	1	-0.99	0.0043	-0.063	0.087
rho	-0.99	1	0.0039	0.047	-0.07
beta_0	0.0043	0.0039	1	-0.81	0.69
beta_1	-0.063	0.047	-0.81	1	-0.98
beta_2	0.087	-0.07	0.69	-0.98	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev	Chi <sup>2</sup>
0	12	504	262	489	226	0.227
42	12	366	194	405	193	-0.708
151	12	263	93	234	121	0.833
307	10	96	71	104	61	-0.393

Model Descriptions for likelihoods calculated

Model A1:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \sigma(i)^2$

Model A3:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \alpha * (\mu(i))^{\rho}$

Model R:  $Y_i = \mu + e(i)$   
 $\text{Var}\{e(i)\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-258.901380	5	527.802760
A2	-247.959417	8	511.918835
A3	-249.489767	6	510.979534
fitted	-249.862341	5	509.724682
R	-272.173814	2	548.347627

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels?

(A2 vs. R)

Test 2: Are Variances Homogeneous? (A1 vs A2)

Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	48.4288	6	<.0001
Test 2	21.8839	3	<.0001
Test 3	3.0607	2	0.2165
Test 4	0.745148	1	0.388

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels  
 It seems appropriate to model the data

The p-value for Test 2 is less than .05. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .05. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .05. The model chosen seems to adequately describe the data

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Relative risk

Confidence level = 0.95

BMD = 11.7644

BMDL = 8.91314

BMDL computation failed for one or more point on the BMDL curve.

The BMDL curve will not be plotted

**ATTACHMENT IV: Summary of Toxicology Data for Imidacloprid**  
<http://www.cdpr.ca.gov/docs/toxsums/pdfs/3849.pdf>

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA  
IMIDACLOPRID

Chemical Code # 3849, Document Processing Number (DPN) # 51950  
SB 950 # N/A  
Original date: 5/24/93  
Revised date: 3/30/04

I. DATA GAP STATUS

Chronic toxicity, rat: No data gap, no adverse effect (other than for oncogenicity, see below)  
Chronic toxicity, dog: No data gap, no adverse effects  
Oncogenicity, rat: No data gap, possible adverse effect  
Oncogenicity, mouse: No data gap, no adverse effects  
Reproduction, rat: No data gap, no adverse effects  
Teratology, rat: No data gap, possible adverse effect  
Teratology, rabbit: No data gap, no adverse effects  
Gene mutation: No data gap, no adverse effects  
Chromosome effects: No data gap, possible adverse effect  
DNA damage: No data gap, possible adverse effect  
Neurotoxicity: No data gap, possible adverse effect

Toxicology one-liners are attached.

All record numbers for the above study types through 209393 (Document No. 51950-0474) were examined.

In the 1-liners below:

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

## indicates a study on file but not yet reviewed.

File name: T033004

Revised by Thomas Moore, 3/30/04

These pages contain summaries only. Individual worksheets may identify additional effects.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

### COMBINED, RAT

**\*\* 009,-010,-011; 119472, 119473, 119475;** Chronic Toxicity and Cancerogenicity Studies on Wistar Rats (Administration in Food over 24 Months), (Authors: R. Eiben, G. Kaliner; 831; Rat; Bayer AG, Dept. of Toxicology, D-56 Wuppertal 1, West Germany; Report Nos. 100652, 101931, 102658; 9/6/91; NTN 33893 Technical (94.3% purity); 60 animals/sex/group; Doses: (Study #1)-0, 100, 300, 900 ppm, (Study #2)-0, 1800 ppm; Mortality: (104 wks)-O (M:16/100, F:26/100), 100 (M/F:6/50), 300 (M:6/50, F:10/50), 900 (M:6/50, F:13/50), 1800 (M:5/50, F:10/50); Clinical Observations: no treatment-related signs; weight gain reduced in 1800 ppm group (M: 5%), (F: 11%); Hematology: no treatment effect; Serum Chemistry: increased alkaline phosphatase activity (F, 1800 ppm) at 6, 12, 18 months; Gross Pathology: no treatment-related lesions; Histopathology: (non-neoplastic lesions) increased incidence of mineralized particles in colloid of thyroid gland, (neoplastic) cholangiocellular carcinoma in livers of 2 males (1800 ppm); **possible adverse effect:** cholangiocellular carcinoma; NOEL: 100 ppm, based on the incidence of mineralized particles in the thyroid glands of males in the 300 ppm group; Study **acceptable**. (Moore, 4/7/93)

### CHRONIC TOXICITY, DOG

**\*\* 013; 119478;** "52-Week Oral Toxicity (Feeding) Study with NTN 33893 Technical in the Dog" (Author: Allen, T.R., et al, Research and Consulting Co., Itingen, Switzerland, Lab Project ID 100015, 10/19/89); NTN 33893 Tech. (Batch No. 180587, 94.9% purity); 0, 200, 500 and 1250/2500 ppm in feed (pellet-form) to 4 dogs/sex/dose for 52 weeks; the 1250 ppm dose was increased to 2500 ppm at week 17 due to the lack of apparent toxicity; no animals died during the study; there were no treatment-related effects on clinical signs, body weights, ophthalmoscopy, hearing, hematology or urinalysis; there was a slight but nonsignificant increase of liver weights in both sexes of the high dose group; there was also a slight increase in plasma cholesterol in females and an increase in liver cytochrome P450 in both sexes at the high dose; NOEL (M/F) = 500 ppm (based on increased liver cytochrome P450); **Acceptable** (Patterson, 4/9/93).

### ONCOGENICITY, MOUSE

**\*\* 014,-015; 119479; 119480;** Carcinogenicity Study on B6C3F1 Mice (Administration in the Food for 24 Months), (Author: B. Watta-Gebert); 832; Mouse; Bayer AG, Department of Toxicology, D-56 Wuppertal 1, West Germany; Study Nos. 100693, 101929; 1/28/91, 10/24/91; NTN 33893 Technical (purity: 95.3%); 60 animals/sex/group; Doses: (Study #1) 0, 100, 330, 1000 ppm, (Study #2) 0, 2000 ppm; Mortality: 0 (M:9/100, F:26/100), 100 (M:6/50, F:7/50), 330 (M:3/50, F:9/50), 1000 (M:8/50, F:9/50), 2000 (M:17/50, F:14/50); Clinical Observations: no treatment-related effects; weight gain reduced (2000 ppm) (M: 29%, F: 26%); Hematology: reduced wbc count (2000 ppm) (1000 ppm, F only); Serum Chemistry: alk. phosphatase activity increased (2000 ppm), cholesterol level decreased (2000 ppm), urea level decreased (2000 ppm, M only); Gross Pathology: no treatment-related lesions; absolute liver, brain, lung, spleen, kidney, and adrenal gland (F only) weights decreased (2000 ppm), liver (F only, 1000 ppm); relative liver, spleen weights decreased (F only, 2000 ppm); Histopathology: slight periacinar hepatocytic hypertrophy (M only, 2000 ppm); mineralization in the thalamus (F only, 2000 ppm); no treatment-related incidence of neoplasms; **no adverse effect identified;** NOEL: 1000 ppm, (estimated compound intake: 143.1 mg/kg/day), based on reduced weight gain and increased mortality of animals in 2000 ppm group; Study acceptable. (Moore, 4/9/93)

016; 119481; Pilot Range-Finding Study for a Cancerogenesis Study on B6C3F1 Mice, (Author: R. Eiben); 821; Mouse; Bayer AG, Department of Toxicology, D-56 Wuppertal 1, West Germany; Report No. 99808; 10/24/88; NTN 33983 Technical (purity: 92.8%); 10 animals/sex/group; Doses: 0, 120, 600, 3000 ppm; Mortality: 0 (M/F:0/10), 120 (M:1/10, F:0/10), 600 (M:1/10, F:0/10), 3000 (M/F:7/10); Clinical Observations: poor appearance (3000 ppm), significant reduction of body weight gain (3000 ppm); Hematology: no treatment-related effects; Serum Chemistry: elevation of alkaline phosphatase (3000 ppm); Gross pathology: no treatment-related lesions, reduced absolute brain, heart, liver, kidneys, spleen (F only), and adrenals (F only) weights (3000 ppm), reduced relative liver (F only), heart, and spleen (F only) weights (3000 ppm); Histopathology: no treatment-related lesions; target organ not identified; no possible adverse effect identified; NOEL: 600 ppm, (estimated daily intake: 85.7 mg/kg/day), based on poor appearance, reduced weight gain and increased mortality in the 3000 ppm group; Study **supplemental**. (Moore, 4/8/93)

#### REPRODUCTION, RAT

\*\* 019; 119496; Multiple Generation Reproduction Study in Rats, (Authors: P. Suter ~7et. al.~1); RCC, Research and Consulting Company AG, Itingen, Switzerland; Study No. 100647; 6/21/90; NTN 33893 Technical (purity: 95.3%); P generation: 30 animals/sex/group, F1B generation: 26 animals/sex/group; 2 litters/generation; Dose: 0, 100, 250, 700 ppm; Mortality: (P) 0 (M:0/30, F:2/30), 100 (M:0/30, F:1/30), 250 (M/F:0/30), 700 (M/F:0/30), (F1B) 0 (M/F:0/30), 100 (M/F:0/30), 250 (M:1/30, F:0/30), 700 (M/F:0/30); Clinical observations: decreased body weight gain (F0-700 ppm M, F1B F); Hematology: no treatment-related effects; Clinical Biochemistry: increased O-demethylase activity (F1B-250 ppm F, 700 ppm M,F), N-demethylase activity (F1B-700 ppm M), and cyt. P450 activity (F1B-700 ppm, M); Necropsy: no treatment-related lesions, no effect on organ weights; Histopathology: no treatment-related lesions; Reproductive factors: no treatment-related effects on fertility index, litter size; Developmental factors: no treatment-related abnormalities, decreased weight gain (F1A, F1B, F2A, F2B-M,F, 700 ppm), no treatment-related effect on gestation index, viability index, or lactation index; **no adverse effects identified**; NOEL: (parental) 700 ppm, (reproductive) 700 ppm, (developmental) 250 ppm (based on decreased weight gain for pups, 700 ppm); **Study acceptable**. (Moore, 4/14/93)

#### TERATOLOGY, RAT

\*\* **017; 119482**; Embryotoxicity Study (including Teratogenicity) with NTN 33893 Technical in the Rat (Authors: H. Becker, ~7et. al.~1); 833; Rat; RCC, Research & Consulting Company AG, Itingen, Switzerland; Study No. 98571; 1/8/92; NTN 33893 Technical (purity: 94.2%); 25 females/group; Doses 0, 8.9, 25.9, 94.1 mg/kg/day (analytical), test material administered by gavage from day 6 post coitum through day 15; No mortality; Clinical observations: no treatment-related signs, mean food consumption and body weight gain decreased during treatment period (94.1 mg/kg/day); Necropsy: no treatment-related lesions; Developmental: high percentage of male fetuses, increased incidence of wavy ribs (94.1 mg/kg/day); **possible adverse effect**: increased percentage of male fetuses; **Maternal NOEL** = 25.9 mg/kg/day (based on decreased body weight gain and reduced food consumption of the 94.1 mg/kg/day treatment group); **Developmental NOEL** = 25.9 mg/kg/day (based on increased incidence of wavy ribs in the fetuses of the 94.1 mg/kg/day treatment group); Study **acceptable**. (Moore, 4/19/93)

#### TERATOLOGY, RABBIT

\*\* 018; 119484; Embryotoxicity Study (including Teratogenicity) with NTN 33893 Technical in the Rabbit, (Authors: H. Becker, K. Biederman); 833; Rabbit; RCC, Research and Consulting Company AG, CH 4452 Itingen, Switzerland; Study No. 98572; 1/8/92; 16 females/group; Doses: 0, 7.0, 20.5, 64.3

mg/kg/day (analytical), doses administered by gavage from day 6 post coitum through day 18; Mortality: 0 (0/16), 7.0 (0/16), 20.5 (0/16), 64.3 (2/16); Clinical observations: reduced food consumption, body weight loss day 6 to 19, one abortion (64.3 mg/kg/day), reduced body weight gain day 6 to 19 (20.5 mg/kg/day); Necropsy: no treatment-related lesions; Developmental: one abortion, two total resorptions, increased post-implantation loss, reduced mean fetal weight (64.3 mg/kg/day); **no adverse effects**; **Maternal NOEL** = 20.5 mg/kg/day (based on mortality of dams, decreased body weight gain for 64.3 mg/kg/day treatment group); **Developmental NOEL** = 20.5 mg/kg/day (based on increased post-implantation loss, decreased fetal weight of the offspring in the 64.3 mg/kg/day treatment group); Study **acceptable**. (Moore, 4/16/93).

## GENE MUTATION

\*\*51950-020; 119497; mutagenicity; 842; "NTN 33893; Reverse Mutation Assay (~7Salmonella typhimurium and Escherichia coli~1)"; author, M. Watanabe; Nihon Tokushu Noyaku Seizo K.K., Basic Research Division, Hino Institute, Toxicological Research Laboratory, Japan; 1/17/91; report #101276; Imidacloprid Technical (NTN 33893; 93.7% purity); doses (+/- S9 microsomes): 312.5, 1250, 2500, & 5000 mg/plate, triplicate cultures, 2 independent trials; ~7S. typhimurium~1 tester strains TA98, 100, 1535, & 1537 and ~7E. coli~1 strain WP2/uvrA; positive controls +/- S9 were successful in all instances; 48 hr exposure; **no adverse effects**: there was no evidence for mutagenicity (~7i.e.~1 an increase in revertants arising in low-histidine or low typtophan medium) in any tester strain, regardless of the presence or absence S9 activating microsomes; **Acceptable**. (Rubin, 4/8/93)

\*\*51950-020; 119498; mutagenicity; 842; "NTN 33893; Mutagenicity Study for the Detection of Induced Forward Mutations in the CHO-HGPRT Assay" author, H. Lehn; Bayer AG, Institute of Toxicology, FRG; 1/6/89; report #98584; Imidacloprid Technical (NTN 33893; 95.2% purity); doses ranged between 0-125 mg/ml in the absence of S9 activating microsomes and between 0-1222 mg/ml in the presence of S9; 5 hr exposure; cytotoxicity was evident directly after treatment with 70 and 80 mg/ml test article, +/- S9, respectively; **no adverse effects**: no increase in 6-thioguanine resistance was measured under any condition, thus NTN 33893 is not considered mutagenic in this system; **Acceptable**. (Rubin, 4/8/93)

\*\* 51950-020; 119499; mutagenicity; 842; "NTN 33893; Salmonella/Microsome Test to Evaluate for Point Mutagenic Effects"; Bayer AG, Institute of Toxicology, FRG; author, B.A. Herbold; 1/6/89; report #98570; Imidacloprid Technical (NTN 33893; 95.0% purity); ~7S. typhimurium~1 strains TA 98, TA 100, TA 1535, & TA 1537; doses, Test #1 (+/- 30% S9): 0, 20, 100, 500, 2500, & 12,500 mg/plate; Test #2 (-S9, +10% S9, & +30% S9): 0, 775, 1550, 3100, 6200, & 12,400 mg/plate; slight cytotoxicity at high dose based on titer determinations in high-histidine agar; **no adverse effects**: no evidence for mutagenicity (~7i.e.~1 an increase in revertants arising in low-histidine agar) in any tester strain, regardless of the presence or absence S9 microsomes and despite the success of the positive control compounds; **Acceptable**. (Rubin, 4/14/93)

## CHROMOSOME EFFECTS

\*\* 51950-020; 119500; structural chromosome aberration; 843; Chinese hamsters; "NTN 33893; In Vivo Cytogenetic Study of the Bone Marrow in Chinese Hamster to Evaluate for Induced Clastogenic Effects"; Bayer AG, Institute of Toxicology, FRG; author, B.A. Herbold; 11/24/89; report #100021; Imidacloprid Technical (NTN 33893; 94.6% purity); dose: 2000 mg/kg body wt., administered by gavage as a suspension in 0.5% aqueous Cremophor (10 ml/kg); positive control: 30 mg/kg cyclophosphamide;

animals sacrificed at 6, 24, & 48 hr post dose (positive & negative controls were sacrificed at 24 hr only); 5/sex/sacrifice group; deaths: 4/34 animals treated with test article from acute toxicity; no variations of biological significance were seen in chromosomal integrity among all treatment groups and negative controls; positive controls exhibited large increases in % metaphases with aberrations; **no adverse effects:** NTN 33893 is not clastogenic in this assay under the conditions tested; **Acceptable.** (Rubin, 4/15/93)

\*\* 51950-020; 119501; structural chromosome aberration; 843; "NTN 33893; In Vitro Cytogenetic Study with Human Lymphocytes for the Detection of Induced Clastogenic Effects"; Bayer AG, Institute of Toxicology, FRG; author, B.A. Herbold; 6/16/89; report #99262; Imidacloprid Technical (NTN 33893; 95.2% and 99.8% purity, 1st & 2nd expts., respectively); cells freshly isolated from 1 male & 1 female volunteer; doses (-/+ S9 microsomes), Expt. #1: 0, 50, 500, & 5000 mg/ml; Expt. #2: 0, 1300, 2600, & 5200 mg/ml; cytotoxicity, indicated by a decline in mitotic index, was most prominent w/o S9 (declines to 64% of control @ 500 mg/ml in Expt. #1 and 41.4% of control @ 1300 mg/ml in Expt. #2) and was only weakly apparent w/S9; clastogenesis, indicated mainly by the appearance of chromosomal gaps & breaks, was also most prominent w/o S9 (metaphases w/aberrations excluding gaps increased from 3.0% in controls to 14% @ 5000 mg/ml w/no effect @ 50 & 500 mg/ml in Expt. #1 and from 2.0% to 10.0 and 28.0% @ 1300 & 2600 mg/ml in Expt. #2); only weak clastogenic effects seen in the presence of S9; **possible adverse effects:** NTN 33893 is clastogenic in this assay under the conditions tested; **Acceptable.** (Rubin, 4/16/93)

\*\* 51950-020; 119503; structural chromosome aberration; 843; Mouse; "NTN 33893; Micronucleus Test on the Mouse to Evaluate for Clastogenic Effects"; author, B.A. Herbold; Bayer AG, Institute of Toxicology, FRG; 6/27/88; report #102652; Imidacloprid Technical (NTN 33893; 95.3% purity); dose: 80 mg/kg body wt., administered by gavage as a suspension in 0.5% aqueous Cremophor (10 ml/kg); positive control: 20 mg/kg cyclophosphamide; animals sacrificed 24, 48, & 72 hr post dose; 5/sex/sacrifice group; **no adverse effects:** no test article-induced statistically significant increase over negative controls was observed in the number of micronucleated polychromatic or normochromatic cells despite the success of the positive controls; no statistically significant alterations occurred in the ratio of polychromatic to normochromatic cells; **Acceptable.** (Rubin, 4/19/93)

\*\* 51950-020; 119504; structural chromosome aberration; 843; Mouse; "Mouse Germ-Cell Cytogenetic Assay with NTN 33893"; author, W. Volkner; Cytotest Cell Research GmbH & Co. KG, In den Leppsteinswiesen 19, Robdorf, FRG; 5/22/90; report #102654; Imidacloprid Technical (NTN 33893; 94.1% purity); dose: 80 mg/kg body wt., administered by gavage as a suspension in 0.5% aqueous Cremophor (10 ml/kg); positive control: 10 mg/kg doxorubicin sulfate HCl dosed in saline; animals sacrificed 6, 24, & 48 hr post dose; 6/males/sacrifice group (only 5 were evaluated); spermatogonia were isolated from both testes and prepared on slides; despite a successful positive control, the test article failed to induce any biologically relevant increase in spermatogonial chromosome aberrations; neither the positive control nor the test article had an effect on mitotic index; **no adverse effects:** under the conditions tested, NTN 33893 is neither clastogenic nor cytotoxic to mouse spermatogonia; **Acceptable.** (Rubin 4/20/93)

#### DNA DAMAGE

51950-020/158; 119502/128284; other genetic effects; 844; Chinese hamsters; "NTN 33893; Sister Chromatid Exchange in Bone Marrow of Chinese Hamsters In Vivo"; author, B.A. Herbold; 6/16/89



(original), 11/11/93 (supplement); Report #99257-1; Imidacloprid Technical (NTN 33893; 95.0% purity); doses: 0, 500, 1000, & 2000 mg/kg body wt., administered by gavage as a suspension in 0.5% aqueous Cremophor (10 ml/kg b.w.); positive control: 10 mg/kg cyclophosphamide (CP); animals sacrificed 24 hr post dose, 2 hr after colcemid treatment to arrest cells in metaphase; 5/sex/dose (50 metaphases/animal analyzed for SCE); marrow preparations made from the femur; no deaths; no toxic clinical signs; cytotoxicity was present at 1000 and 2000 mg/kg (mitotic index declined at both doses to 83.3% of controls); no change in proportion of cells in 1st, 2nd, & 3rd metaphases indicating no effect on cell cycling; sister chromatid exchange rate was also unaffected (SCE mean rate per metaphase was 2.01, 2.17, 2.28, & 2.41 for 0, 500, 1000, & 2000 mg/kg, respectively) despite successful positive control (SCE rate was 15.27 for 10 mg/kg CP,  $p < .01$ ); **Acceptable.** (Rubin, 4/19/93; revised from unacceptable with submission of individual animal data by Rubin, 3/8/94)

\*\* 51950-020; 119505; other genetic effects; 844; "Clastogenic Evaluation of NTN 33893 in an In Vitro Cytogenetic Assay Measuring Sister Chromatid Exchange in Chinese Hamster Ovary (CHO) Cells"; author, R.D.F.M. Taalman; Hazleton Biotechnologies, Landjuweel, Veenendaal, The Netherlands; 4/21/88; report #102655; Imidacloprid Technical (NTN 33893); 95.2% purity; doses, -S9, Trial I: 16.7, 50, 166.7, & 500 mg/ml; Trial II: 100, 250, 500, & 1000 mg/ml; +S9, Trial I: 166.7 & 500 mg/ml and 1.7 & 5.0 mg/ml; Trial III: 500 mg/ml and 1, 2, & 3 mg/ml; Trial II/-S9 and Trial III/+S9 gave results indicating a dose-dependent rise in SCE/diploid cell (4, 44, 56, & 96% over solvent control for Trial II/-S9 and 0, 8, 28, & 70% over solvent control for Trial III/+S9); cytotoxicity was present at concentrations above (and including) 500 mg/ml -S9 and at 3 mg/ml +S9; **possible adverse effects:** NTN 33893 induces SCE in CHO cells in the absence and presence of S9 under the conditions tested; **Acceptable.** (Rubin 4/21/93)

\*\* 51950-020; 119506; other genetic effects; 844; "Sister Chromatid Exchange Assay in Chinese Hamster Ovary Cells"; author, D.L. Putnam & M.J. Morris; Microbiological Associates, Inc., Rockville, MD; 9/12/89; report #99676; Imidacloprid Technical (NTN 33893); 95.2% purity; doses, -S9: 25, 50, 100, 200, & 400 mg/ml; +S9: 157, 313, 625, & 1250 mg/ml; **no adverse effects:** no evidence for induction of SCE in the presence or absence S9 in this system despite cytotoxicity present at each dose tested; **Acceptable.** (Rubin 4/21/93)

\*\* 51950-020; 119507; other genetic effects; 844; ~7Bacillus subtilis~1; "NTN 33893; Rec-assay with Spores in the Bacterial System"; author, M. Watanabe; Nihon Tokushu Noyaku Seizo K.K., Basic Research Division, Hino Institute, Toxicological Research Laboratory, Japan; 6/18/90; report #101275; Imidacloprid Technical (NTN 33893; 94.7% purity; doses (-/+ S9): 312.5, 625, 1250, 2500, 5000 mg/disk; positive controls, mitomycin C (-S9) and 2-aminoanthracene (+S9) successfully generated large differences in growth inhibition zone between the Rec+ and Rec- ~7B. subtilis~1 strains H17 and M45, respectively, indicating a positive gene damaging effect; **no adverse effects:** no test article-induced differences were observed in growth inhibition zones between the 2 strains, thus no damage occurred which a Rec+ DNA repair system might have remedied; **Acceptable.** (Rubin 4/22/93)

\*\* 51950-020; 119508; other genetic effects; 844; "Mutagenicity test on NTN 33893 in the Rat Primary Hepatocyte Unscheduled DNA Synthesis [UDS] Assay"; (author, M.A. Cifone; Hazleton Laboratories America, Inc., Kensington, MD, report #98573, 12/21/88); Imidacloprid Technical (NTN 33893); 95.2% purity; 5 trials, cells isolated from each of 2 rats/trial; Trials 1, 2, & 4 were non-functional; doses, Trial 3: 5 (Rat #2 only), 10, 25, 50, 100, 250, & 500 mg/ml; doses, Trial 5: 50, 100, 250, 375, 500, 750 mg/ml; higher concentrations not analyzed because of excessive toxicity; UDS assessed by

autoradiographic determination of 3H-thymidine incorporation; criteria for positive UDS response (net nuclear grain count more than 6 above negative controls, % nuclei w/≥ 6 grains was at least 10% of the population more than controls, % nuclei w/≥ 20 grains exceeds 2% of the population) not fulfilled at any dose (the positive control, 2-acetyl aminofluorene, was successful); however; there was evidence for a weakly positive response at high doses; **no adverse effects; Acceptable.** (Rubin 4/23/93)

\*\* 51950-020; 119509; other genetic effects; 844; "NTN 33893; Test on ~7S. cerevisiae D7~1 to Evaluate for Induction of Mitotic Recombination"; author, B.A. Herbold; Bayer AG, Institute of Toxicology, FRG; 6/27/88; report #102653; Imidacloprid Technical (NTN 33893); 95.3% purity; 2 trials; single test tube/dose replated onto 10 plates in complete agar medium to detect mitotic crossing over by colony color or in tryptophan-deficient agar to detect mitotic gene conversion; doses: 0, 625, 1250, 2500, 5000, 10000 mg/ml; positive controls: -S9, methyl methane sulfonate; +S9, cyclophosphamide; **no adverse effects:** since there were no changes in the numbers of red or pink colonies or in the ability to grow in tryptophan-deficient medium as compared to negative controls, there was no evidence of the occurrence of recombination events, either in the form of crossing over or gene conversion; positive controls stimulated both types of recombination; **Acceptable.** (Rubin 4/26/93)

#### ACUTE NEUROTOXICITY

51950-0472, -0473; 209391, 209392; "An Acute Oral Neurotoxicity Screening Study with Technical Grade Imidacloprid (NTN 33983) in Rats"; (L.P. Sheets; Miles Inc., Agriculture Division, Toxicology, Stilwell, KS; Study Nos. 106348, 106348-1; 2/16/94 and 6/7/94); Two acute neurotoxicity studies were performed. In the 1<sup>st</sup> study, eighteen Sprague-Dawley rats/sex/group were dosed orally by gavage with 0, 42, 151 or 307 mg/kg of Imidacloprid Technical (NTN 33893 technical, batch no. 2030030, purity: 98.8% (8/92)). Six animals/sex/group were identified as the satellite animals and used for clinical pathology testing. In the 2<sup>nd</sup> study, 12 females/group were likewise dosed orally with 0 or 20 mg/kg of the test material (same batch no., purity: 98.6% (4/94)). In the 1<sup>st</sup> study, 4 males and 10 females in the 307 mg/kg group died within two days of dosing. In the functional observational battery (FOB) performed 90 minutes after dosing, some of the 307 mg/kg group animals displayed tremors and incoordination in their gait in the home cage and open field tests. In the home cage, some of these animals exhibited greater or less than normal activity levels. In the open field test, the animals were generally more sluggish in their movements. The mean frequency of rearing was also reduced for both sexes of this group (M: NS, F: <0.05). In the reflex/physiologic testing, some of the animals in the high dose had no reaction to touch, auditory or pinch stimuli. For the 151 mg/kg group females, one of the 12 animals exhibited tremors in the FOB on Day 0. Mean hindlimb strength was lower for the 307 mg/kg males on Day 0. Mean motor and locomotor activities for both sexes in the 151 and 307 mg/kg groups were lower than those of the control on Day 0. Although some of the values for the hematological and clinical chemical parameters in the 307 mg/kg group were significantly different from those of the control, these differences were not considered to be toxicologically relevant. In the necropsy examination, the mean absolute brain weight for the 307 mg/kg males was less than that of the control (p<0.05), the relative weights were not significantly different. No treatment-related effects were noted in the 2<sup>nd</sup> study. **Possible adverse effect:** tremors and other signs of neurotoxicity; **NOEL (M/F):** 42 mg/kg (based upon the decreased motor and locomotor activity levels and presence of tremors in the 151 mg/kg treatment group); **Study acceptable.** (Moore, 3/3/04)

#### SUBCHRONIC NEUROTOXICITY

51950-0471; 209390; "A Subchronic Dietary Neurotoxicity Screening Study with Technical Grade Imidacloprid (NTN 33983) in Fischer 344 Rats"; (L.P. Sheets; Miles Inc., Agriculture Division,

Toxicology, Stilwell, KS; Study No. 106356; 6/13/94); Eighteen Fischer 344 rats/sex/group received 0, 140, 963 or 3027 ppm of Imidacloprid Technical (NTN 33893 technical, batch no. 2030030, purity: 97.6% (3/93)) in the diet for 13 weeks ((M) 0, 9.3, 63.3, 196 mg/kg/day, (F) 0, 10.5, 69.3, 213 mg/kg/day). Six animals/sex/group were used as satellite animals of use in the hematology and clinical chemistry evaluations. No deaths occurred during the study. The mean body weights and food consumption of both sexes in the 963 and 3027 ppm groups were lower than those of the control group ( $p < 0.05$ ). In the Functional Observational Battery (FOB), although the mean hindlimb grip strength of the 3027 ppm males was lower after 8 weeks of treatment ( $p < 0.05$ ) and a greater number of these males had a slightly uncoordinated righting reflex at 13 weeks ( $p < 0.05$ ), these results did not indicate a consistent effect and were considered to be incidental. Otherwise, no other effects were evident in the FOB. In the clinical chemistry evaluation, serum triglyceride concentrations were lower for both sexes in the 3027 ppm group at both 4 and 13 weeks ( $p < 0.05$ ). Mean phosphate levels were reduced for both sexes in the 3027 ppm group at 4 weeks and for the males in that group at 13 weeks ( $p < 0.05$ ). The mean albumin concentrations for the 3027 ppm females were lower than those of the controls at both 4 and 13 weeks ( $p < 0.05$ ). Although the mean values of other parameters for the 3027 ppm group demonstrated an increase or decrease over the values for the controls, the observed effects were not consistent over the course of the study or were doubtful toxicological significance. There were no treatment-related effects evident in the hematology results, the necropsy or the histopathology examinations. No signs of neurotoxicity were noted. **No adverse effect indicated. Subchronic NOEL (M/F):** 140 ppm ((M) 9.3 mg/kg/day, (F) 10.6 mg/kg/day) (based upon lower mean body and food consumption of the 963 ppm group). **Study acceptable.** (Moore, 3/5/04)

#### DEVELOPMENTAL NEUROTOXICITY

51950-0474 209393 Sheets, L. P., "A developmental neurotoxicity screening study with technical grade Imidacloprid in Wistar Rats," Bayer Corp., Stilwell, KS, 9/14/01. Study # 99-D72-DV: Bayer Report No. 110245. Thirty CrI:W(HAN)BR mated females/group were dosed in diet with 0, 100, 250, or 750 ppm imidacloprid (98.2% purity) throughout gestation and lactation (ending lactation day 21). Estimated mean gestation exposures were 8.2, 19, and 57 mg/kg/day. Estimated mean exposures during lactation days 0-14 were 0, 15, 36, and 104 mg/kg/day. At least 21 litters per group were of sufficient size to maintain offspring until sacrifice at about postnatal day (PND) 75. Maternal NOEL = 250 ppm, based on transient reduction in food consumption during lactation days 0-7. Developmental toxicity NOEL cannot be determined because intermediate groups were not evaluated in the presence of a conspicuous change in 750 ppm in morphometric measurements (see below). Most endpoints other than the morphometric measurements were evaluated in intermediate dose levels, and none of these found treatment effects at 250 ppm. Findings at 750 ppm in offspring were reduced mean pup weight (5 g) at PND 21 weaning, reduced motor activity in PND 17 males and females and in PND 21 females, modest reductions in motor and locomotor activities during the first recording interval in PND 60 males (suggesting a slight reduction in exploratory activity in a novel environment), and a substantial reduction in the thickness of the corpus callosum in PND 11 females only (not reflected in PND 75 rats of either sex). Study is not acceptable, and appears not to be upgradeable. The apparent corpus callosum change in 750 ppm females at PND 11 indicates a need to analyze intermediate groups. The statistic procedures for PND 11 morphometric measurements need to be examined. Morphometric measurements should be performed in intermediate groups wherever an effect is statistically significant at 750 ppm. Cited positive control method validation studies contemporary with this study are requested. See discussion of DPR review for details on concerns

about study conduct and report presentation. Other than these issues, this study addressed the full scope of evaluations that pertain to developmental neurotoxicity studies. Aldous, 3/24/04.

## STUDIES ON METABOLITES

1950-025; 119521; 842; mutagenicity; "WAK 3839; Reverse Mutation Assay (~7*Salmonella typhimurium*~1 and ~7*Escherichia coli*~1)"; author: M. Watanabe; Nihon Tokushu Noyaku Seizo K.K., Basic Research Division, Hino Institute, Tox. Research Lab., Japan; 11/26/90; report #100668; WAK 3839, a metabolite of NTN 33893; 98.3% purity; ~7*S. typhimurium*~1 strains TA98, TA100, TA1535, & TA1537, and ~7*E. coli*~1 strain WP2/uvrA; doses (-/+ S9): 312.5, 625, 1250, 2500, & 5000 mg/plate; positive controls were successful; either no effect or very weak effects of test article on revertant frequency were observed; WAK 3839 is not mutagenic in these systems under the conditions tested; **Acceptable.** (Rubin, 4/26/93)

51950-025; 119522; 842; mutagenicity; "WAK 3839; Mutagenicity Study for the Detection of Induced Forward Mutations in the V79-HGPRT Assay In Vitro"; author: H. Lehn; Bayer AG, Department of Toxicology, Wuppertal, FRG; 8/15/89; report #100662; WAK 3839, a metabolite of NTN 33893; 98.9% purity; doses (based on solubility limit and cytotoxicity test): 500, 1000, 1500, 1750, & 2000 mg/ml for both -S9 trials and 1 of 2 +S9 trials; for the other +S9 trial the doses were 500, 750, 1000, 1250, 1500, & 1750 mg/ml; after plating 4 x 10<sup>6</sup> cells/250 ml flask, the cells were exposed to test article (-/+ S9 microsomes) for 5 hr followed by an "expression period" of exponential growth and subsequent replating under selective conditions (10 mg/ml 6-thioguanine) at 3 x 10<sup>5</sup> cells/100 mm dish; after 7 days the colonies were fixed and counted; duplicate exposure dishes were run, each dish generating 8 replicate dishes in the selection condition; test article did not induce 6-thioguanine resistance at any dose despite success of positive controls (-S9, ethyl methane sulfonate; +S9, DMBA); it is not mutagenic in this system under these conditions; **Acceptable.** (Rubin, 4/26/93)

51950-025; 119523; 842; mutagenicity; "WAK 3839; Mutagenicity Study for the Detection of Induced Forward Mutations in the CHO-HGPRT Assay In Vitro"; author: H. Lehn; Bayer AG, Department of Toxicology, Wuppertal, FRG; 2/22/89; report #100661; WAK 3839, a metabolite of NTN 33893; 94.3% purity; doses (based on solubility limit and cytotoxicity test), -S9: 62.5, 125, 250, 500, 1000, & 2000 mg/ml; +S9: 500, 750, 1000, 1250, 1500, & 2000; after plating 4 x 10<sup>6</sup> cells/250 ml flask, the cells were exposed to test article (-/+ S9 microsomes) for 5 hr followed by an "expression period" of exponential growth and subsequent replating under selective conditions (10 mg/ml 6-thioguanine) at 3 x 10<sup>5</sup> cells/100 mm dish; after 7 days the colonies were fixed and counted; duplicate exposure dishes were run, each dish generating 8 replicate dishes in the selection condition; test article did not consistently induce 6-thioguanine resistance at any dose despite success of positive controls (-S9, ethyl methane sulfonate; +S9, DMBA); it is not mutagenic in this system under these conditions; **Acceptable.** (Rubin, 4/27/93)

51950-025; 119524; 843; structural chromosome aberration; "WAK 3839 or NTN37571; Micronucleus Test on the Mouse After Intraperitoneal Injection"; author: B.A. Herbold; Bayer AG, Department of Toxicology, Wuppertal, FRG; 10/3/89; report #100664; WAK 3839 (aka NTN 37571), a metabolite of NTN 33893; 98.9% purity; dose (based on pilot toxicity test): 0 & 50 mg/kg body wt., administered intraperitoneally as a suspension in 0.5% aqueous Cremophor (10 ml/kg); positive control: 20 mg/kg cyclophosphamide (sacrificed @ 24 hr only); animals sacrificed 24, 48, & 72 hr post dose, bone marrow erythroblasts isolated from femur; 5/sex per sacrifice group; no test article-induced increase over

negative controls was observed in the # of micronucleated polychromatic or normochromatic cells despite the success of the positive controls; **Acceptable**. (Rubin, 4/27/93)

51950-025; 119525; 843; structural chromosome aberration; "NTN 37571: Micronucleus Test on the [sic] Mice After I.P. Treatment; Pilot Study"; author: M. Usami; Nihon Tokushu Noyaku Seizo K.K., Basic Research Division, Agricultural Chemicals Institute, Japan; 11/29/88; report #100679; NTN 37571 (aka WAK 3839), a metabolite of NTN 33893; 96.4% purity; doses: 0, 20, 40, & 80 mg/kg body wt., administered intraperitoneally as a suspension in DMSO:olive oil (1:10, 10 ml/kg); positive control: 4 mg/kg mitomycin C; animals sacrificed 30 hr post dose, bone marrow erythroblasts isolated from femur; 5 males/dose; no test article-induced increase over negative controls was observed in the # of micronucleated polychromatic or normochromatic cells despite the success of the positive controls; no change in the polychromatic/normochromatic cell ratio; **Unacceptable** (no females were tested, only a single sampling time was tested, and no individual data were presented). (Rubin, 4/27/93)

51950-025; 119527; 843; structural chromosome aberration; "WAK 3839; Micronucleus Test on the Mouse After Oral Application"; author: B.A. Herbold; Bayer AG, Department of Toxicology, Wuppertal, FRG; 10/3/89; report #100663; WAK 3839, a metabolite of NTN 33893; 98.9% purity; dose (based on pilot toxicity test): 100 mg/kg body wt., administered by gavage as a suspension in 0.5% aqueous Cremophor (10 ml/kg); positive control: 20 mg/kg cyclophosphamide; animals sacrificed 24, 48, & 72 hr post dose, bone marrow erythroblasts isolated from femur; 5/sex per sacrifice group; the 48-hr sacrifice group showed a statistically significant increase over controls in micronucleated polychromatics (2.0/1000 % 0.8 ~7vs~1 0.7/1000 % 0.9 in controls sacrificed at 24 hr,  $p < 0.01$ ) which may be partially accounted for by the abnormally low value of the controls compared to historical controls; slight non-statistically significant increases over negative controls were also observed in the # of micronucleated polychromatic cells in the 24- and 72-hr sacrifice groups; positive controls sacrificed at 24 hr raised the # of micronucleated cells to 16.1 % 7.9 per 1000 polychromatics; there may be a weak effect of the test article on micronucleus formation under these conditions; **Acceptable**. (Rubin, 4/27/93)

51950-025; 119528; 843; structural chromosome aberration; "NTN 37571: Micronucleus Test on the [sic] Mice After Oral Treatment; Pilot Study"; author: M. Usami; Nihon Tokushu Noyaku Seizo K.K., Basic Research Division, Agricultural Chemicals Institute, Japan; 11/29/88; report #100680; NTN 37571 (aka WAK 3839), a metabolite of NTN 33893; 96.4% purity; doses (based on a preliminary toxicity determination): 0, 40, 80, & 160 mg/kg body wt., administered by gavage as a suspension in DMSO:polyethylene glycol 400 (1:5, 10 ml/kg); positive control: 4 mg/kg mitomycin C, injected intraperitoneally; animals sacrificed 30 hr post dose, bone marrow erythroblasts isolated from femur; 5 males/dose; no test article-induced increase over negative controls was observed in the # of micronucleated polychromatics or change in the polychromatic/normochromatic cell ratio despite the success of the positive controls in raising the # of micronucleated polychromatics and lowering the polychromatic/normochromatic ratio; **Unacceptable** (no females were tested, positive controls were not administered by the same route as the test article, only a single sampling time was used, and no individual data were provided). (Rubin, 4/28/93)

51950-025; 119529; 843; structural chromosome aberration; "Chromosome Aberration Assay in Chinese Hamster V79 Cells In Vitro with WAK 3839"; author: A. Heidemann; Cytotest Cell Research GmbH & Co., Robdorf, FRG; 9/27/89; report #100666; 98.8% purity; doses (based on a preliminary cytotoxicity determination and test article solubility), +/- S9: 0.1, 0.3, & 1.0 mg/ml; cultures harvested 7 (high dose only), 18, & 28 (high dose only) hr after start of the 4 hr exposure; positive controls ethyl

methane sulfonate (-S9) and cyclophosphamide (+S9) showed distinct increases in aberrations; despite cytotoxicity of the test article at the mid and high dose indicated by a decline in mitotic index and at the high dose by a decline in plating efficiency (-S9 only), there was no increase in chromosome aberrations; WAK 3839 is not clastogenic in this system under these conditions; **Acceptable**. (Rubin, 4/28/93)

51950-025; 119530; 843; structural chromosome aberration; "NTN 37571: In Vitro Cytogenetic Assay Measuring Chromosome Aberrations in CHO-K1 Cells"; author: M. Usami; Nihon Tokushu Noyaku Seizo K.K., Basic Research Division, Agricultural Chemicals Institute, Japan; 11/5/88; report #100678; NTN 37571 (aka WAK 3839), a metabolite of NTN 33893; purity not reported; doses, +/- S9 (based on preliminary toxicity tests): 0, 0.25, 0.5 & 1 mg/ml; positive controls: -S9, 1 mg/ml N-methyl-N'-nitro-N-nitrosoguanidine; +S9, 0.5 mg/ml dimethylnitrosamine; exposure time: -S9, 24 & 48 hr; +S9, 4 hr; 4 x 10<sup>3</sup> cells/flask seeded (flask size not given), duplicate cultures exposed/condition, test article exposure began 48 hr later; colchicine added 2 hr prior to harvest to arrest cells in metaphase; 50 metaphases examined/flask (100/condition total); possible slight increase in % cells with chromosome aberrations under -S9 condition (control cells @ 48 hr w/aberrations excluding gaps = 1%, exposed cells = 2, 5, & 4%, respectively), but beneath the 10% limit considered by the investigators to be biologically relevant; no increase in +S9 cells; positive controls were successful; **Unacceptable, but may be upgradeable** upon submission of test article purity and size of flask used in assay. (Rubin, 4/29/93)

51950-025; 119531; 844; other genotoxic effects; "Unscheduled DNA Synthesis [UDS] in Primary Hepatocytes of Male Rats In Vitro with WAK 3839"; author: R. Fautz; 4/24/89; report #100665; 98.9% purity; hepatocytes (derived freshly from male animals because female-derived cells purportedly lack certain activating enzymes) seeded at 10<sup>5</sup>/ml in 35 mm culture dishes containing 1-25 mm cover slip; doses (based on a preliminary cytotoxicity determination and test article solubility), Expt. I & II: .04, .13, .44, 1.33, 4.44, 13.33, 44.44, 133.33, 444.44, & 1333.33 mg/ml (last 2 doses Expt. II only); Expt. III: 13.33, 44.44, 133.33, 444.44, & 1333.33 mg/ml; 18 hr exposure; triplicate dishes run at each concentration; positive control: 11.16 mg/ml 2-acetyl aminofluorene; UDS measured by autoradiographic determination of <sup>3</sup>H-thymidine incorporation into DNA; severe cytotoxicity observed only in Expt. I above 133.33 mg/ml (other expts. were negative); no reproducible test article dependent increase in incorporation was observed under any condition despite the consistent success of the positive control; test article does not induce UDS in this system under the conditions tested; **Unacceptable, but possibly upgradeable** with submission of cytotoxicity data. (Rubin, 4/29/93)

**ATTACHMENT V: Peer Review Comments and Response**

## MEMORANDUM

**TO:** Gary T. Patterson, Ph.D., Chief  
Medical Toxicology Branch  
Department of Pesticide Regulation  
1001 I Street, P.O. Box 4015  
Sacramento, California 95812-4015

**FROM:** Anna M. Fan, Ph.D., Chief  
Pesticide and Environmental Toxicology Branch  
Office of Environmental Health Hazard Assessment  
1515 Clay Street, 16<sup>th</sup> Floor  
Oakland, California 94612

**DATE:** September 30, 2005

**SUBJECT:** COMMENTS AND RECOMMENDATIONS REGARDING THE DRAFT RISK CHARACTERIZATION DOCUMENT FOR THE ACTIVE INGREDIENT IMIDACLOPRID

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Thank you for the opportunity to review the draft risk characterization (RCD) document for imidacloprid dated May 5, 2005, prepared by the Department of Pesticide Regulation (DPR). The Office of Environmental Health Hazard Assessment (OEHHA) reviews risk assessments prepared by DPR under the general authority of California Health and Safety Code (HSC) Section 59004, and also under Food and Agricultural Code (FAC) Section 13129, in which OEHHA provides advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticide active ingredients.

In addition, pursuant to Food and Agricultural Code sections 14022 and 14023, OEHHA provides review, consultation and comments to DPR on the evaluation of the health effects of candidate toxic air contaminants (TAC) included in the TAC documents. As part of its statutory responsibility, OEHHA also prepares findings on the health effects of the candidate toxic air contaminants. This documentation is to be included as part of the DPR report.

This draft RCD evaluates solely dietary exposure to imidacloprid. As stated in the cover letter, the risks from occupational and residential exposures will be included as an addendum to this RCD once the exposure assessment document (EAD) is completed. Additionally, since it is stated in the text of the document that exposures from imidacloprid in ambient air will also subsequently be evaluated, we are assuming that this active ingredient is also a candidate TAC.



Overall, we find the document thorough and well written. Generally, we find the assumptions, considerations and conclusions contained in the RCD appropriate, scientifically defensible and sufficiently supported. OEHHA does have a major concern, however, that the acute regulatory level used to evaluate dietary risks from imidacloprid exposure may not be sufficiently health-protective. This concern and other suggestions and recommendations are outlined below. We hope that you find our comments and recommendations supportive and useful.

Imidacloprid is a neonicotinoid insecticide that is registered to control pests on agricultural and nursery crops, structural pests, and parasites on companion animals. The material is a nicotinic receptor agonist and is structurally and functionally related to nicotine. Imidacloprid is representative of the “new generation” of neurotoxic insecticides that are more selectively toxic to insects than to mammals, in comparison to the more classic neurotoxins.

Our comments on the draft RCD are as follows:

1. Acute oral exposure to imidacloprid is evaluated in the draft RCD using the results from an acute neurotoxicity study in rats (Sheets, 1994). From this study, a no-observed-adverse-effect-level (NOAEL) of 42 mg/kg is identified based on a decrease in motor and locomotor activity in females at the next higher dose of 151 mg/kg versus the controls. The effect on motor and locomotor activity was dose-related and was observed at all doses in the study (42, 151 and 307 mg/kg). Even though the decrease in motor and locomotor activity was not statistically significant versus the controls at the lowest dose tested, since a dose-related trend was observed, a benchmark dose (BMD) analysis of the dataset was conducted and a LED<sub>05</sub> (lower bound on the 5% BMD response) of 9 mg/kg was derived and was used to evaluate risk in the RCD. OEHHA supports the use of BMD methodology in establishing an acute regulatory level from this dataset.

An estimated NOAEL (NOAEL-est) of 5.5 mg/kg-day was derived from a LOAEL of 54.7 mg/kg in a rat developmental neurotoxicity (DNT) study (Sheets, 2001). The LOAEL was based on a statistically significant decrease in the widths of the caudate putamen and thickness of the corpus callosum in female offspring of dams exposed to the highest dose tested, 54.7 mg/kg-day, from gestation day zero (GD 0) to GD 20 versus that observed in the controls. BMD analysis of the dataset was not possible since brain measurements were not made in the pups from the other two dose levels in the study (8 and 19 mg/kg-day).

The regulatory value of 9 mg/kg was selected for evaluating acute exposures to imidacloprid since it was based on a BMD analysis of a dataset that showed a clear dose-response and was from a high-quality study with comprehensive evaluations (clinical observations, functional observational battery, motor activity, neuropathology, etc.) of a

relatively large number of animals (18) per dose level. In addition, the LED<sub>05</sub> is supported by a NOAEL of 10 mg/kg observed in a mouse study that was based on apathy, decreased motility, labored breathing, staggering gait and trembling at the next higher dose of 71 mg/kg. In contrast, considerable uncertainty is associated with the NOAEL-est of 5.5 mg/kg-day from the rat developmental neurotoxicity study since it was an estimated NOAEL from only one data point, the LOAEL. Because of these considerations, the value of 9 mg/kg was selected as the regulatory value for acute oral exposures to imidacloprid.

While we agree that there is less uncertainty associated with the chosen regulatory value of 9 mg/kg versus the NOAEL-est of 5.5 mg/kg, we note that the latter study (Sheets, 2001) is well conducted, utilized sufficient numbers of animals (16 dose/sex) and is deficient only in the sense that brain measurements were not made on the animals at the intermediate doses. The results from this study are particularly and uniquely useful since this is the only study with imidacloprid where these measurements were taken and this effect observed. Indeed, it appears that the authors of the RCD deem the study to be useful and of acceptable quality since it is suggested in the RCD (page 58) that the estimated NOAEL may be applied to assessing imidacloprid risk to women of childbearing age, although the RCD stops short of officially doing so. OEHHA agrees with DPR that this study is of sufficient quality to use for regulatory purposes. Further, we are concerned that the chosen regulatory value is insufficiently protective against developmental effects and/or effects on adults possible at lower doses of imidacloprid. As pointed out in the RCD, there is at least a hypothetical mechanistic link between decreases in the widths of the caudate putamen and corpus callosum and decreases in motor/locomotor activity such as that observed in adult female rats exposed to imidacloprid, implying that the effect may not be limited to *in utero* exposure and that adult animals may be susceptible as well.

Accordingly, OEHHA is concerned that a number of issues regarding the adoption of the acute regulatory level for imidacloprid are left unresolved in the RCD and recommends additional discussion be added to the document. First, are the effects of imidacloprid on the dimensions of specific brain structures solely a developmental effect or, as suggested in the RCD, are they more general and applicable to adults as well? If these effects are applicable to more mature animals, are they responsible for or related to the observed reduction in motor activity observed in female rats? Lastly, what regulatory level would likely protect against the effect of imidacloprid on brain dimensions? These issues should be resolved and or discussed in more detail in subsequent versions of the RCD. Suggested approaches to more satisfactorily address these issues are offered below:

**Adopt the LED<sub>10</sub> of 9 mg/kg for all population groups.** In other words, keep the document essentially the same as it is. While we strongly support and encourage the

application of BMD approaches to determining regulatory values where appropriate, in this case the LOAEL/NOAEL approach gives a slightly lower (more health-protective) value. This results in a quandary, pitting a lower number based on a legitimate toxic endpoint against a statistically superior approach. Both approaches have merit. However, it seems to us that a better rationale is needed to choose the less-health-protective approach. Therefore, if the RCD remains essentially unchanged, we recommend additional discussion be added to the document specifically addressing how adoption of this numerical value will protect adults if the effects of imidacloprid observed in the DNT study are applicable to this age-group.

**Adopt the LED<sub>10</sub> of 9 mg/kg for all population groups except women of childbearing age.** Similar to the above, with the exception of officially adopting the estimated NOAEL of 5.5 mg/kg-day for this specific population sub-group and calculating margins of exposure instead of merely mentioning it in the text of the document. If this approach is taken, justification in addition to that recommended above should be added to the RCD, in support of use of the lower regulatory value for only this sex/age-group.

**Adopt the estimated NOAEL of 5.5 mg/kg-day for all population groups.** Again, although OEHHA strongly supports the use of BMD methodology, adopting the estimated NOAEL is the most health-protective option and is a reasonable approach considering the uncertainty discussed above. If this option is chosen, we recommend additional discussion be added to the document clarifying and strengthening the possible link between the effects of imidacloprid on brain dimensions with decreases in motor activity in adult animals.

Although the third option is preferred by OEHHA, all three of these potential options, assuming appropriate and sufficient justification, address the currently unresolved issues and, therefore, we could support any one of these approaches in the final version of the RCD.

2. If an acute regulatory value of 5.5 mg/kg were adopted, MOEs for acute exposures would be reduced by nearly 40%. MOEs for acute dietary exposures (99<sup>th</sup> percentile point estimates, tier 2) would range from 71 for children 1-2 years of age to 239 for females 13 – 39 years of age. The MOE for children would, therefore, reflect an exposure level of concern for this population subgroup. OEHHA recommends that a more refined exposure analysis and risk evaluation be performed in order to determine if exposure mitigation measures are necessary. See also comment number 3, below.
3. Refined exposure analyses such as Monte Carlo analysis were not performed in this RCD because of a lack of residue data. In light of the low MOEs estimated in the RCD and even lower MOEs if the recommended acute regulatory value of 5.5 mg/kg is adopted,

OEHHA recommends that additional residue data be generated and collected and a more refined exposure analysis be performed so that the actual risks from dietary exposure to imidacloprid may be better characterized.

4. Chronic dietary exposure to imidacloprid is evaluated in the RCD using a NOAEL of 5.7 mg/kg-day based on a statistically significant increased incidence and severity of mineralized particles in the thyroids of male rats at the next higher dose of 25 mg/kg versus the controls (Eiben and Kaliner, 1991). In the risk appraisal section of the document (page 88), it is stated that this value (5.7 mg/kg-day) “was sufficiently close to the estimated-no-effect-level of 5.5 mg/kg-day for developmental toxicity, and therefore, would be adequate for protection against the potential effects of imidacloprid on the developing nervous system.” Since chronic exposure is normalized over extended periods of time, typically years, it is expected that “spikes” of relatively high exposure exceeding the normalized daily dose occur during the chronic time frame, which would constitute a significant acute exposure. Accordingly, OEHHA is unsure how evaluating chronic exposures with a NOAEL that is essentially equivalent to an acute NOAEL would protect against the acute effects associated with that NOAEL. We recommend that additional discussion be added to the RCD to clarify this concept.
5. In the cover memorandum and in the body of the RCD it is stated, “this document pertains to the assessment of dietary and drinking water exposures.” No drinking water exposure or risk assessment is found in the current version of the RCD. OEHHA recommends correcting this inconsistency.
6. A number of typographical and grammatical errors are found in the RCD. Most notable is the incorrect use of the word principle (should be principal). We recommend that the document be thoroughly proofread and spellchecked.

Again, thank you for the opportunity to review this document and we hope that you find our comments useful. Should you have any questions regarding OEHHA’s review of this RCD, please contact Dr. David Rice at (916) 324-1277 (primary reviewer), Mr. Robert Schlag at (916) 323-2624, or me at (510) 622-3165.

cc: See next page

Gary T. Patterson, Ph.D., Chief  
September 30, 2005  
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cc: Val F. Siebal  
Chief Deputy Director  
Office of Environmental Health Hazard Assessment

George V. Alexeeff, Ph.D., D.A.B.T.  
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Gary T. Patterson, Ph.D., Chief  
September 30, 2005  
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Mary-Ann Warmerdam  
Director

MEMORANDUM

TO: Anna M. Fan, Ph.D., Chief, Pesticide and Environmental Toxicology Section, OEHHA

FROM: Gary T. Patterson, Ph.D., Chief, Medical Toxicology Branch, DPR

DATE: February 9, 2006

SUBJECT: Response to OEHHA Comments to the Risk Characterization Document for Imidacloprid

---

Thank you for the comments on our draft risk characterization document (RCD) for imidacloprid. The following is our response:

OEHHA: Comment No.1:

*We are concerned that the chosen regulatory value for acute oral exposures to imidacloprid is insufficiently protective against developmental effects and/or effects on adults possible at lower doses of imidacloprid. As pointed out in the RCD, there is at least a hypothetical mechanistic link between decreases in the widths of the caudate putamen and corpus callosum and decreases in motor/locomotor activity such as that observed in adult female rats exposed to imidacloprid, implying that the effect may not be limited to in utero exposure and that adult animals may be susceptible as well.*

*Accordingly, OEHHA is concerned that a number of issues regarding the adoption of the acute regulatory level for imidacloprid are left unresolved in the RCD and recommends additional discussion be added to the document. First, are the effects of imidacloprid on the dimensions of specific brain structures solely a developmental effect or, as suggested in the RCD, are they more general and applicable to adults as well? If these effects are applicable to more mature animals, are they responsible for or related to the observed reduction in motor activity observed in female rats? Lastly, what regulatory level would likely protect against the effect of imidacloprid on brain dimensions? These issues should be resolved and or discussed in more detail in subsequent versions of the RCD. Suggested approaches to more satisfactorily address these issues are offered below:*

***Adopt the LED05 of 9 mg/kg/day for all population groups.***

***Adopt the LED05 of 9 mg/kg/day for all population groups except women of childbearing age.***

***Adopt the estimated NOAEL of 5.5 for all population groups.***

*Although the third option is preferred by OEHHA, all three of these potential options, assuming appropriate and sufficient justification, address the currently unresolved issues and, therefore, we could support any one of these approaches in the final version of the RCD.*

DPR. It was stated in the RCD that the NOEL of 9 mg/kg/day was used to address the acute exposures to imidacloprid for all of the evaluated population subgroups. In addition, the acute MOE for women of childbearing age was estimated with the ENEL of 5.5 mg/kg/day, based on the presupposition that decreases in brain structures could theoretically result from a single exposure *in utero* (See Conclusions in Sections I.F. under Summary; Section IV.A.2a. under Risk Assessment and Section IV.C.2.1. under Risk Characterization). Hence, the second approach suggested by OEHHA was already used in the RCD.

As a response to OEHHA comments, Table 21 was modified accordingly and the following sentence was added for clarification in Section I.C. under Summary:

“Two acute oral NOELs (No-Observed-Effect Level) were used to address the acute dietary exposure to imidacloprid. The NOEL of 9 mg/kg/day was utilized in estimating the risk for acute dietary exposure to imidacloprid to the general population. The NOEL for developmental neurotoxicity in rats was 5.5 mg/kg/day, based on significant decreases in the dimensions of brain structures in PND 11 pups. This NOEL was estimated from the LOEL (ENEL) by applying a 10-fold default factor. The ENEL of 5.5 mg/kg/day was pertinent to acute exposures to imidacloprid in women of childbearing age to protect against fetal exposure”.

With regard to the hypothetical mechanistic link between decreases in the widths of the caudate putamen and corpus callosum and decreases in motor/locomotor activity, it should be emphasized that this link was proposed only in the context of the DNT study. Theoretically, *in utero* exposure to a single dose of imidacloprid at a critical time for brain development could result in decreases in the aforementioned brain structures. Since these brain structures are known to be involved in motor functioning, a potential link to the decreased motor activity in the PND 17 female pups should not be dismissed. However, an assumption that a single exposure to imidacloprid of adult rats would cause significant decreases in the brain structures leading to a decreased motor activity 2.5 hours after treatment (as in the acute neurotoxicity study, Sheets 1994) would be highly speculative. Consequently, no further discussion was added with respect to a link between brain effects and decreased motor activity in adult rats treated with imidacloprid.

As a response to OEHHA comments, the following sentence in Section III.I. under Developmental Neurotoxicity was modified for clarification:

“In this respect, a possible link between the decrease in the caudate putamen and the corpus callosum widths in the PND 11 females exposed *in utero* to imidacloprid and the



decrease in the motor/locomotor activity in these animals at PND17 should not be dismissed without further investigation”.

In addition, the following sentence that was related to the NOEL from the acute neurotoxicity study was deleted from section V.B.1.under Risk Appraisal.

“Finally, data from the developmental neurotoxicity study suggested that the decrease in the motor/locomotor activity in the female rats may be related to changes in dimensions of brain areas, which control motor functioning and voluntary motion (Sheets, 2001); see Section III.I. DEVELOPMENTAL NEUROTOXICITY.”

OEHHA: Comment No.2:

*If an acute regulatory value of 5.5 mg/kg were adopted, MOEs for acute exposures would be reduced by nearly 40%. MOEs for acute dietary exposures (99<sup>th</sup> percentile point estimates, tier 2) would range from 71 for children 1-2 years of age to 239 for females 13 – 39 years of age. The MOE for children would, therefore, reflect an exposure level of concern for this population subgroup. OEHHA recommends that a more refined exposure analysis and risk evaluation be performed in order to determine if exposure mitigation measures are necessary. See also comment number 3, below.*

DPR. In the RCD, the ENEL of 5.5 mg/kg/day was used to estimate only the acute MOEs for women of childbearing age. These MOEs were 366 and 239 at the 95<sup>th</sup> and 99<sup>th</sup> percentiles, respectively; and thus exceeded the general health protective benchmark MOE of 100. With regard to a more refined dietary exposure assessment, such analysis could not be performed at this time due to a lack of sufficient residue data. A lengthy discussion on the imidacloprid residue database was presented in various sections of the RCD (see Sections IV.B.2.4. and IV.B.2.5. under Exposure Assessment and V.C.1.a. and b. under Risk Appraisal; see also Tables 17 and 18).

OEHHA: Comment No.3:

*Refined exposure analyses such as Monte Carlo analysis were not performed in this RCD because of a lack of residue data. In light of the low MOEs estimated in the RCD and even lower MOEs if the recommended acute regulatory value of 5.5 mg/kg is adopted, OEHHA recommends that additional residue data be generated and collected and a more refined exposure analysis be performed so that the actual risks from dietary exposure to imidacloprid may be better characterized.*

DPR. It was clearly stated in the RCD that quality monitoring residue data would be required for a comprehensive dietary risk assessment and that dietary exposure would be refined when residue data become available (see Sections V.C.1.a. and V.C.1b. under Risk Appraisal). The RCD stated that a Monte Carlo analysis was performed, but was not presented because the high-end exposures were not significantly different from the point estimate exposure (see last two paragraphs in Section IV.B.2.5. under Exposure Assessment).

OEHHA: Comment No.4:

*Chronic dietary exposure to imidacloprid is evaluated in the RCD using a NOAEL of 5.7 mg/kg/day based on a statistically significant increased incidence and severity of mineralized particles in the thyroids of male rats at the next higher dose of 25 mg/kg versus the controls (Eiben and Kaliner, 1991). In the risk appraisal section of the document (page 88), it is stated that this value (5.7 mg/kg-day) “was sufficiently close to the estimated-no-effect-level of 5.5 mg/kg-day for developmental toxicity, and therefore, would be adequate for protection against the potential effects of imidacloprid on the developing nervous system.” Since chronic exposure is normalized over extended periods of time, typically years, it is expected that “spikes” of relatively high exposure exceeding the normalized daily dose occur during the chronic time frame, which would constitute a significant acute exposure. Accordingly, OEHHA is unsure how evaluating chronic exposures with a NOAEL that is essentially equivalent to an acute NOAEL would protect against the acute effects associated with that NOAEL. We recommend that additional discussion be added to the RCD to clarify this concept.*

DPR. While the ENEL of 5.5 mg/kg/day was used for acute exposures in women of childbearing age, it was clearly indicated that this ENEL was not only applicable to a single day exposures (see last two paragraphs in Section III.I. under Developmental Neurotoxicity; and Section I.d. under Summary). The ENEL of 5.5 mg/kg/day was pertinent to repeated (subchronic or chronic) exposures to all population subgroups, because the brain effects in the pups were observed following a total of 32 doses of imidacloprid to the dams (21 doses in utero and 11 doses during lactation). The chronic NOEL of 5.7 mg/kg/day for thyroid effects in rats was nearly the same as the 32-day ENEL for developmental neurotoxicity. Consequently, the RCD concluded that the chronic NOEL of 5.7 mg/kg/day would be adequate for protection against potential developmental effects of imidacloprid.

OEHHA: Comment No.5:

*In the cover memorandum and in the body of the RCD it is stated, “this document pertains to the assessment of dietary and drinking water exposures.” No drinking water exposure or risk assessment is found in the current version of the RCD. OEHHA recommends correcting this inconsistency.*

DPR. The exposure to imidacloprid from drinking water was assessed in the RCD based on residue data from the PDP (see Sections I.C. under Summary; IV. B.2.4. under Exposure Assessment; V.E.2. under Issues Related to the Food Quality Protection Act). The residue level of 15 ppt (see Table 17) was entered in the DEEM™ program to calculate the combined dietary exposure from food and drinking water. As a response to OEHHA comments, the heading “Dietary Exposure” wherever it appears, has been modified to “Dietary and Drinking Water Exposure” for clarification.

OEHHA: Comment No.5:

*A number of typographical and grammatical errors are found in the RCD. Most notable is the incorrect use of the word principle (should be principal). We recommend that the document be thoroughly proofread and spellchecked.*

DPR. Typographical and grammatical errors were corrected.

Note: In addition to the revisions made in the RCD in response to comments from OEHHA and Bayer CropScience, the dietary sections have been modified to include acute exposures at the 95<sup>th</sup> percentile instead of 97.5<sup>th</sup> percentile. The revised RCD presents the exposures at the 99<sup>th</sup> percentile as well, as in the draft of May 5, 2005. This addition has no impact on the risk assessment per se but was made for comparison with the USEPA acute deterministic analyses.

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