RISK TO HUMANS FROM DIETARY EXPOSURE TO THE NEONICOTINOID INSECTICIDE IMIDACLOPRID

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ABSTRACT

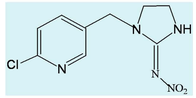
Imidacloprid represents the new generation of neurotoxic insecticides, which have more selective toxicity for insects relative to mammals. It is structurally related to nicotine and acts as an agonist of the nicotinic acetylcholine receptor (nAChR). It is registered to control insect pests on agricultural and nursery crops, structural pests and parasites on companion animals. Imidacloprid ranked as one of the top selling pesticides in the world in 2006.

We evaluated the risk for health effects in humans from exposure to residues of imidacloprid in food and drinking water. The toxicity was assessed in animal studies. Two acute oral NOELs (No-Observed-Effect Level) were used to address the acute dietary exposure. The acute NOEL of 9 mg/kg/day for decreases in motor activity in adult rats was used for the general population. The acute NOEL of 5.5 mg/kg/day for developmental neurotoxicity in rats was pertinent to women of childbearing age to protect against fetal exposure. The chronic NOEL of 5.7 mg/kg/day was based on an increase in incidence and severity of mineralized particles in the thyroid gland in rats. Dietary exposures were estimated for 16 population subgroups under acute and chronic scenarios using the deterministic point estimate model. The exposure estimates were based primarily on the maximum allowed residue level (tolerance) as surrogate for residue concentration. The risk was evaluated by comparing the margins of exposure (MOE=NOEL/exposure) to a benchmark MOE of 100. The acute MOEs ranged from 115 to 614 at the high-end (95th–99th) dietary percentiles. The chronic MOEs for all population subgroups were greater than 770.

In conclusion, the acute and chronic dietary MOEs for imidacloprid exceeded the general health protective MOE of 100. However, these MOEs reflected only the risk from the dietary exposure. Additional exposures from ambient air, occupational activities and residential uses will lead to reductions in the aggregate MOEs.

INTRODUCTION

Imidacloprid is a neonicotinoid, which emerged as the most important new synthetic insecticide in the past 2 decades. It is structurally related to nicotine and acts as agonist of the cholinergic nAChR in insects and vertebrates. Prolonged activation of the nAChR by imidacloprid causes desensitization and blocking of the receptor and leads to paralysis and death. Imidacloprid has more selective toxicity for insects relative to mammals.



Imidacloprid is registered to control insect pests on agricultural and nursery crops, structural pests and parasites on companion animals, and is also extensively used for soil application, seed and foliar treatment.

Imidacloprid is a Category II toxicant, based on its acute toxicity. It did not show clear potential to cause chromosome damage or cancer in rodents. The U.S. Environmental Protection Agency (USEPA) established for imidacloprid an oral chronic reference dose (RfD) of 0.057 mg/kg/day.

In California, imidacloprid was evaluated for human health effects, because liver and the thyroid gland toxicity was observed in subchronic and chronic studies with laboratory animals. We evaluated the potential health hazard to humans from exposure to imidacloprid residues in the food and drinking water.

- The complete DPR's Risk Characterization Document for imidacloprid is posted at:
  http://www.cdpr.ca.gov/docs/risk/rcd/imidacloprid.pdf
- The source of data for this poster is attached.

METHODS

Toxicological Profile and Hazard Identification: Evaluations were based on oral toxicity studies submitted to the DPR by the registrants or published in the open literature.

- Acute Toxicity: Five studies were evaluated: acute toxicity studies in rats and mice, acute neurotoxicity in rats and developmental toxicity studies in rats and rabbits.
- Subchronic Toxicity: Eight studies: 13- and 24-weeks studies in rats, 4- and 13-weeks studies in dogs, 14-weeks study in mice, 13-weeks neurotoxicity study, reproductive toxicity study and developmental neurotoxicity (DNT, 41-days) study in rats.
- Chronic Toxicity: Three studies: 2-year studies in rats and mice and a 52-week study in dogs.
- Critical NOELs were determined with the NOEL/LOEL approach or with the Benchmark Dose (BMD) approach. The BMD was the lower, 95% confidence limit of the effective dose (LED) required to cause a 5% toxic response.

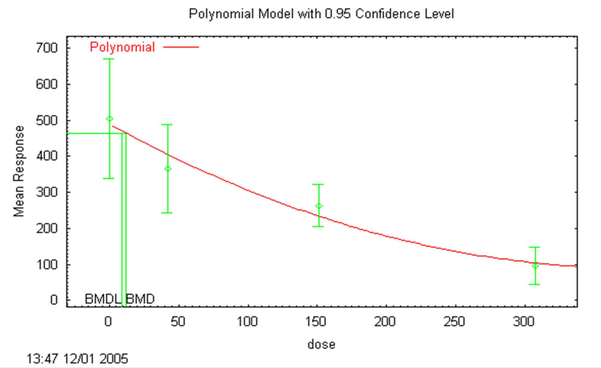
Dietary and Drinking Water Exposure: Exposure was estimated for more than 270 individual plant and animal commodities.

- Residue data: Based primarily on the maximum allowed residue level (tolerance) as surrogate for residue concentration. Residue data from monitoring databases (i.e., PDP and DPR) were available for 22 commodities and drinking water.
- Model: Acute and chronic exposures were calculated with the deterministic approach (Point Estimate) using the Dietary Exposure Evaluation Model (DEEM™ v. 7.74; Exponent Inc.).

Risk Characterization: Risk was calculated in terms of margin of exposures (MOE=NOEL/exposure) for 16 population subgroups. The MOEs for 7 selected populations are presented

- A MOE of 100 was used as the benchmark to determine the level of human health protection. The benchmark of 100 includes an uncertainty factor of 10 for interspecies sensitivity and 10 for intraspecies variability.

Figure 1. Estimation of the Threshold of the Imidacloprid Acute Oral Toxicity with the BMD model.



Imidacloprid-Induced Decrease in the Motor Activity in Rats. A single dose of imidacloprid was given by gavage to Sprague-Dawley rats at doses 0, 42, 151 and 307 mg/kg/day. The lowest tested dose produced 27% decrease in the motor activity of the female rats (assessed with 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 caused a 5% reduction in the motor activity. The Polynomial model generated the best curve fit among the several available algorithms. The LED_{05} and ED_{05} were estimated as 9 and 12 mg/kg/day, respectively.

RESULTS AND DISCUSSION

Hazard Identification:

- Two Acute NOELs:
  1. General Population: NOEL=9 mg/kg/day was LED_{05}, which caused a 5% reduction in the motor activity of rats (Figure 1).
  2. Women of Childbearing Age: NOEL=5.5 mg/kg/day was estimated from the LOEL for significant decreases in the dimensions of brain structures in immature rats (Table 1).
- Subchronic NOEL=7.3 mg/kg/day for morphological changes of the liver (hypertrophy) and the thyroid gland (follicular atrophy), and tremors in dogs treated for 4-13 weeks (Table 1).
- Chronic NOEL=5.7 mg/kg/day for increased incidence and severity of mineralized particles in thyroid gland in (Table 1).

Table 1. Critical NOELs and Endpoints for the Risk Characterization of Imidacloprid

Duration/Route	NOEL mg/kg/day	Critical Endpoint	Reference Dose[a] mg/kg/day
Acute Oral	9.0[b]	Decreased motor activity (25-27%*) in rat	0.09
32-Day-Oral	5.5[c,d]	Decreased widths of corpus callosum (27%*) and caudate putamen (6%)* in PND11 rats	0.06
Subchronic Oral	7.3	Morphologic changes in liver and thyroid and tremors in dog	0.07
Chronic Oral	5.7	Increased thyroid lesions (62%*) in rat	0.06

a/ Reference Dose (RfD) = NOEL/uncertainty factor (UF). UF=100, 10 each for inter and intra-species extrapolation.
b/ NOEL=LED_{05}. LED_{05} 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. This NOEL was used for acute exposures to the general population.
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 for 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).

Dietary Exposure and Risk

Exposures and MOEs for 7 selected populations (out of 16) are presented in Tables 2 and 3.

- Acute Exposure for General Population:
  1. Exposures ranged from 15 to 51 mg/kg/day at 95th percentile and from 23 to 78 mg/kg/day at the 99th percentile of user-days. Children 1-2 yrs. and Infants were identified as the most highly exposed population subgroups.
  2. The MOEs ranged from 115 to 614 at the 95th and 99th exposure percentiles, and thus, were greater than the benchmark MOE of 100.
- Acute Exposure for Women of Childbearing Age (13-49 yrs):
  1. The exposure was 15 mg/kg/day (95th percentile) and 23 mg/kg/day (99th percentiles).
  2. MOE was 366 (95th percentile) and 239 (99th percentiles, which exceed the general health protective benchmark MOE of 100.
- Chronic Exposure:
  1. Exposures ranged from 1.75 to 7.41 mg/kg/day.
  2. MOEs were greater than 770. The chronic NOEL of 5.7 mg/kg/day for thyroid effects was sufficiently similar to the ENEL for DNT (5.5 mg/kg/day), and thus, would be adequate for protection against potential developmental effects of imidacloprid.

Table 2. Acute (Point Estimate) Dietary Exposure and Risk Estimates for Imidacloprid[a].

Population Subgroup	Acute Dietary Exposure[b] (mg/kg/day)		Acute MOE[c]	
	95th Percentile	99th Percentile	95th Percentile	99th Percentile
US Population	20	38	429	237
All infants	45	70	198	128
Children (1-2 yrs)	**51**	**78**	**175**	**115**
Children (3-5 yrs)	38	57	234	157
Children (6-12 yrs)	24	42	370	186
Adults 50+	26	25	554	359
Females (13-49 yrs)	15	23	614	394

a/ DEEM™ program was used for the Point Estimate analysis with the following input parameters: (*i*) USDA CSFII from 1994-1998, (*ii*) acute NOEL of 9 mg/kg for the general population, (*iii*) acute NOEL of 5.5mg/kg/day for Females 13-49 yrs.
b/ Acute dietary exposure was presented at the 95th and 99th percentiles of user-days for all population subgroups.
c/ MOE =NOEL/Acute Dietary Intake. Highest exposures and lowest MOEs are indicated in bold.

Table 3. Chronic Dietary Exposure and Risk Estimates for Imidacloprid[a].

Population Subgroup	Chronic Exposure[b] (mg/kg/day)	Chronic MOE[c]
US Population	2.37	2407
All infants	4.35	1311
Children (1-2 yrs)	**7.41**	**770**
Children (3-5 yrs)	5.47	1041
Children (6-12 yrs)	3.24	1762
Adults 50+	1.89	3015
Females (13-49 yrs)	1.75	3251

a/ The DEEM™ program was used for the Point Estimate 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 rats.
b/ MOE is defined as NOEL/Chronic Dietary Intake. Highest exposures and lowest MOEs are indicated in bold.

SUMMARY

The risk from imidacloprid residues in food and drinking water was evaluated for 16 population subgroups by comparing the MOEs to benchmarks. Critical NOELs were derived from studies with laboratory animals. A MOE of 100 was used as the benchmark to determine the level of human health protection. Acute and chronic dietary exposures were based primarily on the tolerance as surrogate for residue concentration.

- The acute and chronic dietary MOEs were at or greater than the benchmark MOE of 100, and therefore, did not indicate a health concern.
- These MOEs reflect only the risk form the dietary exposure. Aggregate exposures to humans from ambient air, occupational activities and residential uses of imidacloprid are currently being evaluated. 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.