



Acetamiprid – Expert Statement on the carcinogenic profile



22/03/2019

Confidential Document
Page 1 of 10

**- Acetamiprid -
Expert Statement on the
carcinogenic profile**





Acetaminiprid – Expert Statement on the carcinogenic profile

[Redacted]

22/03/2019

Confidential Document
Page 2 of 10

Authentication

We, the undersigned, hereby declare that this expert evaluation was prepared under our supervision. The review represents a true and accurate record of the results on the active substance(s).

Scientific Evaluation:

[Redacted]

[Redacted]

██████████ and its affiliates hereby request a confidential treatment. This request takes into account the provision of Article 14 of Directive 91/414/EEC and of Council Directive 90/313/EEC of 7 June 1990 and Article 63 of Regulation 1107/2009 on the freedom of access to information. Information given includes trade secrets and confidential know-how related to the active substance(s) and the respective products which represent a considerable commercial value to ██████████.

Table of Contents

1. OBJECTIVE	4
2. INTRODUCTION	4
3. CARCINOGENIC PROFILE OF ACETAMIPRID	6
3.1 Data on official Classification of Acetamiprid	6
3.2 Data on Carcinogenicity	8
4. CONCLUSION	9
5. REFERENCES	10

1. Objective

The purpose of this expert statement is to compile the available information on the toxicological profile of Acetamiprid (CAS-No. 135410-20-7) with a special focus on available data on carcinogenicity. At present extensive toxicological data on Acetamiprid is available to assess the carcinogenic potential and encompasses information on the legal classification, data from databases, the Material Safety Data Sheet and, furthermore, toxicological studies which are considered as reliable and conclusive for the assessment of the carcinogenic and reprotoxic potential. A public consultation on classification under CLP has been opened for Acetamiprid until 22nd March 2019. This document proposes responses to the CLH proposals for classification as Carcinogenicity Cat 2 (“C2”) and Reproductive Toxicity Cat 2 (“R2”).

2. Introduction

The active substance Acetamiprid is approved and used as insecticide to control herbivorous (sucking and biting) insects and is applied as a foliar spray, granular product or plant rodlets on ornamental and edible crops.

Acetamiprid is currently not classified as carcinogenic or reprotoxic, nor is it known as a potential carcinogen based on the results from reliable animal studies and publicly available information from toxicological databases (EU and global). In the EFSA Peer review in 2016, Acetamiprid was proposed to be classified as carcinogenic category 2 but not as toxic for reproduction category 2 (EFSA, 2016).

During the EFSA peer review, the majority of the experts agreed on a proposal for classification as Carc. Cat 2, however, the rapporteur member state (The Netherlands) expressed disagreement (EFSA, 2016).

In this report a summary of the available information from toxicological studies and information from toxicological databases with regards to carcinogenicity of Acetamiprid is provided. Overall, the available data clearly indicate that Acetamiprid is not carcinogenic.

A detailed summary on global data on carcinogenicity is presented in the following table. The authors are not aware of any obvious difference between other schemes and the CLP Criteria for carcinogenicity that might enable such a different conclusion.

22/03/2019

Overview on the carcinogenic data from EU and global data base and cross-reference

Different databases were searched against entries on Acetamiprid and carcinogenicity which are publicly available. The results and information of the data base search are summarized in the table below.

Table 2-1 Overview on data base entries and cross references on Acetamiprid (CAS-No. 135410-20-7) with regards to carcinogenicity

Database/ Source	Data base area	Published / date	Conclusion
IARC Carcinogens	International	n.a.	Not carcinogenic
WHO	International	n.a.	
U.S. NTP Carcinogens	US	n.a.	Not carcinogenic
California Prop 65 Known Carcinogens	US	n.a.	Not carcinogenic
IPCS INCHEM (International Programme on Chemical Safety Poisons Information)	US	n.a.	Not carcinogenic
TOXNET (U.S. National Library of Medicine,)	US	2005	Not Likely to be Carcinogenic to Humans
California Environmental Protection Agency Department Of Pesticide Regulation	US	n.a.	Not carcinogenic
EXTOXNET	US	n.a.	Not carcinogenic
New Jersey Department of Health and Senior Services Hazardous Substance Fact Sheet	US	n.a.	Not carcinogenic
TRI Carcinogen	US	n.a.	Not carcinogenic
US EPA Carcinogens	US	n.a.	Not carcinogenic
EU Pesticide database	EU	n.a.	Not carcinogenic
ECHA	EU	n.a.	Not carcinogenic
JMPR (Joint FAO/WHO Meeting on Pesticide Residues)	International	2011	Not carcinogenic

n.a.: not applicable

3. Carcinogenic Profile of Acetamiprid

3.1 Data on official Classification of Acetamiprid

Besides information on the official classification of Acetamiprid, toxicological data is available, including acute, repeated dose toxicity and chronic toxicity / carcinogenicity & mutagenicity studies in different test species, as well as data on primary skin & eye irritation, skin sensitisation in mammals. As this report is focused on the data on long-term toxicity / carcinogenicity, for detailed and overall information on the toxicological studies and results please refer to the Draft Assessment Report on Acetamiprid (RAR 2016) and the EFSA Peer Review (EFSA, 2016).

Acetamiprid is officially classified according to the GHS and EU classification and labelling system in Tables 3 of Annex VI of the CLP Regulation (Regulation (EC) No. 1272/2008). The key data have not changed since the existing entry into Annex VI of the CLP regulation, so there does not appear to be good reason for a change in classification. In the following tables information on the official classification and labelling of Acetamiprid is depicted.

Table 3-1 Entry of Acetamiprid according to Table 3.1, Part 3 of Annex VI of the CLP

International Chemical Identification	CAS No.	Classification	Labelling	Specific Concentrations on Limits, M-factors
		Symbol, H-phrases	Symbol, H-phrases	
Acetamiprid	135410-20-7	Acute Tox. 4*, H302 Aquatic Chronic 3, H412	GHS07; Dgr	-

From the data on the official classification & labelling of Acetamiprid it is evident that the substance is classified as “Harmful if swallowed” and “Harmful to aquatic life with long lasting effects”.

-> Based on the official classification, Acetamiprid is not classified with regards to carcinogenicity or reproductive toxicity.

Information on the classification and labelling of Acetamiprid is also provided in the current MSDS for the substance (Anonymous, 2018) and the results from the MSDS are indicated in the table below.

Table 3-2 Classification & labelling of Acetamiprid according to MSDS data

International Chemical Identification	CAS No.	Classification	Labelling	Specific Concentration Limits, M-factors
		Symbol, H-phrases	Symbol, H-phrases	
Acetamiprid	135410-20-7	Acute Tox. 4*, H302 Aquatic Chronic 3, H412	GHS07; Dgr	-

From the Material Safety Data Sheet on Acetamiprid it is evident that the substance is classified as “Harmful if swallowed” and “Harmful to aquatic life with long lasting effects”.

Table 3-3 Self-classification & labelling of Acetamiprid according to MSDS data

International Chemical Identification	CAS No.	Classification	Labelling	Specific Concentration Limits, M-factors
		Symbol, H-phrases	Symbol, H-phrases	
Acetamiprid	135410-20-7	Acute Tox. 3*, H302 Aquatic Acute 1, H400 Aquatic Chronic 1, H410	GHS07; Dgr GHS09; Wng	- M-Factor = 10 (acute and chronic)

From the proposed self-classification in the Material Safety Data Sheet on Acetamiprid it is evident that the is classified as „ Toxic if swallowed” and “Very toxic to aquatic life” and “Very toxic to aquatic life with long lasting effects”.

-> Based on the available MSDS, Acetamiprid is not classified with regards to carcinogenicity or reproductive toxicity.

3.2 Data on Carcinogenicity

The long-term toxicity and carcinogenicity of acetamiprid was studied in rats (Anonymous, 1999e) and mice (Anonymous, 1999e), showing no carcinogenic potential. In the rat study, the target organs were the liver in males and females, and the kidney in males. Body weight was reduced and histopathological findings were observed in liver and kidney. In the mouse study, the target organ was the liver. Body weight was reduced and histopathological findings were observed in liver (RAR, 2016).

Long-term toxicity / carcinogenicity studies in rats

In a GLP compliant long-term toxicity / carcinogenicity study according to OECD TG 453 with Sprague-Dawley rats the No Observed Adverse Effect Levels (NOAEL) was determined to be 160 ppm (i.e. 7.1 mg/kg bw/day and 8.8 mg/kg bw/day for male and female rats, respectively) based on body weight gain reductions and increased incidence of adenocarcinoma in the mammary gland in females. However, incidence levels were within normal limits for ageing Crl:CD rats, and therefore these lesions are considered to be unlikely to be due to an endocrine or carcinogen effect of Acetamiprid (JMPR, 2011). In males histopathological changes in the liver were observed at 400 ppm (DAR, 2014). However, the nature of these findings in males is consistent with an adaptive hypertrophic response of the liver to an increase in metabolic demand with subsequent development of proliferative changes and hepatocellular toxicity. There was no evidence of any carcinogenic effect in rats.

In a 18 months carcinogenicity study in mice receiving dietary administration at 0, 130, 400 and 1200 ppm Acetamiprid, body weight was reduced in both sexes at 400 ppm. The liver was identified microscopically as the target organ in both sexes at the top-dose with increased liver-to-body weight ratio, associated with increased incidences of centrilobular hepatocellular hypertrophy, considered to be an adaptive response of the liver to xenobiotic exposure. The NOAEL is set at 130 ppm, equivalent to 20.3 and 25.2 mg/kg bw/day for males and females, respectively, based on transient decreased body weight observed at 400 ppm in males and increased liver weight in females (DAR, 2014). There was no evidence of any carcinogenic effect in mice.

In addition the available studies on genotoxicity (*in-vitro* and *in-vivo*) lead to the conclusion that Acetamiprid has no genotoxic potential in vivo (CLH, 2018). In view of the lack of genotoxicity in vivo and the absence of carcinogenicity in rats and mice, Acetamiprid is unlikely to pose a carcinogenic risk to humans.

Table 3-4 Summary of the available chronic toxicity / carcinogenicity studies on Acetamiprid

Study	Dose Level [ppm]	NOAEL	Effects observed at the LOAEL
Long -term – 2-year dietary toxicity and carcinogenicity in the rat	0, 160, 400, 1000	NOAEL: 160 ppm M: 7.1 mg/kg bw/day F: 8.8 mg/kg bw/day	M: centrilobular hepatocellular hypertrophy/vacuolation at 400 ppm; reduced bw gain, microconcretions in renal papillae at 1000 ppm. F: reduced bw gain, centrilobular hepatocellular hypertrophy at 1000 ppm. No oncogenic potential
18-month dietary oncogenicity study in mice	0, 130, 400, 1200	NOAEL: 130 ppm M: 20.3 mg/kg bw/day F: 25.2 mg/kg bw/day	M: transient decreased bw at 400 ppm. F: increased liver weight at 400 ppm. No oncogenic potential

4. Conclusion

The purpose of this statement is to characterise the carcinogenic profile of the active substance Acetamiprid which is used as an insecticide in plant protection. During the EFSA Peer Review a classification as carcinogenic category 2 had been proposed by the experts, but was not agreed by the rapporteur.

The results of the combined chronic toxicity / carcinogenicity studies performed in rats and mice demonstrate the absence of a carcinogenic potential of Acetamiprid. These studies were also considered as reliable and acceptable by the European Food Safety Authority (EFSA) for the pesticide risk assessment of Acetamiprid. Read-across of secondary literature and current toxicological data base entries do not indicate any carcinogenic potential of Acetamiprid either. Therefore, it can be concluded that Acetamiprid is unlikely to possess a carcinogenic potential in rodents.

Taking into account all the available information and toxicological data on Acetamiprid, it is, therefore, justified to conclude that the active substance Acetamiprid has not to be classified as a category 2 carcinogen.

5. References

Anonymous (2018): Material Safety Data Sheet Acetamiprid TG. Nisso Chemical Europe GmbH; Version: 13 / EN, Revision date: 04th April 2018.

(Anonymous, 1999a): 18-Month Dietary Oncogenicity Study in Mice, GLP

(Anonymous, 1999e): Two Year Dietary Toxicity and Oncogenicity Study in Sprague Dawley rats, GLP

CLH Report (2018): Proposal for Harmonised Classification and Labelling. Acetamiprid. RIVM, Bureau REACH. Version. 03, Oct.2018.

RAR (2016): Renewal Assessment Report on Acetamiprid, DOCUMENT M-CA, Section 5, Toxicology and Metabolism, 31st October 2014.

EFSA (2016): Peer review of the pesticide risk assessment of the active substance acetamiprid. EFSA Journal 2016;14(11):4610

JMPR (2011): Pesticide residues in food 2011. Joint FAO/WHO Meeting on Pesticide Residues. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues Geneva, Switzerland, 20–29 September 2011