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ACETAMIPRID LITERATURE REVIEW REPORT

Summary of methodology and results fulfilling Japan MAFF requirements

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1. Scope and Objectives

To review literature published from **February 2014 to September 2021** in accordance with Japan MAFF guidance

2. Databases

Dialog (ProQuest) search engine[1] was used to obtain articles from Science Citation Index database (SCISEARCH). This is the same database used for the Web of Science core collection[2]:

Summary of the Science Citation Index / Web of Science core collection

Database name	Database characteristics, fields covered, etc	Scope of publication, number of documents at the time of document search	Update frequency	Search date	Search period
SCISEARCH (Science Citation Index)	Science Citation Index is one of the largest multidisciplinary scientific databases. Contains bibliographic information and cited references from approximately 8,600 of the world's leading scientific, technical, and medical journals. Subjects covered: Agriculture, Engineering, Pharmacology, Anatomy, Environmental sciences, Physics, Astronomy, Genetics, Plant sciences, Behavioral sciences, Immunology, Psychiatry, Biology, Materials science, Reproductive systems, Biotechnology, Mathematics, Surgery, Chemistry, Medicine, Technical & applied sciences, Computer Sciences, Neuroscience, Veterinary science, Ecology, Oncology, Zoology, Energy, Pediatric	1974 – present More than 47.7 million records (as of August 2019)	Weekly	9 November 2021 26 January 2022	February 2014 to June 2021 July 2021 to September 2021

[1] Please note that while the STN search engine was selected for the literature research for European renewal of registration of pesticide (searches from 2004 to 2014), it did not work well as an algorithm for narrowing search terms etc. Dialog, is now used because it is much more effective for this purpose and covers most of the same databases as STN. In addition, only Dialog was used for searches in this research report from February 2014 onwards, as it can be used to search the Science Citation Index, which covers all of the same databases as the Web of Science.

[2] The Web of Science core collection uses Science Citation Index database as the source for science articles, see: https://clarivate.com/webofsciencegroup/support/wos/wos-core-collection/

3. Search strategy

Full details of the search terms are presented in Appendix 1. These terms were used to interrogate Science Citation Index. Using the "AND" connector in the search algorithm, Part 1 'active substance and product terms' were sequentially be added to Part 2 'technical search terms', and then Part 3 'keywords related to the species to be evaluation'.

A separate search was conducted on the most recent US-EPA, EFSA, and JMPR acetamiprid reviews. Public literature articles used within these reviews were identified and are presented as Reference articles. For the EU review, all studies identified in as relevant in Appendix 4 of the August 2014 EU Literature review report (indicated by 'Y' for relevance criteria) were included as Reference articles.

Please note that the 11 metabolites, which were included as keywords in the literature search for European renewal of registration of pesticide from 2004 to 2014, were not included in the scope of this report on the literature search for the following reasons:
- The European requirements at that time for literature searches (2014) were to cover active substances and metabolites of toxicological concern (relevant to health, environment and adverse effects on non-target species) published within the past 10 years from the date of submission of the re-evaluation application.
- Although the 11 metabolites were not considered to be of toxicity concern from the viewpoint of applicant, the 11 metabolites were included in the scope of investigation to avoid delays in evaluation due to additional requests for metabolites information by the EU authorities. When acetamiprid was re-approved, the EU EFSA[3] and EU Commission[4] concluded that there were no critical issues of concern and none of the hazard criteria were met, therefore applicant decided not to include the metabolites in the key word for the survey scope after February 2014.

4. Conformity assessment of search results

Note: Any article by the European Food Safety Authority (EFSA), the US Environmental Protection Agency (USEPA), and the Joint FAO/WHO Expert Committee on Pesticide Residues (JMPR), are Reference Documents, no need for conformity assessment[5].

Phase 1. Confirmation of conformity by study title and summary (abstract)

Article titles and abstracts were carefully checked. The conditions for rapid exclusion of documents were as follows:

1. Papers unrelated to the pesticide active substance.
2. Paper on policy, social and economic analysis
3. Papers on the production and distribution of agricultural products
4. Papers on drug efficacy, phytotoxicity, and physicochemical properties
5. Papers on analytical methods and their development
6. Papers describing new synthetic methods and basic chemistry
7. Patent related literature
8. Summary, review, and composition of academic presentations that do not contain sufficient data or information for risk assessment
9. Opinions that do not present new data that can be used for risk assessment

[3] EFSA Conclusion EFSA Journal 2016;14(11):4610
[4] EU Commission Renewal Report for acetamipid SANTE/10502/2017 Rev 4 13 December 2017
[5] Articles identified in these overseas evaluations are provided and included in separate tabs the accompanying Excel spreadsheet of results.

10. Secondary information, including scientific papers and regulatory reviews, for which the primary source (original) referenced in the literature cannot be identified
11. Paper on exposure to common pesticides (Information on a wide range of active substances other than the one which is concerned)
12. Papers on the toxicity of mixed formulations derived from different active ingredients
13. Papers not related to the four specialist area fields
14. Articles on formulations other than those registered in Japan
15. Articles based computer simulation, etc.

Articles were categorised according to the above criteria. Those falling into the categories were not studied any further.

Phase 2. Full text conformity assessment

Remaining documents that are not excluded by Phase 1 were evaluated further based on the article full text. All articles must be included and presented to MAFF. All epidemiology articles were presented separately and were not subject to Phase 2 assessment.

(I). Conditions for excluding documents that do not meet the purpose of the evaluation:

1. Test design, test system, test species, test substance, route of exposure, etc. are not appropriate from the viewpoint of their use in the evaluation, due to:
    a) Those for which test methods are not described.
    b) Not a relevant test species that can be properly evaluated
    c) Not administered/treated by appropriate route
    d) No indication of the amount of test substance administered or treated
    e) Substances whose media used for addition cannot be confirmed
    f) An analytical method is not described.
2. Literature that cannot be used for evaluation in typical usage/conditions in Japan (Field conditions, soil properties, etc.)

(II). Articles not excluded in (I) are reviewed (full text) and classified as follows:

Classification	
a	Documents judged to be available for setting end points or reviewing risk assessment parameters (e.g. ADI, ARfD, AOEL, Residue Standards, environmental exposure parameters, etc.)
b	Literature that could be used as supplemental data in setting risk assessment parameters
c	Documents not classified as a or b

To determine the above, the following is used as decision support for the classification criteria:

- The test environment being conducted meets the conditions specified in the test guidelines.
- The purity of the administered or treated test substance should be specified.
- The number of animals/animals that can be analyzed statistically must be secured.
- Multiple doses (at least 3 doses)
- A no-treatment area (control area) has been established and the results are appropriate according to the test guidelines.
- Analytical method and results are reported.

The following criteria, classified as "quantitative data" by the Food Safety Commission, may be used as a reference for determining whether a substance falls under category a with respect to toxicity to humans.

- The dose used in the published literature is lower than the lowest dose used in a safety study that is comparable to the study.
- The results of studies in the published literature are reported in units that can be compared with the results of other studies.
- Sufficient information is provided in the published literature to demonstrate that the study conclusions, endpoints, and doses are accurate, reliable, and valid, and it can be concluded that the results of the study are likely to be reproduced.

5. Reliability assessment

Articles concluded as 'Category A' in conformity assessment Phase 2 should be assessed in detail for reliability and classified according to Klimisch *et al*. (1997) criteria.

Code	Category
1	Reliable without restriction
2	Reliable with restriction
3	Not reliable
4	Not assignable

All studies considered relevant and sufficiently reliable, i.e. reliable or reliable with minor restrictions (reliability scores 1 and 2) are presented in detail in the dossier.

1 Reliable without restriction

This includes studies or data from the literature or reports which were carried out or generated according to generally valid and/or internationally accepted testing guidelines (preferably performed to GLP, but not obligatory) or in which the test parameters documented are based on a specific (national) testing guideline (preferably performed to GLP, but not obligatory) or in which all parameters described are closely related/comparable to a guideline method.

2 Reliable with restrictions

This includes studies or data from the literature, reports (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable.

3 Not reliable

This includes studies or data from the literature/reports in which there are interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g. unphysiologic pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for an assessment and which is not convincing for an expert judgement.

4 Not assignable

This includes studies or data from the literature, which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.).

Use of ToxRTool

Where appropriate, ToxRTool (published on the Commission website) was used to assign scores in the area of toxicology. The Outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology (EFSA Supporting publication 2016:EN-1074) recommends the use of the ToxRTool as a harmonized approach for the evaluation of reliability of the published data.

6. Summary of findings

A summary of the numbers of articles identified by the search strategy is presented below.

Search Keywords	**Number of documents (before narrowing down by species)**	**Number of documents (after narrowing down by species) AND Part 3a-c**	**Number of documents (after Phase 1 conformity assessments) based on titles and abstracts**	**Number of category A documents (after Phase 2 conformity assessments) based on full text articles**
Part 1 (active/product terms only)	1090	Not applicable	Not applicable	Not applicable
AND Part 2a. Toxicology to humans	642	122	27	0
			(+ 14 epidemiology)	(+ 14 epidemiology)
AND Part 2b. Residues in agricultural and livestock products	414	37	0	-
AND Part 2c. Toxicity to Living Environment Animals and Livestock (Ecotoxicology)	743	153	44	0
AND Part 2d. Environmental dynamics	685	203	0	-
Total		515	85	14
Total with duplicates removed		**410**	**85**	**14**

In addition to above results from this literature search, the most recent EPA, JMPR and EU reviews of acetamiprid were reviewed. Public literature identified as relevant in these reviews are provided as Reference documents.

2003/2004 EPA review of acetamiprid	No public literature was identified in the 2003/2004 EPA review of acetamiprid.
2011 JMPR review of acetamiprid	5 public literature articles relevant to toxicology
2014 EU review of acetamiprid	47 public literature articles were identified to be relevant in the areas of toxicology, ecotoxicology and residues. These are studies identified with 'Y' for relevance criteria in Appendix 4 of the August 2014 EU Literature review report.

Full details of the searches and conformity assessments are presented in the accompanying Excel spreadsheet. An explanation of the information presented in each Excel sheet is provided below:

Excel sheet number	Description of information presented
1	Summary of results of the searches (as above). Hyperlinks are provided to the relevant Excel sheets
2	List of all 410 search titles identified by the searches (duplicates were removed)
3	Phase 1 conformity check following strategy explained in section 4 of this report. Abstracts are also presented. Numbers in column B indicate rapid exclusion conclusion. Articles not excluded are indicated by category of relevance (Toxicology, Ecotoxicology, Epidemiology).
4	Phase 2 conformity check following strategy explained in section 4 of this report. All required article details are presented. Column Q presents Phase 2(I) exclusion conditions. Column R presents Phase 2(II) classification (a-c). Column S presents reliability assessment.
5	List of epidemiological articles identified in Phase 1
6	Detailed information presented from epidemiological articles
7	Reference documents: public literature presented in the 2011 JMPR review of acetamiprid
8	Reference documents: public literature presented in the 2014 EU review of acetamiprid

7. Conclusions

Documents and classification results that were found to be compatible in the second stage of compatibility assessment

Field	Number of applicable literatures		
	Category a	Category b	Category c
Toxicity to humans	0	0	6*
Residues in agricultural and livestock products	0	0	0
Toxicity to animals, plants in the living environment, and livestock	0	0	0
Environmental fate	0	0	0
Total	0	0	6*

* In accordance with comments from the Food Safety Commission of Japan, the number of applicable literatures was changed from 4 to 6 in 27 June, 2023.

In addition to the above findings there were 14 epidemiological studies identified, and a total of 52 Reference documents identified, 5 from JMPR and 47 from EU reviews of acetamiprid.

Appendix 1. Summary of search terms

Part 1: Active substance and product search terms

Active substance:	**Search terms**	**Search fields** For search terms, the fields to be searched in a database must be indicated.
Common name(s)	acetamiprid	Title and Abstract
Chemical names of active component:		
Trivial names / synonyms / developmental codes	NI-25 EXP60707B	Title and Abstract
IUPAC	(E)-N1-[(6-Chloro-3-pyridyl)methyl]-N^2-cyano-N^1-methylacetamidine	Title and Abstract
CAS Number	135410-20-7 160430-64-8	Title and Abstract
CIPAC No.:	649	Title and Abstract
Product(s):	Mospilan SP Mospilan G Mospilan Jet Yielder SG Mospilan Liquid Matsugreen Liquid Mospilan SL Liquid Kadan Matsugreen Liquid2 Mospilan-TopsinM Spray Mospilan One G Mospilan WSG Mos-Topsin R Spray Maitemin Spray Dairigu G Avail G Image Liquid Mospilan Bait	

Part 2: Technical search terms

Specialist area	**Refinement terms**	**Search fields** For search terms, the fields to be searched in a database must be indicated. For example [Full text], [Title and Abstract], [Title].

a. Toxicology to humans	Mortality, skin irritation, eye irritation, sensitivity, allergy, hypersensitivity metabolic, distribution, absorption, depletion, kinetic, PK, TK, cytochromes, enzymes mutagen, DNA, genotoxicity, Carcinogen, cancer, tumor, oncology, immune, neurotoxicity, endocrine disruption/disruptors, hormone, development, developmental toxicity, reproduction, malformation, material toxicity, pregnancy, embryo, fetus, offspringdermal, epidermal, exposure, operator, worker, occupant, biomonitoring, Medical, poison, apoptosis, necrosis, cytotoxic, cohort, epidemiology inverse effect, case control	Title and Abstract
b. Residues in agricultural and livestock products	uptake, metabolism, metabolic, breakdown, translocation, degradation storage, stability determination, process, preharvest, postharvest, preplant, pre-/post-emergence processing factor, conversion factor hydroxylation, photosis, rotation, succeeded, supervened trial, field trial	Title and Abstract
c. Toxicity to Living Environment Animals and Livestock	bioaccumulation, bioconcentration, biomagnification, effect, diversity, protection goals, eco, impact, population, pest, endocrine disruption, acute, chronic, long-term, ecotoxicology colony, hive, aquatic, freshwater Macro-organization, micro-organization, microbial	Title and Abstract
d. Environmental dynamics	degradation, photo, hydrolysis, accumulate, dispation, vapor pressure	Title and Abstract

	mobility, adsorption, desorption, persistent, pollution, contamination aged residue, column leaching, leach, lysimeter, drift, run-off, atmosphere, transport, long-range transport, short-range transport monitoring, surveillance, environmental, exposure, fate, residue	

Part 3: Keywords related to the species to be evaluated

Specialist area	**Refinement terms**	**Search fields** For search terms, the fields to be searched in a database must be indicated. For example [Full text], [Title and Abstract], [Title].
a. toxicity to humans	rat, mouse, dog, rabbit, monkey, pig, human, hen, S. typhimurium, E. coli	Title and Abstract
b. Residues in agricultural and livestock products	crop, comfort, feed, livestock, hen, cattle, goat, pig, ruminant, cow, poltry	Title and Abstract
c. Toxicity to Living Environment Animals and Livestock	avian, bird, mallard duck, quail, bobwhite, lemna, algae, fish, crustacean, aquatic, chironomus, bumble/honey/solitarybee, pollinator, apis,	Title and Abstract
d. environmental dynamics	soil, water, sediment	Title and Abstract