公表文献に関する報告書

有効成分名：トプラメゾン

日本曹達株式会社　提出

提出日：令和６年 12 月 18 日

修正日：令和７年５月 21 日

RD-12666N

Topramezone-Literature search report according to JMAFF Guidelines

NIPPON SODA CO., LTD.

Topramezone – Literature search report according to JMAFF Guidelines

Report version Amendment No.1 to the report

[redacted]

Authors: [redacted]

Date 07 May 2025

Address: [redacted]

Sponsor: **Nippon Soda Co. Ltd.**
JP TOWER, 7-2, MARUNOUCHI 2-CHOME,
CHIYODAKU, TOKYO 100-7010, JAPAN

Table of Contents

1. Introduction:

This document presents the result of a systematic search of the open scientific literature in English language, following JMAFF Guidelines, for the active substances Topramezone, for the period 01.01.2009 - 31.12.2022. An analysis of the relevance and reliability of each article relevant to the active substance is also presented.

2. Methodology:

The literature search was performed according to the recommendations presented in the JMAFF Guidelines, using Web of Science (Core Collection) as the searched database.

The method consists of several steps:

- Definition of a search strategy which consist of selecting search keywords
- Performance of the search using Web of Science and sorting out of results
- Systematic review of the retrieved literature including relevance and reliability evaluations
- Reporting of results

2.1. Search strategy:

The keyword selection is performed via a 3-step approach:

- **Step 1**: selection of keywords relative to the target active substance using:
  - Common name
  - IUPAC name
  - CAS name
  - CAS number
  - EC number
  - Other available names
  - Formulation product names

  The following resources were used to search for active substance name and identification:
  - ChemIDplus: https://chem.nlm.nih.gov/chemidplus/
  - Pubchem: https://pubchem.ncbi.nlm.nih.gov/
  - CAS registry: https://commonchemistry.cas.org/

- **Step 2**: selection of keywords relative to observed effects according to four areas:
  - Toxicity/adverse effects on human
  - Crop and livestock residue
  - Ecotoxicity and animal toxicity
  - E-fate

  In Web of Science, this keyword selection is performed by refining the search from step 1, selecting the relevant category field for each area of search (see section “b. Search process”), according to the following table:

Effect area	**Category field**
Toxicity/adverse effects on human	agriculture multidisciplinary allergy biochemistry molecular biology cell biology clinical neurology critical care medicine developmental biology emergency medicine endocrinology metabolism environmental sciences genetic heredity immunology medicine general internal medicine research experimental multidisciplinary sciences neurosciences oncology pediatrics pharmacology pharmacy physiology public environmental occupational health reproductive biology toxicology veterinary science
Crop and livestock residue	agriculture multidisciplinary agriculture dairy animal science environmental sciences food science technology multidisciplinary sciences pharmacology pharmacy plant sciences veterinary sciences zoology
Ecotoxicity and animal toxicity	agriculture multidisciplinary biochemistry molecular biology biodiversity conservation biology cell biology developmental biology ecology endocrinology metabolism entomology environmental sciences environmental studies fisheries marine freshwater biology microbiology multidisciplinary sciences neurosciences ornithology

	pharmacology pharmacy plant sciences reproductive biology toxicology veterinary sciences zoology
E-fate	agriculture multidisciplinary ecology environmental sciences environmental studies fisheries limnology marine freshwater biology multidisciplinary sciences soil science water resources

- **Step 3**: selection of keywords relative to target species relative to the four effect area categories:

  In Web of Science, this keyword selection is performed by refining the search from step 2, selecting the relevant species-specific keywords for each area of search (see section "b. Search process"), according to the following table:

Effect area	**Species-specific keywords**
Toxicity/adverse effects on human	Rat, mouse, dog, rabbit, monkey, pig, human, hen, S.typhimurim, E.coli
Crop and livestock residue	Crop, commodity, feed, livestock, hen, cattle, goat, pig, Ruminant, cow, poultry
Ecotoxicity and animal toxicity	Avian, bird, mallard duck, quail, bobwhite, lemna, algae, fish, crustacean, aquatic, chironomus, bumble/honey/solitary bee, pollinator, apis,
E-fate	Soil, water, sediment

2.2. Literature search:

The literature search was performed for the active substance Topramezone on 18.01.2024. The 3-step approach described above was followed.

2.3. Systematic review of retrieved literature

The open literature searched and collected according to methodology described previously was then classified based on its relevance to the purpose of the evaluation. In addition, the relevance evaluation was carried out in two stages as follows, and the relevant literature was then classified into three provisional categories, and then the reliability was evaluated.

2.3.1. Relevance evaluation

- Step 1: Initial rapid assessment:

The first step of the relevance evaluation is based on screening the title and abstracts of obtained hits. Irrelevant literature/publications are ruled out based on the following reasons:

① Publication of no relevance to the agrochemicals (as an alternative to the agrochemicals for example)

② Publication relevant to policy, society and economic analysis

③ Publication relevant to the production and distribution of agricultural products etc.

④ Publication relevant to efficacy, phytotoxicity or physicochemical properties of the active substance

⑤ Publication relevant to analytical methods and their development

⑥ Publication relevant to new synthesis methods or basic chemistry

⑦ Publication relevant to patents

⑧ Summary and review of conference presentations or books, which are not providing enough data or information to conduct risk assessment

⑨ Written opinion that it is not showing any new data useful for risk assessment

⑩ Secondary source: introduction relevant to scientific publication or regulation that is not confirmed in the primary source (original)

⑪ Publication relevant to typical exposure of agrochemicals (focus on a wide range of agrochemicals without limiting the focus to the target agrochemical)

⑫ Publication relevant to the toxicity of mixtures of formulation products coming from different active ingredients

⑬ Publication not relevant to 4 effect areas described in section 1.a. step 2

⑭ Publication relevant to unregistered formulation products (different formulation) in Japan

⑮ Publication regarding dry lab (*In silico* methods, computer simulations)

- Step 2: Detailed assessment:

The second step of the relevance evaluation is based on screening the full text of obtained hits. Irrelevant literature/publications are ruled out based on the following reasons:

① to ⑮ Same as described above during the initial rapid assessment

⑯ Study design, study system, study type, test Item, exposure route, etc. are not appropriate from the viewpoint of utilisation for the evaluation, as follows:

a) Study methods are not (sufficiently) documented.

b) The test was conducted according to a study type other than one that can be evaluated appropriately.

c) The test substance has not been dosed/treated by an appropriate route.

d) The dose or treatment equipment is not (sufficiently) documented.

e) The agent for adding of test substance are not confirmed.

f) The chemical analysis method is not documented.

⑰ Literatures that can't be used for evaluation for typical application/condition of use in Japan (Field condition, type of soil, etc.)

- Step 2: Relevance category classification:

Publication not excluded after the initial rapid and detailed assessments were then regarded as relevant, and the full text of literatures were reviewed by setting classification criteria and by classifying them into the following three categories:

Category	**Relevant literature of the classification**
a	Literature/publication is judged as available for the setting or reviewing risk assessment parameters［ADI, ARfD, AOEL, MRL, Registration standard of human living environment (meaning flora and fauna), PEC］
b	It is literature that can be used as supplementary data when setting risk assessment parameters
c	Not classified literature to a and b

The following items were considered as the classification criteria:

- The test environment being conducted matches the conditions specified in the test guidelines.
- The test material (including its purity and impurity profile) is well defined
- The number of animals per group is sufficient to establish a statistical significance
- Several dose levels (at least 3) are tested
- A control was set for the test, and the result compared with the test guideline was appropriate
- Analytical methods and results have been well reported.

In deciding whether or not a literature/publication meets the "category a" criteria and regarding the "Toxicity/adverse effects on human" category, the following criteria classified as "quantitative data" presented by the Food Safety Commission of Japan (FSC) were referred to:

- The dose used in publish literature is lower than the lowest dose used in the safety study, which is comparable to the study.
- Research results from open literature are reported using units that can be compared with other test results

- Sufficient information is provided in the open literature to demonstrate that the conclusions, endpoints and dose are accurate, reliable and valid. Moreover, it can be judged that there is a possibility of reproducibility for the research results

2.3.1. Reliability evaluation

Literature/publications classified as "Category a" in the evaluation of relevance described above were then subjected to the classification of the Klimisch standard (see table below), which is widely enforced internationally as a method for evaluating the reliability of literatures.

Score	Reliability	Standard for judgment
1	Reliable without restriction	・guideline study (preferably performed according to GLP) ・comparable to guideline study ・test procedure in accordance with national standard methods ・ test procedure in accordance with generally accepted scientific standards and described in detail
2	Reliable with restriction	・guideline study with acceptable restrictions ・comparable to guideline study with acceptable restrictions ・test procedure in accordance with national standard methods with acceptable restrictions ・study well documented, meets generally accepted scientific principles and acceptable for assessment
3	Not reliable	・significant methodological deficiencies for expert judge ・unsuitable system for expert judge
4	Not assignable	・abstract ・secondary literature (book, Overview etc.) ・documentation insufficient for assessment

More specifically, Klimisch scores were established as follows, for each effect area category:

(1) For the “Toxicity/adverse effects on human” effect area category, ToxRtool (Toxicological data Reliability assessment Tool) was used

(2) For the “Crop and livestock residue” effect area category, the following subsequent criteria were used:
- the test crop is the main crop by test guideline

- condition of test system (grow stage of crop, field condition, amount of treatment, Dose rate, use period, PHI, sampling method) are adequate
- the sample storage stability is verified after sampling
- the storage condition for the sample after sampling is described
- the cultivation condition (density and raising method) is appropriate
- the dose rate is within the limits of GAP specified by the registration

(3) For the "Ecotoxicity and animal toxicity" effect area category, the following subsequent criteria were used:
- the test item dissolves in water, for aquatic organism test
- the origin of test species, rearing condition, route, age, weight or length, etc. is clearly described
- the test environment (temperature etc.) is comparable to the recommendations of the test guideline during the whole test
- the concentration of the test sample is maintained as planned throughout the exposure period
- time-dependant results and observation are observed

(4) For the "E-fate" effect area category, the following subsequent criteria were used:
- test conditions (type of substrate, type of soil, pH, total organic carbon content, density, water content, activating microorganism etc) are clearly described.
- test conditions (e.g. condition of the used soil etc.) satisfy the test guideline.
- the sampling method satisfies the test guideline.
- the sample storage stability is verified after sampling
- the storage condition for the sample after sampling is described

2.4. Reporting of results

Apart from the result section of this literature report, which provides a summary of the findings, including the detailed relevance and reliability assessment, individual excel files presenting all the literature retrieved (including initial relevance assessment) for each field of search (Toxicity/adverse effects on human, Crop and livestock residue, Ecotoxicity and animal toxicity and E-fate) are also provided. Furthermore, all the publications that have undergone the detailed relevance assessment and potential subsequent reliability assessments are also provided. ToxRtool files for the reliability assessment of publication related to the "Toxicity/adverse effects on human" field are also provided.

3. Results:

3.1. Search strategy: keyword selection and summary of search strategy

Step 1 of the keyword selection process was performed as described in Table *1* and Table *2*.

Table 1: Retrieved keywords for the active substance Topramezone

Common name	Topramezone
IUPAC	[3-(4,5-dihydro-1,2-oxazol-3-yl)-4-mesyl-o-tolyl](5-hydroxy-1-methylpyrazol-4-yl)methanone OR 1-[3-(4,5-Dihydroisoxazol-3-yl)-4-methanesulfonyl-2-methylphenyl]-1-(5-hydroxy-1 -methyl-1H-pyrazol-4-yl)methanone OR 4-[3-(4,5-dihydro-1,2-oxazol-3-yl)-2-methyl-4-methylsulfonylbenzoyl]-2-methyl-1H-pyrazol-3-one OR 4-[3-(4,5-dihydro-1,2-oxazol-3-yl)-4-methanesulfonyl-2-methylbenzoyl]-1-methyl-1H-pyrazol-5-ol
CAS name	3-(4,5-dihydro-3-isoxazolyl)-2-methyl-4-(methylsulfonyl)phenyl](5-hydroxy-1-methyl-1H-pyrazol-4-yl)methanone
CAS Number / EC number	210631-68-8 / 606-699-4

Table 2: Retrieved keywords for the formulation product containing the active substance Topramezone

Common name	ALPHARD

The summary of the search strategy for Topramezone, including search dates and the various steps of the search process and number of hits obtained, are presented in

Table *3*.

Table 3: Summary of the search strategy for the active substance Topramezone

Database name	Web of Science (Core Collection) / All editions		
Date of the search	18.01.2024		
Date span of the search	From 01.01.2009 to 31.12.2022		
Used keyword to Retrieve	① AND ② AND ③		
	①	②*	③
Toxicity/adverse effects on human	Common name OR IUPAC/CAS name OR CAS Number / EC number (see Table 1) OR Formulation product name (see Table 2)	agriculture multidisciplinary OR biochemistry molecular biology OR Environmental Sciences OR genetics heredity OR medicine general internal OR multidisciplinary sciences OR pharmacology pharmacy OR physiology OR public environmental occupational health OR Toxicology	Rat OR mouse OR dog OR rabbit OR monkey OR pig OR human OR hen OR S.typhimurium OR E.coli
Crop and livestock residue		agriculture multidisciplinary OR Environmental sciences OR food science technology OR multidisciplinary sciences OR pharmacology pharmacy OR plant sciences OR zoology	Crop OR commodity OR feed OR livestock OR hen OR cattle OR goat OR pig OR ruminant OR cow OR poultry
Ecotoxicity and animal toxicity		Agriculture multidisciplinary OR biochemistry molecular biology OR biology OR ecology OR entomology OR Environmental sciences OR multidisciplinary	Avian OR bird OR mallard duck OR quail OR bobwhite OR lemma OR algae OR fish OR crustacean OR aquatic OR chironomus OR bumble bee OR honeybee OR solitary

		sciences OR pharmacology pharmacy OR plant sciences OR toxicology OR zoology	bee OR pollinator OR apis
E-fate		agriculture multidisciplinary OR ecology OR Environmental Sciences OR multidisciplinary sciences	Soil OR water OR sediment
Retrieved results			
Retrieved condition (Keyword)	①	① AND ②	① AND ② AND ③
Total number of retrieved literatures for target active substance name	158	NA	NA
Toxicity/adverse effects on human	NA	30	0
Crop and livestock residue	NA	88	35
Ecotoxicity and animal toxicity	NA	94	5
E-fate	NA	22	6

*: only the categories that were available in the search from the full list of categories to be selected for the 4 respective effect areas at step 2 of the keyword selection process are listed.

3.2. Systematic review of retrieved literature

A summary of the relevance assessment for the Topramezone search is presented in Table 4.

Table 4: Summary of results of the relevance assessment (Step1, Step2) of obtained hits for the active substance Topramezone

Field	**Total number of Available literatures**	**Step 1**		**Step 2**	
		Non-relevant	**Potentially Relevant (Go to Step2)**	**Non-relevant**	**Relevant**
Toxicity/adverse effects on human	0	0	0	0	0

Crop and livestock residue	35	35	0	0	0
Ecotoxicity and animal toxicity	5	4	1	1	0
E-fate	6	5	1	1	0
Total	46	44	2	2	0

Table *5* presents the list of non-relevant hits/literature studies after step2 of the relevance assessment and the reason for the decision to justify non-relevance.

Table 5: List of non-relevant hits/literature studies after step2 of the relevance assessment and reason for decision for the active substance Topramezone

List No.	Field	Data requirement (Item No.)	Authors	Date of publication	Title of literature	Journal name, No., Page etc.	Reasons for the decision
5-1	Ecotoxicity and animal toxicity		Zhao, FF; Xiang, QQ; Zhou, Y; Xu, X; Qiu, XY; Yu, Y; Ahmad, F	2017	Evaluation of the toxicity of herbicide topramezone to Chlorella vulgaris: Oxidative stress, cell morphology and photosynthetic activity.	Ecotoxicology and Environmental Safety, 143: 129-135	⑯b - Study design, study system, study type, test Item, exposure route, etc. are not appropriate from the viewpoint of utilisation for the evaluation. The test was conducted according to a study type other than one that can be evaluated appropriately. Species used (*Chlorella vulgaris*) not a standard species according to OECD 201. Test duration of 96 hours when standard test is 72 hours. Study did not include the control, but only a solvent control was included. Study not sufficiently documented to evaluate study validity. ⑯f - The chemical analysis method is not documented. Test solutions were not measured by analytical equipments.
5-2	E-fate		Chen, PP; Shi, MC; Liu, XA; Wang, XY; Fang, ML; Guo, ZR; Wu, XW; Wang, Y	2022	Comparison of the binding interactions of 4-hydroxyphenylpyruvate dioxygenase inhibitor herbicides with humic acid: Insights from multispectroscopic techniques, DFT and 2D-COS-FTIR.	Ecotoxicology and Environmental Safety, 239: 113699	⑯b - Study design, study system, study type, test Item, exposure route, etc. are not appropriate from the viewpoint of utilisation for the evaluation. The test was conducted according to a study type other than one that can be evaluated appropriately.

The number of hits/literature studies classified as “Category a”, ”Category b” or “Category c” after steps 2 of the relevance assessment for the active substance Topramezone is presented in Table *6*.

Table 6: Number of hits/literature studies classified as “Category a”, ”Category b” or “Category c” after steps 2 of the relevance assessment for the active substance Topramezone

Field	**Total number of Available literatures**		
	Category a	**Category b**	**Category c**
Toxicity/adverse effects on human	0	0	0
Crop and livestock residue	0	0	0
Ecotoxicity and animal toxicity	0	0	0
E-fate	0	0	0
Total	0	0	0

4. References:

JMAFF Guideline full reference:

「公表文献の収集、選択等のためのガイドライン」（令和 3 年 9 月 22 日　農業資材審議会農薬分科会決定/令和 5 年 7 月 27 日一部改正）

Appendix 1: Topramezone form 8:

EFSA reports:

The following documents were found and screened for literature data about Topramezone:

- EFSA (European Food Safety Authority, 2014. Conclusion on the peer review of the pesticide risk assessment of the active substance topramezone. EFSA Journal 2014;12(2):3540, 82 pp. doi:10.2903/j.efsa.2014.3540

- Topramezone public Draft Assessment Report (2007, RMS: France) with the following volumes in PDF format:
  - Topramezone_DAR_01_Vol1_public: 88 pp
  - Topramezone_DAR_02_Vol2_public: 48 pp
  - Topramezone_DAR_03_Vol3_B1-B5_public: 50 pp
  - Topramezone_DAR_04_Vol3_B6_public: 137 pp
  - Topramezone_DAR_05_Vol3_B7_public: 65 pp
  - Topramezone_DAR_06_Vol3_B8_public: 126 pp
  - Topramezone_DAR_07_Vol3_B9_public: 94 pp

There was not mention of any literature search or no publications form the open peer-reviewed literature identified in any of these documents.

US EPA reports:

The following documents in PDF format were found and screened for literature data about Topramezone after consultation and screening of the US EPA Docket (https://www.regulations.gov/docket/EPA-HQ-OPP-2015-0127; 10 documents with relevant literature information out of the 30 listed):

- Problem Formulation for the Ecological Risk and Drinking Water Exposure Assessments to be Conducted For the Registration Review for Topramezone. 2015. EPA-HQ-OPP-2015-0127-0002. 44 pp
- Topramezone. Human-Health Assessment Scoping Document in Support of Registratio n Review. 2015. EPA-HQ-OPP-2015-0127-0003. 25 pp
- BEAD Chemical Profile for Registration Review: Topramezone. 2015. EPA-HQ-OPP-2015-0127-0005. 9 pp
- Topramezone Preliminary Work Plan. Registration Review: Initila Docket Case Number 7268. EPA-HQ-OPP-2015-0127-0007. 14 pp
- Topramezone: Draft Ecological Risk Assessment for Registration Review. 2020. EPA-HQ-OPP-2015-0127-0014. 61 pp
- Topramezone: Draft Risk Assessment in Support of Registration Review. 2020. EPA-HQ-OPP-2015-0127-0015. 39 pp
- Registration Review of Topramezone: Drinking Water Exposure Assessment. 2019. EPA-HQ-OPP-2015-0127-0017. 1 pp
- Topramezone: Tier I Update Review of Human Incidents and Epidemiology for Draft Risk Assessment. 2020. EPA-HQ-OPP-2015-0127-0020. 4 pp
- Topramezone. Chronic Dietary (Food and Drinking Water) Exposure and Risk Assessment to Support the Draft Human Health Risk Assessment for Registration Review.2020. EPA-HQ-OPP-2015-0127-0021. 8 pp
- Proposed Interim Registration Review Decision Case Number 7268. 2021. EPA-HQ-OPP-2015-0127-0034. 33 pp

No literature was identified in any of the documents. There is however a mention of a literature search performed in the "EPA-HQ-OPP-2015-0127-0015_Draft Risk Assessment.pdf" document but the outcome is that not a single hit was obtained from this toxicology-oriented search. Here is a exert of the document below:

"**B.3 Literature Search for Topramezone**

Date and Time of Search: 10/24/2019; 11:15 am

Date and Time of Search: 03/26/2020; 12:24 pm (No change zero hits)

Search Details:

((Topramezone)) AND (rat OR mouse OR dog OR rabbit OR monkey OR mammal)

PubMed hits: 0

Number of Swift Articles: 0 for Animal

Number of Swift Articles: 0 for Human

Number of Swift Articles: 0 for No Tag

All studies identified in the PubMed search were screened when the citation list was <100. Screening of larger citations lists (>100 citations) was conducted after prioritization in SWIFT-Review and focused on studies identified with the "Animal" and/or "Human" tag.

Conclusion of Literature Search: No studies were identified.

*PubMed is a freely available search engine that provides access to life science and biomedical references predominantly using the MEDLINE database.

**SWIFT-Review is a freely available software tool created by Sciome LLC that assists with literature prioritization. SWIFT-Review was used to prioritize studies identified in the PubMed search based on the model of interest in the study (e.g., human, animal, in vitro, etc.).

Studies could have resulted in multiple tags which would account for citations identified in PubMed not matching the number of tagged citations.”””

JMPR reports:

The following document was found and screened for literature data about Topramezone:

- Pesticide residues in food 2017. 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, 12–21 September 2017. FAO PLANT PRODUCTION AND PROTECTION PAPER. 104 pp

This document did not contain any Topramezone-specific information and no literature was identified.

Only a small mention to Topramezone was made as it share a similar mode of action than other herbicide active ingredients. (See screenshot below).

5.3 BICYCLOPYRONE (295)

TOXICOLOGY

Bicyclopyrone is the common name approved by the International Organization for Standardization (ISO) for 4-hydroxy-3-[2-(2-methoxy-ethoxymethyl)-6-(trifluoromethyl)-pyridine-3-carbonyl]-bicyclo[3.2.1]oct-3-en-2-one (International Union of Pure and Applied Chemistry [IUPAC] name), with the Chemical Abstracts Service (CAS) number 352010-68-5. Bicyclopyrone is a herbicide that acts by inhibiting 4-hydroxyphenylpyruvate dioxygenase (HPPD), leading to the destruction of chlorophyll in plants. This mode of action is shared with several other herbicide active ingredients, for example, mesotrione, isoxaflutole, topramezone, tembotrione and pyrasulfatole.