CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

International Chemical Identification: 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo [4.1.0]heptane-3-carboxylate

EC Number: 219-207-4

CAS Number: 2386-87-0

Index Number: -

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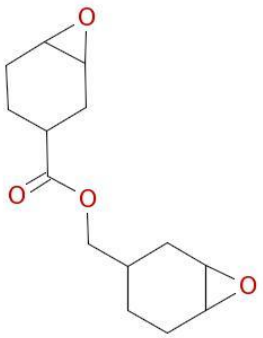
Version number: 2.0 **Date: July 2021**

CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	7-oxabicyclo[4.1.0]heptan-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate.
Other names (usual name, trade name, abbreviation)	7-oxabicyclo 4.1.0 heptane-3-carboxylic acid, 7-oxabicyclo 4.1.0 hept-3-ylmethyl ester.
ISO common name (if available and appropriate)	Not applicable.
EC number (if available and appropriate)	219-207-4
EC name (if available and appropriate)	7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate.
CAS number (if available)	2386-87-0
Other identity code (if available)	Not applicable.
Molecular formula	C14H20O4
Structural formula	
SMILES notation (if available)	O=C(OCC1CCC2OC2C1)C3CCC4OC4C3
Molecular weight or molecular weight range	252.306
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable.
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not applicable.
Degree of purity (%) (if relevant for the entry in Annex VI)	Not applicable.

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)
7-oxabicyclo[4.1.0]heptan-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate.	Mono-constituent substance.	None.	Skin Sens. 1B; H317.

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling

No impurities relevant for classification.

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling

No additives relevant for classification.

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5:

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitter's proposal	TBD	7-oxabicyclo[4.1.0]heptan-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate	219-207-4	2386-87-0	Skin Sens. 1 Muta. 2 STOT RE 2	H317 H341 H373 (nasal cavity)	GHS07 GHS08 Wng	H317 H341 H373 (nasal cavity)	-	-	-
Resulting Annex VI entry if agreed by RAC and COM	TBD	7-oxabicyclo[4.1.0]heptan-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate	219-207-4	2386-87-0	Skin Sens. 1 Muta. 2 STOT RE 2	H317 H341 H373 (nasal cavity)	GHS07 GHS08 Wng	H317 H341 H373 (nasal cavity)	-	-	-

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not assessed in this dossier.	No.
Flammable gases (including chemically unstable gases)	Hazard class not assessed in this dossier.	No.
Oxidising gases	Hazard class not assessed in this dossier.	No.
Gases under pressure	Hazard class not assessed in this dossier.	No.
Flammable liquids	Hazard class not assessed in this dossier.	No.
Flammable solids	Hazard class not assessed in this dossier.	No.
Self-reactive substances	Hazard class not assessed in this dossier.	No.
Pyrophoric liquids	Hazard class not assessed in this dossier.	No.
Pyrophoric solids	Hazard class not assessed in this dossier.	No.
Self-heating substances	Hazard class not assessed in this dossier.	No.
Substances which in contact with water emit flammable gases	Hazard class not assessed in this dossier.	No.
Oxidising liquids	Hazard class not assessed in this dossier.	No.
Oxidising solids	Hazard class not assessed in this dossier.	No.
Organic peroxides	Hazard class not assessed in this dossier.	No.
Corrosive to metals	Hazard class not assessed in this dossier.	No.
Acute toxicity via oral route	Hazard class not assessed in this dossier.	No.
Acute toxicity via dermal route	Hazard class not assessed in this dossier.	No.
Acute toxicity via inhalation route	Hazard class not assessed in this dossier.	No.
Skin corrosion/irritation	Hazard class not assessed in this dossier.	No.
Serious eye damage/eye irritation	Hazard class not assessed in this dossier.	No.
Respiratory sensitisation	Hazard class not assessed in this dossier.	No.
Skin sensitisation	Harmonised classification proposed.	Yes.
Germ cell mutagenicity	Harmonised classification proposed.	Yes.
Carcinogenicity	Hazard class not assessed in this dossier.	No.
Reproductive toxicity	Hazard class not assessed in this dossier.	No.
Specific target organ toxicity-single exposure	Hazard class not assessed in this dossier.	No.
Specific target organ toxicity-repeated exposure	Harmonised classification proposed.	Yes.
Aspiration hazard	Hazard class not assessed in this dossier.	No.
Hazardous to the aquatic environment	Hazard class not assessed in this dossier.	No.
Hazardous to the ozone layer	Hazard class not assessed in this dossier.	No.

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

There is no harmonised classification and labelling for 7-oxabicyclo[4.1.0]heptan-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate and it was not previously discussed by the Technical Committee for Classification and Labelling under Directive 67/548/EEC.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate was included on the CoRAP for evaluation by Ireland in 2013 to clarify concerns including skin sensitisation, mutagenicity and developmental toxicity. During the evaluation, an additional concern was identified relating to effects in the nasal tissue observed in an oral repeated dose toxicity study. The conclusion by the evaluating MSCA was that harmonised classification and labelling for germ cell mutagenicity, specific target organ toxicity – repeated exposure (STOT RE) and skin sensitisation is warranted[1].

There is no requirement for justification that action is needed at Community level

In accordance with Article 36(1) of CLP, justification for action is not required for substances, which fulfil the classification criteria for carcinogenicity, germ cell mutagenicity or reproductive toxicity. The dossier submitter proposes classification as a category 2 germ cell mutagen and therefore no justification for this hazard class is required.

Justification that action is needed at Community level is required

In accordance with Article 36(3) of CLP, justification for action is required for hazard classes other than those referred to in Article 36(1). The REACH registrant has self-classified 7-oxabicyclo[4.1.0]heptan-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate as a skin sensitiser category 1B. They have not self classified the substance for germ cell mutagenicity or STOT RE. The dossier submitter considers that the data presented in this dossier supports classification as category 2 germ cell mutagen and category 2 specific target organ toxicant following repeated exposure. In addition, the dossier submitter considers that the available data on skin sensitisation does not allow sub-categorisation and thus considers that classification as category 1 skin sensitiser is more appropriate. Thus, in addition to category 2 germ cell mutagen, harmonised classification for the hazard classes skin sensitisation and STOT RE is also proposed due to the disagreement by the dossier submitter with the current self-classification.

5 IDENTIFIED USES

7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate is a cycloaliphatic liquid epoxy resin used in a number of industrial sectors including inks and coatings, electricity and electronics. It also used in the manufacture of polymers.

6 DATA SOURCES

Data for 7-oxabicyclo[4.1.0]heptan-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate are taken from:

- Publically disseminated REACH registration dossier (ECHA dissemination site, 2021.).

[1] The substance evaluation conclusion and evaluation report for 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate can be found at: https://echa.europa.eu/documents/10162/b8804bf1-592d-b25e-9f72-89f6f9dedc6b

- Unpublished study reports provided by the registrants for the repeated dose toxicity, mutagenicity and reproductive toxicity endpoints.

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Liquid.	ECHA dissemination site, 2021	Measured.
Melting/freezing point	No true melting point.	ECHA dissemination site, 2021	Measured. Softening to viscous liquid at -35 to -30°C.
Boiling point	None.	ECHA dissemination site, 2021	Measured. Decomposes on heating without boiling.
Relative density	1.172	ECHA dissemination site, 2021	Measured at 20.1 ^{0}C.
Vapour pressure	2 x 10^{-3} Pa	ECHA dissemination site, 2021	Measured at 25 ^{0}C.
Surface tension	61 mN/m	ECHA dissemination site, 2021	Measured at 20 ^{0}C.
Water solubility	13850 mg/L	ECHA dissemination site, 2021	Measured at 20.2 ^{0}C and pH 7.
Partition coefficient n-octanol/water	Log Pow 1.34	ECHA dissemination site, 2021	Measured at 20 ^{0}C and pH 7.
Flash point	202 ^{0}C	ECHA dissemination site, 2021	Measured at 19.6 ^{0}C and 52.2 % humidity.
Flammability	Non-flammable	ECHA dissemination site, 2021	Estimated based on flash point data.
Explosive properties	Not explosive.	ECHA dissemination site, 2021	Calculated.
Self-ignition temperature	375 ^{0}C.	ECHA dissemination site, 2021	Measured at 1013 hPa.
Oxidising properties	Not oxidising.	ECHA dissemination site, 2021	Calculated.
Granulometry	Not applicable.		
Stability in organic solvents and identity of relevant degradation products	No data.		
Dissociation constant	Not applicable.		
Viscosity	241 mPa/s.	ECHA dissemination site, 2021.	Measured at 20 ^{0}C.

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated as part of this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

No data available.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity - oral route

Not evaluated as part of this dossier.

10.2 Acute toxicity - dermal route

Not evaluated as part of this dossier.

10.3 Acute toxicity - inhalation route

Not evaluated as part of this dossier.

10.4 Skin corrosion/irritation

Not evaluated as part of this dossier.

10.5 Serious eye damage/eye irritation

Not evaluated as part of this dossier.

10.6 Respiratory sensitisation

No data available.

10.7 Skin sensitisation

Table 8: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
Similar to OECD 406: skin sensitisation (guinea pig maximisation test) GLP compliant. Incomplete reporting of the results of the range finding	Guinea pig, Hartley albino. 10/sex in treatment group and 5/sex in vehicle control group.	ERL-4221 (trade name of 7-oxabicyclo[4.1.0]heptan-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate) (purity: not reported). Vehicle: propylene glycol Positive control: dinitrochlorobenzene (not concurrent).	Range finding studies: 2 animals administered 5 % test material in propylene glycol via intradermal injection. Observations made 24 and 48 hours post injection. 6 animals administered 10 %, 25 %, 50 % and 100 % test material to sites on dorsal and lateral areas for 24 hours. Observations made 24 and 48 hours post patch removal. Main study:	Range finding studies: 5 % intradermal dose resulted in “local necrosis”. No results reported but 100 % selected for main study.	Anonymous, 1991a. ECHA dissemination site, 2021.

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
studies. No rationale for the selection of the intradermal induction dose. No individual animal data reported. No positive control data reported.			Induction: 3 pairs of injections of: - FCA/water emulsion - 5 % test material in propylene glycol - 5 % test material in FCA/water emulsion Topical application of 100 % test material on day 7. Duration of topical induction not specified. Challenge: Topical application of 100 % test material for 24 hours on day 21. Dermal assessments 24 and 48 hours post challenge patch removal.	Main study: Result: positive 1/10 males died on day 11. Cause of death was not established. At 24 hours 12/19 animals had positive skin reactions. At 48 hours, 8/19 animals had positive skin reactions. No positive skin reactions observed in the vehicle control group at 24 or 48 hour assessments. Positive skin reactions reported in 100 % of animals in the positive control.	

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

A guinea pig maximisation test conducted with 7-oxabicyclo[4.1.0]heptan-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate is reported in the REACH registration dossier for the substance. The study is similar to OECD 406 although it was conducted before the adoption of the test guideline, and it is GLP compliant. The dose levels for the main study were selected based on the results of two range finding studies. In the first, 5 % test material in propylene glycol was administered intradermally to two guinea pigs and observations made at 24 and 48 hours post administration. The study summary reports that “local necrosis”, described as no extensive necrosis or ulceration, was observed. No further details are reported. In the second, 10 %, 25 %, 50 % and 100 % test material were applied to patches on different sites on six guinea pigs and observations made 24 hours after removal of the patches. No results are reported, but 100 % test material was used in the main study for topical application.

In the main study, Hartley albino guinea pigs, 10/sex, received three pairs of intradermal injections on day 0: Freunds Complete Adjuvant (FCA)/water emulsion, 5 % test material in propylene glycol and 5 % test material in FCA/water emulsion. On day 7, the same animals received a topical application of 100 % test material using an occlusive dressing. Animals in the vehicle control (5/sex) were treated in the same way as the test group except that they received propylene glycol or 70 % ethanol instead of the test material. On day 21, the animals in the test and vehicle control groups received a topical application of 100 % test material for 24 hours. Dermal assessments were made 24 and 48 hours later. 1/10 males in the test group died on day 11. The study summary reports that the animal had discoloured lungs, yellow liver colouring and an abdominal cavity filled with blood. The cause of death was not established. No other clinical signs were reported for animals in the test group.

At 24 hours, positive reactions were observed in the test group in 12/19 animals – 11/19 with score of 1 and 1/19 with a score of 2. At 48 hours, 8/19 animals in this group had positive reactions, all with a score of 1. In

the test group, the sensitisation rate was 63 % at 24 hours and 42 % at 48 hours. No positive reactions were observed in the vehicle control group (0/10) at either time point.

Table 9: Summary of the skin sensitisation reactions in the guinea pig maximisation test with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate (Anonymous, 1991a. ECHA dissemination site, 2021)

Group	No. of animals	Time (hours)	Dermal scores							
			0	0.5	1	2	3	Ed*	N*	E*
Test material	19	24	0	7	11	1	0	5	0	0
	19	48	4	7	8	0	0	0	0	0
Vehicle control	10	24	0	0	0	0	0	0	0	0
	10	48	0	0	0	0	0	0	0	0

* These abbreviations are not defined in the study summary however, the dossier submitter considers they could refer to oedema, necrosis and eschar.

Under the conditions of the study, the test material is considered to be a skin sensitiser. Based on the results of this study, the REACH registration dossier for 7-oxabicyclo[4.1.0]heptan-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate applies a self-classification of skin sensitiser category 1B.

No human data on the skin sensitising effects of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate are available. The dossier submitter notes that the available guinea pig maximisation study summary has some limitations, in particular that there was no rationale provided for the selection of the intradermal induction dose, no individual animal data and no data supporting the statement that the periodic testing of the positive control resulted in 100 % positive reactions. Despite these limitations, a significant increase in positive reactions were observed in the test group. The dossier submitter considers that based on the results of this study, 7-oxabicyclo[4.1.0]heptan-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate is a skin sensitiser.

Further details on the above study is provided in Annex I to this report

10.7.2 Comparison with the CLP criteria

According to Annex I to the CLP Regulation, substances may be classified as skin sensitisers category 1:

(a) if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons; or

(b) if there are positive results from an appropriate animal test"

No human data on the skin sensitising effects of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate are available. A positive guinea pig maximisation test with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate is available. Based on the results of this study, classification as skin sensitiser category 1 is warranted.

Section 3.4.2.2.1.1 of Annex I to the CLP Regulation states that where data are not sufficient for sub-categorisation, skin sensitisers should be classified in Category 1. An assessment of the need for subcategorization is outlined below.

According to Annex I to the CLP Regulation, substances may be classified as skin sensitisers category 1A where *"…a high potency in animals can be presumed to have the potential to produce significant*

sensitisation in humans". According to Table 3.4.3 of Annex I to the CLP Regulation, for a guinea pig maximisation test this corresponds to a positivity rate of ≥ 30 % at ≤ 0.1 % intradermal induction dose or ≥ 60 % at > 0.1 % to ≤ 1 % intradermal induction dose. According to Annex I to the CLP Regulation, substances may be classified as skin sensitisers category 1B where "…*a low to moderate potency in animals can be presumed to have the potential to produce sensitisation in humans."* According to Table 3.4.4 of Annex I to the CLP Regulation, for a guinea pig maximisation test this corresponds to a positivity rate of ≥ 30 % to < 60 % at > 0.1 % to ≤ 1% intradermal induction dose or ≥ 30 % at > 1 % intradermal induction dose.

In the available guinea pig maximisation test with 7-oxabicyclo[4.1.0]heptan-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate, a positive rate of 63 % (at the 24 hour assessment) was observed at an intradermal dose of 5 %. These results are within the range for classification in category 1B. However, the dossier submitter notes that the study summary did not include a rationale for selecting the intradermal dose of 5 % in the range finding study or in the main guinea pig maximisation test. Therefore, it cannot be excluded that a lower (i.e. ≤ 1 %) intradermal dose would have led to positive skin reactions supporting classification as a skin sensitiser category 1A.

ECHA's Guidance on the application of the CLP criteria (version 5.0, July 2017)[2] (CLP Guidance), states, *"when category 1A cannot be excluded, category 1 should be applied instead of category 1B."* Based on the available data, sub-categorisation is not appropriate and classification as skin sensitiser category 1 is warranted.

10.7.3 Conclusion on classification and labelling for skin sensitisation

Based on the available data, classification of 7-oxabicyclo[4.1.0]heptan-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate as a skin sensitiser category 1 (without sub-categorisation) is warranted. Based on the available data, the assignment of a specific concentration limit is not warranted.

10.8 Germ cell mutagenicity

Table 10: Summary table of mutagenicity/genotoxicity tests *in vitro*

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
OECD 471: bacterial reverse mutation test. GLP compliant. Triplicate plates per dose, test run in duplicate. Mean number of revertant colonies per dose level and	7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate (purity: not reported).	*S. typhimurium strains* TA 98, TA 100, TA 1535 and TA 1537 and *E. coli* strain WP2 uvrA. 156, 313, 625, 1250, 2500 and 5000 µg/ plate. ± Metabolic activation with S9 mix. Preparation details not reported. Vehicle control: Dimethyl	Result: positive ± metabolic activation. ↑ Revertant colonies in *S. typhimurium strains* TA 100 and TA 1535 (+S9) & *E. coli* strain WP2 uvrA	Anonymous, 1995. ECHA dissemination site, 2021.

[2] https://echa.europa.eu/documents/10162/23036412/clp_en.pdf/58b5dc6d-ac2a-4910-9702-e9e1f5051cc5

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
strain not reported. No information on cytotoxicity.		sulfoxide Positive controls: 2-aminoanthracene (+S9) 2-acetylaminofluorene, sodium azide, 9-aminoacridine, N-ethyl-N-nitro-N-nitrosoguanidine (-S9) Number of replicates: 3 plates/dose and test run in duplicate. Reliability: reliable.	(± S9) No information on cytotoxicity reported.	
Non-guideline: *in vitro* gene mutation study in bacteria. Not GLP compliant. Study pre-dated the adoption of OECD 471 (bacterial reverse mutation test) but the method employed was reported to be similar, with the following deviations: positive controls per strain, the number of replicates per dose and the mean number of revertant colonies per dose level/strain were not reported.	Celloxide 2021P (trade name of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate) (purity: not reported).	*S. typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 and *E coli* strain WP2 uvrA. 100, 250, 500, 1000, 2000 and 5000 µg/plate. ± Metabolic activation with S9 mix. Preparation details not reported. Vehicle control: dimethyl sulfoxide Positive controls: 2-aminoanthracene; 2-acetylaminofluorene, 9-aminoacridine and N-ethyl-N-nitro-N-nitrosoguanidine. Number of cells evaluated: not reported. Number of replicates: Not reported. Reliability: unreliable.	Result: positive + metabolic activation. ↑ Revertant colonies in *S. typhimurium* strains TA 100 and TA 1535 (+S9). No cytotoxicity up to 5000 µg/plate.	Anonymous, 1987. ECHA dissemination site, 2021.
Non-guideline: *in vitro* gene mutation in mammalian cells. Not GLP compliant Study pre-dated adoption of OECD 476 (*in vitro* mammalian gene mutation test) but the method employed was similar with the	Epoxy resin ERL-4221 (trade name of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate) (purity: not reported).	Chinese hamster ovary cells (*HGRPT* gene). Five concentrations between 6.25 x 10^{-4} % and 100 x 10^{-4} % (-S9) and 12.5 x 10^{-4} % and 200 x 10^{-4} % (+S9). Exact concentrations not reported. ± Metabolic activation with rat liver S9 (Arochlor 1254 induced). Vehicle control: dimethyl	Result: negative ± metabolic activation. Cytotoxicity reported at 100 x 10^{-4} % (-S9). No cytotoxicity data available for (+S9).	Anonymous, 1980. ECHA dissemination site, 2021.

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
following deviations: limited reporting of the method, no information on culture/cell density, a longer expression time used, no information on whether the reported mutant frequency was corrected for cloning efficiency and no reporting of cytotoxicity or mutant frequency per dose.		sulfoxide Negative control: untreated cells. Positive controls: N-dimethylnitrosamine (+S9); ethylmethanesulphonate (-S9) Exposure time: 16 hours (-S9), 5 hours (+S9). Expression period: 7-9 days. Number of cells evaluated: 200 cells/dose for frequency of mutants per 10^6 viable cells. Number of replicates: 2 Reliability: reliable.		
Non-guideline: *in vitro* gene mutation in mammalian cells. GLP compliant. Study pre-dated the adoption of OECD 490 (*in vitro* mammalian gene mutation test using the thymidine kinase gene) but the method employed was similar with the following deviations: limited reporting of the method, different positive controls and selective agent used to those recommended in OECD 490, no information reported on the acceptable spontaneous mutant frequency, no sizing of mutant colonies and no reporting of cytotoxicity or	TK 10 310 (ARALDIT CY 179) (trade name of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate) (purity: not reported).	Mouse lymphoma (L5178Y), subline TK $^{+/-}$ 12.5, 25, 50, 100, 150, 200 and 250 µg/ml. ± Metabolic activation with S9 mix. Preparation details not reported. Vehicle control: dimethyl sulfoxide. Negative control: untreated cells. Positive controls: N-dimethylnitrosamine (+S9); ethylmethanesulphonate (-S9) Exposure period: 4 hours. Expression period: 3 days. Selection time: 14 days for mutant selection and 11-12 for viability. Selection agent: 5-bromodeoxyuridine. Number of cells evaluated: 4 x 10^5 cells/tube for mutant selection and 200 cells/tube for viability	Result: positive ± metabolic activation. ↑ Mutant colony count at ≥ 150 µg/ml (+S9) and ≥ 100 µg/ml (-S9). No cytotoxicity reported up to 250 µg/ml.	Anonymous, 1984. ECHA dissemination site, 2021.

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
mutant frequency data per dose.		control. Number of replicates: not reported. Reliability: reliable.		
Non-guideline: *in vitro* sister chromatid exchange (SCE) assay in mammalian cells. Not GLP compliant. Study pre-dated the adoption of the now deleted OECD 479 (*in vitro* sister chromatid exchange assay in mammalian cells) but the method employed was similar, with the following deviations: limited reporting of the method, a lower number of cells/ concentration assessed, the test was performed without metabolic activation and there was no reporting of cytotoxicity or mutant frequency data per dose.	Epoxy resin ERL-4221 (trade name of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate) (purity: not reported).	Chinese hamster ovary cells. 3.125 x 10^{-4} % to 100 x 10^{-4} % by volume. Exact concentrations not reported. No metabolic activation. Vehicle control: dimethyl sulfoxide. Negative control: untreated cells. Positive control: ethylmethanesulphonate. Medium: BrdU-containing medium. Pre-incubation time: 20 hours. Exposure duration: 5 hours. Expression time: 24 hours. Spindle inhibitor: 0.2 µg/ml colchicine or 0.1 µg/ml colcemide 1- 2 hours prior to harvest. Number of cells evaluated: Minimum of 15 cells/dose. Number of replicates: 3 Reliability: reliable.	Result: positive – metabolic activation. ↑ SCE frequency in 3 of 6 concentrations tested (exact concentrations not reported). Excessive toxicity reported in first two replicates, reported as ↓ in the number of mitotic cells and chromosome preparations not suitable for scoring. Based on this, SCE scoring from only one replicate reported.	Anonymous, 1980. ECHA dissemination site, 2021.
Non-guideline: *in vitro* unscheduled DNA synthesis in mammalian cells. Not GLP compliant. Study pre-dated the adoption of OECD 482 (DNA damage and repair/unscheduled DNA synthesis in mammalian cells *in vitro*) but the	Epoxy resin ERL-4221 (trade name of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate) (purity: not reported).	Hepatocytes derived from rat liver. Six concentrations between 1.0 x 10^{-4} % and 1000 x 10^{-4} % by volume. Exact concentrations not reported. Vehicle control: dimethyl sulfoxide. Positive controls: N-dimethylnitrosamine, 4-nitroquinoline-N-oxide. Pre-incubation period: 1	Result: equivocal. ↑ UDS in 2 of 6 concentrations (exact concentrations not reported). 3 lowest concentrations also reported to have ↑ levels of UDS activity (exact concentrations not reported).	Anonymous, 1980. ECHA dissemination site, 2021.

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
method employed was similar with the following deviations: the number of replicates and the number of cells per culture assessed were not reported, no reporting of cytotoxicity or mutant frequency data per dose and limited reporting of the method.		hour. Exposure duration: 2 hours. Number of replicates: not reported. Reliability: unreliable.		

Table 11: Summary table of mutagenicity/genotoxicity tests in mammalian somatic or germ cells *in vivo*

Method, guideline, deviations if any	Test substance	Relevant information about the study (as applicable)	Observations	Reference
OECD 488: transgenic rodent somatic and germ cell gene mutation (TGR) assay. GLP compliant. Sampling time of "28 +3 days" not optimal for germ cell mutagenicity assessment.	7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate (purity: 96 %).	5 male CD2-LacZ80/HazfBR (MutaMouse)/group. 0, 250, 500 and 1000 mg/kg bw/day via gavage for 28 days. Vehicle: corn oil. Positive control: N-ethyl-N-nitrosourea. Sampling time: "28 + 3 days". Three days after the final dose, animals were sacrificed and genomic DNA extracted. Tissue selection: liver, forestomach, nasal tissue & germ cells (spermatozoa, spermatid and spermatocytes from seminiferous tubules and vas deferens/caudia epididymis). Reliability: reliable.	Result: positive. ↑ Mutant frequency in forestomach & liver at 1000 mg/kg bw/day. No ↑ in mutant frequency in nasal tissue or germ cells. ↑ Absolute & relative liver weight at 1000 mg/kg bw/day.	Anonymous, 2016.
OECD 486: unscheduled DNA synthesis (UDS) test with mammalian liver cells *in vivo.* GLP compliant. Number of slides evaluated per animal,	Union Carbide Cycloaliphatic Epoxy Resin ERL-4221 (trade name of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate) (purity: 89 %).	10 male Sprague Dawley rats/ group. 0, 500, 1000 and 2000 mg/kg bw via oral gavage as a single administration. Vehicle: water. Positive control: N-	Result: negative. No ↑ in mean net nuclear grain counts at any dose.	Anonymous, 1999. ECHA dissemination site, 2021.

Method, guideline, deviations if any	Test substance	Relevant information about the study (as applicable)	Observations	Reference
the number of cells score per animal, and individual and group data not reported.		dimethylnitrosamine. Post exposure period: 2 – 4 hours or 12 – 16 hours. Reliability: reliable.		
OECD 474: mammalian erythrocyte micronucleus test. GLP compliant. Study did not meet currently guideline requirements requiring at least 4000 polychromatic erythrocytes (PCEs) per animal.	ERL-4221 (trade name of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate) (purity: not reported).	5/sex Swiss Albino Crl:CD-1 (ICR)BR mice/sampling point. 0, 500, 1000 and 2250 mg/kg bw via i.p. as a single administration. Vehicle: peanut oil Positive control: cyclophosphamide via i.p. Sampling time: 24, 48 and 72 hours post treatment. Tissue selection: bone marrow. ≥ 1000 erythrocytes were counted. 1000 polychromatic erythrocytes (PCE) were scored for the presence of micronuclei (MN). The number of normochromatic erythrocytes (NCE) was also counted. Reliability: reliable.	Result: negative. No ↑ in mean number of MN PCE at any sampling point. ↓ Ratio of PCE/ (NCE & PCE) in females at 500 & 2250 mg/kg bw at 48 hours. Clinical signs of toxicity included ↓ motor activity, collapse, weakness, ataxia and laboured breathing at 2250 mg/kg bw.	Anonymous, 1991b.

10.8.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

***In vitro* studies**

In a bacterial reverse mutation test with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate, an increase in revertant colonies was observed in *S. typhimurium* strains TA 100 and TA 1535 in the presence of metabolic activation and in *E. coli* strain WP2 uvrA in the presence and absence of metabolic activation. In a second bacterial reverse mutation study, an increase in revertant colonies was reported for *S. typhimurium* strains TA 100 and TA 1535 in the presence of metabolic activation.

Two *in vitro* gene mutation studies with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate are available. 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate was not mutagenic in Chinese hamster ovary cells at the *HGRPT* locus either with or without metabolic activation, but was mutagenic in mouse lymphoma (L5178Y) $TK^{+/-}$ cells in the presence and absence of metabolic activation. In a sister chromatic exchange assay in mammalian cells with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate, an increase in sister chromatid exchanges was observed in the presence of metabolic activation. An *in vitro* unscheduled DNA synthesis assay in mammalian cells with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate was reported to be equivocal.

The dossier submitter notes that the *in vitro* study summaries reported in the REACH registration dossier for 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate provide limited details. However, the dossier submitter considers that the available *in vitro* data indicates a concern for gene mutation. In addition, the positive results in *E. coli* strain WP2 uvrA and in mouse lymphoma (L5178Y) $TK^{+/-}$ cells in the absence of metabolic activation indicate a concern for a direct action of the substance as a mutagen at the sites of first contact.

***In vivo* studies**

In a transgenic rodent somatic and germ cell mutation (TGR) assay conducted in accordance with OECD 488, 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate was administered to groups of 5 male transgenic mice (MutaMouse) at 0, 250, 500 and 1000 mg/kg bw/day via oral gavage for 28 days. Three days after the final dose, animals were sacrificed and genomic DNA extracted from the liver, forestomach, nasal cavity and germ cells. No clinical signs of toxicity or effect on body weight was observed at any dose. A slight increase in absolute (1.25 g) and relative (4.6 %) liver weight was observed at 1000 mg/kg bw/day when compared with the control (1.15 g and 4.21 %, respectively).

A statistically significant increase in mutant frequency was observed in the forestomach and liver at 1000 mg/kg bw/day when compared to the concurrent negative control. The mean mutant frequencies (x 10^{-6}) in the forestomach were reported to be 49.1 ± 11.7, 52.2 ± 15.4, 54.9 ± 5 and 78.5 ± 10.7 at 0, 250, 500 and 1000 mg/kg bw/day, respectively. The study report notes that although the increase in mutant frequencies observed in the forestomach at 1000 mg/kg bw/day (78.5 ± 10.7 x 10^{-6}) was only marginally outside the acceptable range of the test laboratory (15.6 x 10^{-6} – 78.0 x 10^{-6}), the increase was considered to be biologically relevant. Therefore, the study authors concluded that under the conditions of the study, the test material induced gene mutations in the forestomach. The mean mutant frequencies (x 10^{-6}) in the liver were reported to be 48.2 ± 14.1, 62 ± 12.5, 61.2 ± 13.8 and 78.2 ± 18.1 at 0, 250, 500 and 1000 mg/kg bw/day, respectively. The study report noted that as the increase in the mutant frequency in the liver at 1000 mg/kg bw/day group (78.2 ± 18.1 x 10^{-6}) was within the acceptable ranges of the test laboratory for this tissue (0.6 x 10^{-6} – 99.6 x 10^{-6}), it was considered by the study authors to be marginal and not biologically significant. No increase in mutant frequency was observed in nasal tissue or germ cells at any dose. The positive control substance elicited a statistically significant increase in mutant frequency in the four tissue samples when compared with the concurrent negative control.

Table 12: Mutant frequencies in male mice in the TGR assay with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate (Anonymous, 2016)

Dose group (mg/kg bw/day)	Mean mutant frequency (x 10^{-6})			
	Liver	Forestomach	Nasal tissue	Germ cells
0	48.2 ± 14.1	49.1 ± 11.7	53.7	32.6 ± 5.8
250	62.0 ± 12.5	52.2 ± 15.4	40.6*	33.7 ± 5.5
500	61.2 ± 13.8	54.9 ± 5.0	50.2	40.3 ± 17.8
1000	78.2 ± 18.1*	78.5 ± 10.7*	54.3	42.4 ± 8.8
Positive control	143.8 ± 21.7*	624.7 ± 96.1	215.7*	82.1 ± 26.4*

***** $P \leq 0.05$

The negative historical control data for the test laboratory is presented in table 14 below. The acceptable range was based on pooled control data per tissue from studies conducted from 1998 to 2015. The dossier

submitter notes time range of this data is large (17 years). No laboratory historical control data was available for the nasal tissue.

Table 13: Historical negative control data for the TGR assay (*lacZ* assay) (Anonymous, 2016)

Organ	n	Mutant frequency (x 10^{-6})		
		Mean	Range	Acceptable range#
Liver	137	50.1 ± 16.5	16.6 – 95.0	0.6 – 99.6
Stomach	43	46.8 ± 10.4	31.1 – 84.7	15.6 – 78.0
Testis	10	46.6 ± 27.7	12.2 – 83.5	-
Nasal tissue	-	-	-	-

Acceptable range reported as mean ± 3 SD.

The dossier submitter considers the increase in mean mutant frequency in the forestomach, a site of first contact, at 1000 mg/kg bw/day to be statistically and biologically significant, and indicative of a direct acting mutagen. With respect to the liver, the dossier submitter agrees with the conclusion of the study author that as the increase in the mean mutant frequency observed at 1000 mg/kg bw/day is marginal and within the acceptable limits of the test laboratory, it is not considered to be biologically relevant. With respect to the nasal tissue, the dossier submitter notes that due to the small amount of tissue available, samples per dose group were pooled and thus individual animal data was not reported. No increase in mutant frequency was observed in any of the test material pooled samples but a statistically significant increase in mutant frequency was observed in the pooled sample of the positive control. Therefore, while the sample preparation for this tissue was not optimal, the dossier submitter considers that the increase in mutant frequency in the positive control supports the validity of the negative response in this tissue in the 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate treated groups.

With respect to germ cells, the dossier submitter agrees with the study author that no increase in mutant frequency was observed. It is noted that the sampling of germ cells following "28 + 3 day" sampling regime, as used in this study, results in a mixed population of spermatogonia, spermatocytes and spermatids at different stages of development and thus does not provide complete coverage of germ cell development. In accordance with paragraph 35 of OECD 488, a negative result in germ cells after a "28 + 3 day" sampling regime is not sufficient to negate the possibility that a test substance is a germ cell mutagen. In addition, the dossier submitter notes that the result for the positive control is within the laboratory historical control range for this tissue, supporting the view that the assessment of germ cells with this sampling regime is not very sensitive. Therefore, the dossier submitter considers that based on this study no conclusion can be drawn regarding the potential for 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3- carboxylate to act as a germ cell mutagen.

In an unscheduled DNA synthesis (UDS) test with mammalian liver cells *in vivo* conducted in accordance with OECD 486 but with deviations, 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate was administered as a single dose to 10 males at 0, 500, 1000 and 2000 mg/kg bw via oral gavage. Liver cells were sampled 2 to 4 hours and 12 to 16 hours following exposure. No increase in mean net nuclear grain counts were reported at any dose. In hepatocytes isolated 2 to 4 hours post exposure, the mean net nuclear grain counts were 0.2, 0.1, -0.2 and -0.3 for the 0, 500, 1000 and 2000 mg/kg bw groups, respectively, compared with 17.6 in the positive control. In hepatocytes isolated 12 to 16 hours post exposure, the mean net nuclear grain counts were -0.2, -0.4, -0.2 and 0.4 for the 0, 500, 1000 and 2000 mg/kg bw groups, respectively, compared with 10.5 in the positive control.

In a mammalian erythrocyte micronucleus test conducted in accordance with OECD 474, a single dose of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate was administered to 5 male and 5 female mice per sampling point via intraperitoneal injection at 0, 500, 1000 and 2250 mg/kg bw. The study deviated from the current version of the test guideline in that 1000 rather than 4000 polychromatic erythrocytes per animal were scored. Clinical signs of toxicity including decreased motor activity, collapse, weakness, ataxia and laboured breathing were observed at 2250 mg/kg bw A significant decrease in the ratios of (polychromatic erythrocyte) / (normochromatic and polychromatic erythrocytes) was reported in females in the 500 and 2250 mg/kg bw groups at 48 hours, which the study authors conclude as evidence of cytotoxicity (values not reported). No increase in the mean number of micronucleated polychromatic erythrocytes was observed at any dose or sampling time.

Table 14: Results from the mammalian erythrocyte micronucleus test with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate) (Anonymous, 1991b)

Dose (mg/kg bw)	Sex	Mean number of micronucleated polychromatic erythrocytes per 1000 polychromatic erythrocytes		
		24 hour	48 hour	72 hour
0	M	1.2	0.0	0.4
	F	0.4	0.2	0.2
500	M	0.8	1.0	0.8
	F	1.8	0.2	1.2
1000	M	1.0	1.4	0.8
	F	0.6	0.6	0.6
2250	M	2.0	0.6	0.6
	F	0.8	0.2	1.4
Cyclophosphamide (25 mg/kg bw)	M	9.8*	Not tested	Not tested
	F	11.0*	Not tested	Not tested
Cyclophosphamide (50 mg/kg bw)	M	14.2*	Not tested	Not tested
	F	16.2*	Not tested	Not tested

* $p < 0.01$

Overall, the dossier submitter considers that the statistical and biologically significant increase in mutant frequency observed in the forestomach in the TGR assay indicates that 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate induces gene mutation at sites of first contact. The negative results in the *in vivo* UDS and mammalian erythrocyte micronucleus studies do not negate this concern since neither test is designed to investigate site of first contact tissues.

Further details on the above studies are provided in Annex I to this report.

10.8.2 Comparison with the CLP criteria

According to Annex I to the CLP Regulation, substances may be classified as category 1A germ cell mutagens *"if they induce heritable mutations in the germ cells of humans*" and that classification is based on

positive evidence from human epidemiological studies. No epidemiological data are available to demonstrate heritable gene mutations in humans. Therefore, classification in category 1A is not warranted.

According to Annex I to the CLP Regulation, substances may be classified as category 1B germ cell mutagens if there are:

- *"positive results from in vivo heritable germ cell mutagenicity tests in mammals or*
- *positive results from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells…or*
- *positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny…"*

In the TGR assay with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate, no increase in the mutant frequency in germ cells was observed. Therefore, the first criterion above is not met. However, it is noted the "28 + 3-day" sampling regime used in the study results in a mixed population of cells at different stages of development and thus does not provide complete coverage of germ cell development. In accordance with paragraph 35 of OECD 488, a negative result in germ cells after a "28 + 3-day" sampling regime is not sufficient to negate the possibility that a test substance is a germ cell mutagen.

An increase in mutant frequency was observed in the forestomach (site of first contact following oral administration) in the TGR assay, indicating 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate induces gene mutations at the site of first contact. No biologically significant increase in mutant frequency was observed in the other somatic tissues investigated (liver and nasal tissue). In addition, no increase in the mean number of micronucleated polychromatic erythrocytes was observed in the *in vivo* erythrocyte micronucleus test and no increase in mean net nuclear grain counts was observed in the *in vivo* UDS test, both conducted with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate. In a 90-day oral repeated dose toxicity study with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3- carboxylate (see section 10.12), there was no indication that the test substance reached the male reproductive organs: no effect on mean testicular and epididymal sperm count, sperm production rate, sperm motility or sperm morphology was observed. Therefore, the second criterion above is not met.

No data is available demonstrating that 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate would show mutagenic effects in the germ cells of humans and so the third criterion above is not met. Therefore, classification in category 1B is not warranted.

According to Annex I to the CLP Regulation, substances may be classified as category 2 germ cell mutagens if positive evidence are obtained from *"somatic cell mutagenicity tests in vivo… or other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays."*

In the available TGR assay, a statistically and biologically significant increase in mutant frequency was observed in the forestomach, which is a site of first contact following oral administration. No increase in mutant frequency was observed in the other somatic tissues investigated (liver and nasal tissue). The concern for gene mutation at sites of first contact is supported by the positive results *in vitro* in *E. coli* strain WP2 uvrA and in mouse lymphoma (L5178Y) $TK^{+/-}$ cells in the absence of metabolic activation. Therefore, classification in category 2 is warranted.

10.8.3 Conclusion on classification and labelling for germ cell mutagenicity

Based on the available data, classification of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate as a category 2 germ cell mutagen is warranted.

10.9 Carcinogenicity

No classification proposed.

The carcinogenicity study reported below is provided only as supporting information for the assessment of STOT RE.

Table 15: Summary table of animal studies on carcinogenicity

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Non-guideline: dermal carcinogenicity study. Test materials applied dermally to groups of 40 male C3H/Anf mice/group by brushing 3 times per week up for to 29 months. Animals were examined for the development of skin papillomas or carcinomas. Limited details provided in the study summary. Not GLP compliant.	EP-4221 (7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate) (purity: 100 %). One treatment group of 4000 – 8000 mg kg/bw (undiluted). Exact dose not reported. Applied 3 times per week up for to 29 months. Positive control: dermal application of 3-methylcholanthrene. Vehicle control: acetone. Reliability: unreliable.	Result: negative Incidence of skin papillomas was 1/40 in the test group, 2/40 in the vehicle control group and 39/40 in the positive control group.	Anonymous, 1964. ECHA dissemination site, 2021.

10.9.1 Short summary and overall relevance of the provided information on carcinogenicity

In a non-guideline dermal carcinogenicity study, 0.1 – 0.2 g (corresponding to 4000 – 8000 mg/kg bw) of undiluted 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate was applied dermally to 40 male C3H/Anf mice three times per week for up to 29 months. The negative (acetone) and positive (3-mehtylcholanthrene) control groups were treated in the same way. Animals were examined for the development of dermal papillomas or carcinomas. There was no increase in the mortality rate in the 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate group when compared with the negative control. One animal in the 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate group developed a skin tumour at 23 months, which was characterised as a papilloma. Two animals in the negative control group developed skin tumours at 23 months, which were characterised as papillomas. In the positive control group, 39/40 animals developed skin tumours from 3 months and the vast majority were characterised as carcinomas. No further details are reported.

Table 16: Tumour incidence observed in a dermal carcinogenicity study with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate (Anonymous, 1964. ECHA dissemination site, 2021)

Group	Appearance of first tumour	Number of mice with papillomas	Number of mice with carcinomas	Tumour index	Cancer index
Test	23 months	1/40	0/40	6.7	0.0
Negative control	23 months	2/40	0/40	40.0	0.0
Positive control	3 months	39/40	37/40	100.0	94.9

Under the conditions of the study, 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate did not induce the formation of skin tumours in male mice.

10.9.2 Comparison with the CLP criteria

No classification proposed.

10.9.3 Conclusion on classification and labelling for carcinogenicity

No classification proposed.

10.10 Reproductive toxicity

No classification proposed.

The pre-natal developmental toxicity study reported below is provided only as supporting information for the assessment of STOT RE.

10.10.1 Adverse effects on sexual function and fertility

No data available.

10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

Not applicable.

10.10.3 Comparison with the CLP criteria

Not applicable.

10.10.4 Adverse effects on development

Table 17: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
OECD 414: prenatal developmental toxicity study. GLP compliant. Rat, Crl:CD(SD)IGS BR, male/female. 25/female dose.	Cycloaliphatic Epoxy Resin ERL-4221 (trade name of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate) (purity: 92 %) Vehicle: Corn oil. 0, 5, 25, 125 and 500 mg/kg bw/day administered daily from gestation day 6 to 19. Reliability: reliable	Maternal effects: ↓ Body weight at 500 mg/kg bw/day. ↓ Food consumption at ≥ 125 mg/kg bw/day. ↑ Kidney weight at ≥ 125 mg/kg bw/day. Reproductive parameters: No effect on the number of corpora lutea, implantation sites, viable foetuses, sex ratio, resorptions (both early and late) or pre-/post implantation loss. Foetal effects: ↓ Foetal body weight at 500 mg/kg bw/day. ↑ Skeletal variations at 500 mg/kg bw/day.	Anonymous, 2007.

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

In a prenatal developmental toxicity study conducted in accordance with OECD 414, 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate was administered to female rats via oral gavage from gestation day (GD) 6 to 19 at 0, 5, 25, 125 and 500 mg/kg bw/day. All females survived to scheduled sacrifice. A significant decrease in mean body weight gain was observed between GD 6-20 at 500 mg/kg bw/day (94 g) compared with the control (115 g). A decrease in food consumption was observed at ≥ 125 mg/kg bw/day, which reached statistical significance at various time points.

Absolute mean kidney weights were statistically significantly increased at ≥ 125 mg/kg bw/day. The reported weights were 2.09 g, 2.18 g, 2.15 g, 2.29 g and 2.34 g at 0, 5, 25, 125 and 500 mg/kg bw/day, respectively. There was a non-statistically significant increase in absolute mean liver weights at at ≥ 125 mg/kg bw/day. The reported weights were 17.46 g, 17.60 g, 17.47 g, 18.52 g and 18.41 g at 0, 5, 25, 125 and 500 mg/kg bw/day, respectively.

There was no effect on the number of corpora lutea, implantation sites, viable foetuses, sex ratio or resorptions (both early and late). Pre- and post-implantation losses in the treatment group were comparable to the control group. No skeletal or visceral malformations associated with treatment were observed.

At 500 mg/kg bw/day, mean foetal body weigh was significantly decreased. The mean foetal body weights were reported as 3.6 g, 3.6g, 3.5 g, 3.6 g and 3.3 g at 0, 5, 25, 125 and 500 mg/kg bw/day, respectively. At the same dose, the mean litter incidence of ossified cervical centrum number 1 was statistically significantly decreased (11.7 %) when compared with the control (25.7 %). The study report notes that the incidence at 500 mg/kg bw/day was within the historical control range of the test laboratory (6.58 % - 27.6 %). There was also a non-statisitically significant increase in the mean litter incidence of unossified sternebrae numbers 5

and/or 6 (26.4 % compared with 7.6 % in the control) and unossified sternebrae numbers 1, 2, 3 and/or 4 (1.6 % compared with 0.3 % in the control). The study report notes that the incidence of these two variations at 500 mg/kg bw/day was outside the historical control range of the test laboratory (2.13 % – 21.4 % for unossified sternebrae numbers 5 and/or 6 and 0.0 % - 1.0 % for unossified sternebrae numbers 1, 2, 3 and/or 4). The study authors considered that the skeletal variations observed at 500 mg/kg bw/day were indicative of developmental delay.

10.10.6 Comparison with the CLP criteria

No classification proposed.

10.10.7 Conclusion on classification and labelling for reproductive toxicity

No classification proposed.

10.11 Specific target organ toxicity-single exposure

Not evaluated as part of this dossier.

10.12 Specific target organ toxicity-repeated exposure

Table 18: Summary table of animal studies on STOT RE

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
OECD 408: repeated dose 90-day oral toxicity study in rodents. GLP compliant. Rat, Crl:CD(SD)IGS BR, male/female. 25/sex at 0 and 500 mg/kg bw/day; 20/sex at 5 and 50 mg/kg bw/day. No functional observation battery performed. Thyroid hormone levels not measured.	Cycloaliphatic Epoxy Resin ERL-4221 (trade name of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate) (purity: 87 %). 0, 5, 50 and 500 mg/kg bw/day. Daily administration via oral gavage for 91-92 days. Vehicle: Corn oil. 5/sex in the 5 mg/kg bw/day and 50 mg/kg bw/day groups and 10/sex in the 0 and 500 mg/kg bw/day groups were subject to a 28-day recovery period. Reliability: reliable.	Week 13: ↓ Body weight in males at 500 mg/kg bw/day. ↓ Neutrophil count & ↑ lymphocyte count in females at ≥ 50 mg/kg bw/day. ↑ Blood urea nitrogen, mean phosphorus & sorbitol dehydrogenase in males & females at ≥ 50 mg/kg bw/day; ↑ potassium in females at 500 mg/kg bw/day, ↓ creatine kinase in males at ≥ 50 mg/kg bw/day & females at 500 mg/kg bw/day, ↓ cholesterol in males at 500 mg/kg bw/day & females at ≥ 50 mg/kg bw/day, ↓ direct bilirubin in males & females at 500 mg/kg bw/day. ↓ Urine pH & urine creatine in males at 500 mg/kg bw/day. ↑ Absolute liver weight in females at ≥ 50 mg/kg bw/day & males at 500 mg/kg bw/day. ↑ relative liver weight in males & females at ≥ 50 mg/kg bw/day; ↑ Absolute & relative kidney weight in males & females at 500 mg/kg bw/day. Degeneration of olfactory epithelium of nasal tissue in males & females at ≥ 50 mg/kg bw/day. Pale liver observed at 500 mg/kg bw/day. Periportal hepatocellular vacuolation in males &	Anonymous, 2001.

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
		females at ≥ 50 mg/kg bw/day. Week 17 (end of recovery period): ↓ Body weight in males at 500 mg/kg bw/day. Degeneration of olfactory epithelium of nasal tissue in males & females at ≥ 50 mg/kg bw/day. NOAEL: 5 mg/kg bw/day.	
Repeated dose 14-day oral toxicity study. Range finding study for the OECD 408 study (Anonymous, 2001). GLP compliant. Rat, Crl:CD(SD)IGS BR, male/female. 10/sex/dose. No haematological, clinical chemistry or urine analysis was performed. Incidences of effects observed per dose group not reported.	Cycloaliphatic Epoxy Resin ERL-4221 (trade name of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate) (purity: 83 %). Vehicle: Corn oil. 0, 100, 500, 750 and 1000 mg/kg bw/day. Daily administration via oral gavage for 14 days. Reliability: reliable.	↓ Body weight in males at ≥ 500 mg/kg bw/day & females at 1000 mg/kg bw/day. ↓ Body weight gain in males at ≥ 750 mg/kg bw/day & females at 1000 mg/kg bw/day. ↓ Food consumption in males in week 1 at ≥ 750 mg/kg bw/day. 1/10 males at both 500 and 1000 mg/kg bw/day had small testes and epididymis. ↑ Absolute liver weight in males at ≥ 100 mg/kg bw/day and in females at ≥ 500 mg/kg bw/day. ↑ Relative liver weight in males at ≥ 100 mg/kg bw/day and in females at ≥ 500 mg/kg bw/day. Significant "changes" in absolute or relative weights of spleen, heart, kidneys and thymus noted in the study summary but no information on doses or weights reported. Periportal hepatocellular vacuolation in males and females at ≥ 100 mg/kg bw/day. LOAEL: 100 mg/kg bw/day.	Anonymous, 2000. ECHA dissemination site, 2021.
Non-guideline: dermal carcinogenicity study. Not GLP compliant. Mouse, C3H/Anf, male.40 male/group. Test materials applied dermally by brushing 3 times per week for 26 months. Animals were examined for the development of skin papillomas or carcinomas. Limited details provided in the study summary.	EP-4221 (reported to be 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate) (purity: 100 %). Single dose between 4000 – 8000 mg kg/bw (undiluted). Dermal administration 3 times per week for 26 months. Positive control: dermal application of 3-methylcholanthrene. Vehicle control: acetone. Reliability: unreliable.	Result: negative Incidence of skin papillomas was 1/40 in the test group, 2/40 in the vehicle control group and 39/40 in the positive control group. Body weights & organ weights not reported. No non-neoplastic histopathological evaluation performed.	Anonymous, 1964. ECHA dissemination site, 2021.
OECD 414: prenatal developmental toxicity study	Cycloaliphatic Epoxy Resin ERL-4221 (trade name of 7-oxabicyclo[4.1.0]hept-3-	Maternal effects: ↓ Body weight at 500 mg/kg bw/day.	Anonymous, 2007.

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
GLP compliant. Rat, Crl:CD(SD)IGS BR, male/female. 25/female dose. Kidney and liver weights recorded.	ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate) (purity: 92 %). Vehicle: corn oil. 5, 25, 125 and 500 mg/kg bw/day administered daily from gestation day 6 to 19. Reliability: reliable.	↓ Food consumption at ≥ 125 mg/kg bw/day ↑ Kidney weight at ≥ 125 mg/kg bw/day. No histopathological examination of liver or kidney performed. NOAEL maternal toxicity: 25 mg/kg bw/day. Reproductive parameters: No effect on the number of corpora lutea, implantation sites, viable foetuses, sex ratio, resorptions (both early and late) or pre-/post implantation loss. Foetal effects: ↓ Foetal body weight at 500 mg/kg bw/day. ↑ Skeletal variations at 500 mg/kg bw/day.	

10.12.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

In a 90-day oral repeated toxicity study conducted in accordance with OECD 408, 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate was administered via oral gavage to male and female rats at 0, 5, 50 and 500 mg/kg bw/day. At the end of the 90-day dosing period, 10/sex in the 0 and 500 mg/kg bw/day groups and 5/sex in the 5 and 50 mg/kg bw/day groups were subject to a 28-day recovery period.

All animals survived to scheduled sacrifice. Clinical signs of toxicity observed at 500 mg/kg bw/day included salivation, and yellow material on the urogenital area, hind limbs, neck and trunk. A non-statistically significant decrease in body weight was reported in males at 500 mg/kg bw/day during the treatment period, which remained lower than the control group at the end of the recovery period. At week 13, the mean body weight in males at 500 mg/kg bw/day was 546 ± 53 g compared with 585 ± 56 g in the control group. At the end of the recovery period (week 17), the mean body weight in males at 500 mg/kg bw/day was 575 ± 68 g compared with 617 ± 73 g in the control group. There was no effect on body weight in females.

At the end of the 13-week treatment period, a number of clinical chemistry and urinalysis parameters were statistically significantly altered (see table 19 below). At the end of the recovery period, no significant difference in any of the clinical chemistry or urinalysis parameters was observed.

Table 19: Clinical chemistry and urinalysis findings at week 13 in the repeated dose 90-day oral toxicity study with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate (Anonymous, 2001)

Parameter	Week	Dose (mg/kg bw/day)							
		Males				Females			
		0	5	50	500	0	5	50	500
Urea nitrogen (mg/dL)	5	13.5 ± 2.8	13.6 ± 1.2	23.2 ± 2.1**	25.6 ± 3.9**	16.3 ± 2.1	17.0 ± 3.0	23.5 ± 3.0**	20.8 ± 3.1**
	13	12.9 ± 2.4	13.6 ± 2.0	22.7 ± 2.1**	22.4 ± 3.6**	14.1 ± 2.5	13.8 ± 2.8	18.7 ± 3.1**	17.1 ± 4.3**
	17	17.8 ± 4.3	17.7 ± 3.5	15.2 ± 1.4	16.7 ± 1.4	17.0 ± 2.8	18.2 ± 2.0	19.0 ± 3.0	16.2 ± 2.8
Phosphorus (mg/dL)	5	8.4 ± 0.6	8.6 ± 0.3	8.8 ± 0.5	9.2 ± 0.7*	7.6 ± 0.6	7.9 ± 0.6	8.0 ± 0.7	8.4 ± 0.7
	13	6.2 ± 0.6	6.4 ± 0.6	6.9 ± 0.6 **	7.4 ± 0.5 **	6.0 ± 0.9	6.4 ± 0.6	6.8 ± 0.5**	6.9 ± 0.6 **
	17	6.3 ± 1.7	7.1 ± 0.3	6.4 ± 0.6	6.7 ± 0.8	5.7 ± 0.5	5.6 ± 0.6	5.8 ± 0.6	5.9 ± 0.6
Creatine kinase (U/L)	5	379 ± 155.9	368 ± 145.1	375 ± 102.5	192 ± 77.3 **	567 ± 387.8	658 ± 449.0	465 ± 201.4	135 ± 67.8 *
	13	243 ± 127.2	161 ± 56.6 *	157 ± 57.5 **	67 ± 27.7**	273 ± 170.8	316 ± 193.2	259 ± 158.2	106 ± 56.7 *
	17	251 ± 126.1	362 ± 199.6	218 ± 118.9	494 ± 329.7	324 ± 169.1	345 ± 227.5	337 ± 94.4	425 ± 311.9
Cholesterol (mg/dL)	5	60 ± 7.8	65 ± 12.5	48 ± 12.4	36 ± 13.6**	66 ± 10.5	72 ± 12.8	63 ± 18.2	51 ± 12.0
	13	69 ± 11.4	75 ± 17.8	56 ± 15.7	45 ± 16.3**	67 ± 13.5	74 ± 16.7	52 ± 16.0*	56 ± 18.8
	17	88 ± 15.9	88 ± 25.1	90 ± 10.4	80 ± 22.4	90 ± 31.9	89 ± 7.4	76 ± 7.3	74 ± 23.1
Potassium (mEq/L)	5	5.37 ± 0.5	5.64 ± 0.4	5.58 ± 0.6	5.68 ± 0.4	5.37 ± 0.5	5.59 ± 0.5	5.56 ± 0.3	5.63 ± 0.4
	13	5.09 ± 0.3	5.21 ± 0.3	5.16 ± 0.4	5.32 ± 0.5	4.93 ± 0.6	5.27 ± 0.5	5.32 ± 0.5	5.54 ± 0.6 **
	17	5.52 ± 0.5	5.65 ± 1.0	5.24 ± 0.3	5.79 ± 0.4	5.14 ± 0.3	6.22 ± 1.6*	4.5 ± 0.3	5.16 ± 0.6
Direct bilirubin (mg/dL)	5	0.04 ± 0.0	0.04 ± 0.0	0.05 ± 0.0	0.08 ± 0.0 **	0.06 ± 0.0	0.04 ± 0.0	0.04 ± 0.0	0.07 ± 0.0
	13	0.04 ± 0.0	0.04 ± 0.0	0.05 ± 0.0	0.06 ± 0.0**	0.04 ± 0.0	0.05 ± 0.0	0.05 ± 0.0	0.08 ± 0.0**
	17	0.00 ± 0.0	0.01 ± 0.0	0.00 ± 0.0	0.02 ± 0.0	0.01 ± 0.0	0.03 ± 0.0	0.01 ± 0.0	0.00 ± 0.0
Sorbitol dehydrogenase (U/L)	5	16.7 ± 4.7	26.8 ± 17.3	22.3 ± 5.9	43.4 ± 20.7**	12.5 ± 2.9	14.1 ± 4.8	22.2 ± 11.1	30.4 ± 18.5**
	13	17.5 ± 4.4	19.6 ± 4.1	20.8 ± 4.2	33.4 ± 13.1**	17.6 ± 5.4	17.9 ± 5.8	21.9 ± 7.9	27.5 ± 8.2**

Parameter	Week	Dose (mg/kg bw/day)							
		Males				Females			
		0	5	50	500	0	5	50	500
	17	20.7 ± 5.5	17.4 ± 6.5	26.4 ± 8.0	30.2 ± 28.6	31.8 ± 29.9	18.3 ± 3.3	22.2 ± 8.8	15.3 ± 7.3
Urine pH	5	7.3 ± 1.1	7.9 ± 0.7	6.8 ± 1.0	6.0 ± 0.7**	7.2 ± 1.1	6.5 ± 1.2	6.7 ± 1.1	5.8 ± 0.4*
	13	6.3 ± 1.0	6.2 ± 0.7	6.3 ± 0.7	5.6 ± 0.5*	6.4 ± 1.2	6.0 ± 0.7	6.0 ± 0.6	5.6 ± 0.8
	17	7.9 ± 1.2	6.9 ± 1.0	7.0 ± 1.0	6.8 ± 1.2	6.9 ± 0.8	7.4 ± 1.5	6.4 ± 0.2	6.3 ± 0.9
Urine creatinine (mg/dL)	5	140.7 ± 64.1	90.5 ± 40.0*	131.4 ± 35.6	85.6 ± 18.0*	72.3 ± 32.7	97.8 ± 30.5	84.3 ± 63.4	64.3 ± 16.8
	13	267.8 ± 115.9	226.2 ± 99.8	249.1 ± 89.0	135.9 ± 38.2**	101.7 ± 75.8	123.1 ± 74.4	107.2 ± 59.3	107.8 ± 44.0
	17	146.1 ± 83.4	187.2 ± 59.1	124.0 ± 92.6	141.1 ± 81.1	101.2 ± 46.5	84.7 ± 27.4	105.5 ± 17.2	81.9 ± 35.6

* p< 0.05 ** p < 0.01

Absolute liver weights were statistically significantly increased in females at ≥ 50 mg/kg bw/day and males at 500 mg/kg bw/day. The absolute liver weights were 8.3 g, 8.21 g, 9.48 g and 9.98 g in females and 16.36 g, 16.38 g, 18.09 g and 19.64 g in males at 0, 5, 50 and 500 mg/kg bw/day, respectively. Relative liver weights were statistically significantly increased in females and males at ≥ 50 mg/kg bw/day. Absolute kidney weights were statistically significantly increased in females at 500 mg/kg bw/day and there was a non-statistically significant increase in males at the same dose. The absolute kidney weights were 1.89 g, 1.96 g, 1.97 g and 2.14 g in females and 3.96 g, 3.82 g, 3.91 g and 4.57 g in males at 0, 5, 50 and 500 mg/kg bw/day, respectively. Relative kidney weights were statistically significantly increased in females and males at 500 mg/kg bw/day. At the end of the recovery period at week 17, there was no significant difference in absolute or relative weights of either organ.

Table 20: Organ weights in the repeated dose 90-day oral toxicity study with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate (Anonymous, 2001)

Organ weights	Dose (mg/kg bw/day)							
	Males				Females			
	0	5	50	500	0	5	50	500
Week 13								
Absolute kidney (g)	3.96 ± 0.4	3.82 ± 0.3	3.91 ± 0.5	4.57 ± 0.6**	1.89 ± 0.2	1.96 ± 0.1	1.97 ± 0.2	2.14 ± 0.1**
Relative kidney (g/100 g)	0.714 ± 0.1	0.690 ± 0.1	0.721 ± 0.1	0.875 ± 0.1**	0.665 ± 0.1	0.705 ± 0.1	0.700 ± 0.1	0.817 ± 0.1 **
Absolute liver (g)	16.36 ± 1.9	16.38 ± 2.7	18.09 ± 2.3	19.64 ± 2.9 **	8.30 ± 0.7	8.21 ± 1.7	9.48 ± 0.9**	9.98 ± 1.0**
Relative liver (g/100 g)	2.932 ± 0.2	2.928 ± 0.2	3.318 ± 0.2**	3.751 ± 0.3**	2.923 ± 0.2	2.937 ± 0.6	3.375 ± 0.3**	3.809 ± 0.3**
Week 17								
Absolute kidney (g)	3.94 ± 0.6	3.96 ± 0.5	4.03 ± 0.6	4.2 ± 0.4	2.02 ± 0.1	1.77 ± 0.2	2.07 ± 0.2	2.16 ± 0.2
Relative kidney (g/100 g)	0.677 ± 0.1	0.670 ± 0.0	0.708 ± 0.0	0.766 ± 0.1	0.696 ± 0.0	0.655 ± 0.0	0.696 ± 0.1	0.719 ± 0.0
Absolute liver (g)	16.18 ± 2.0	16.82 ± 2.5	15.76 ± 3.1	16.52 ± 2.4	8.93 ± 0.7	7.69 ± 1.0	9.25 ± 1.4	9.26 ± 1.4
Relative liver (g/100 g)	2.75 ± 0.1	2.836 ± 0.1	2.757 ± 0.3	2.997 ± 0.4	3.074 ± 0.2	2.842 ± 0.2	3.097 ± 0.2	3.066 ± 0.2

* p< 0.05 ** p < 0.01

An increased incidence of periportal hepatocellular vacuolation was observed in males and females at ≥ 50 mg/kg bw/day. The incidence was reported as 4/15, 5/15, 15/15 and 15/15 in males and 2/15, 2/15, 12/15 and 15/15 in females at 0, 5, 50 and 500 mg/kg bw/day, respectively. The severity was reported to be minimal at 0, 5 and 50 mg/kg bw/day and mild at 500 mg/kg bw/day. At the end of the recovery period, the incidence in the treatment groups was comparable to that in the control group.

Degeneration of the olfactory epithelium of the nasal tissue was observed in males and females at ≥ 50 mg/kg bw/day. The study report states that the degeneration was characterised by the loss of sustentacular cells, vacuolation and desquamation of neuroepithelial cells, which resulted in decreased height of the olfactory epithelium. The incidence was reported as 0/15, 0/15, 2/15 and 12/15 in males and 0/15, 0/15, 3/15 and 13/15 in females at 0, 5, 50 and 500 mg/kg bw/day, respectively. No effect on basal cells, the underlying structures or connective tissue was reported.

Table 21: Incidence of degeneration of olfactory epithelium at week 13 in the repeated dose 90-day oral toxicity study with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate (Anonymous, 2001)

Olfactory epithelium degeneration	**Dose (mg/kg bw/day)**							
	Males				**Females**			
	0	**5**	**50**	**500**	**0**	**5**	**50**	**500**
Number of animals examined	15	15	15	15	15	15	15	15
Cross section of nasal cavity level 1	0	0	0	1	0	0	0	0
Mild	-	-	-	1	-	-	-	-
Cross section of nasal cavity level 2	0	0	2	12	0	0	0	10
Minimal	-	-	-	1	-	-	-	-
Mild	-	-	2	4	-	-	-	2
Moderate	-	-	-	3	-	-	-	8
Severe	-	-	-	4	-	-	-	-
Cross section of nasal cavity level 3	0	0	2	11	0	0	3	13
Minimal	-	-	-	-	-	-	3	-
Mild	-	-	2	2	-	-	-	2
Moderate	-	-	-	7	-	-	-	11
Severe	-	-	-	2	-	-	-	-
Cross section of nasal cavity level 4	0	0	2	11	0	0	1	11
Minimal	-	-	1	-	-	-	1	-
Mild	-	-	1	6	-	-	-	5
Moderate	-	-	-	4	-	-	-	6
Severe	-	-	-	1	-	-	-	-

At the end of the recovery period, olfactory epithelium degeneration was observed in both sexes at ≥ 50 mg/kg bw/day but at a lower incidence than that observed at week 13. The incidence was 0/10, 0/5, 2/5 and 9/10 in males and 0/10, 0/5, 3/5 and 7/10 in females at 0, 5, 50 and 500 mg/kg bw/day, respectively. The study report notes that there was some evidence of regenerative changes: basal cell proliferation and regeneration of sustentacular and neuroepithelial cells was reported. Foci of replacement of olfactory epithelium by ciliated columnar epithelium was observed in 6/10 males and 9/10 females at 500 mg/kg bw/day and the study report considered this change to be part of the repair process, suggesting that local damage to basal cells prevented repair to olfactory epithelium.

Table 22: Incidence of degeneration of olfactory epithelium at the end of the recovery period (week 17) in the repeated dose 90-day oral toxicity study with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate (Anonymous, 2001)

Olfactory epithelium degeneration	Dose (mg/kg bw/day)							
	Males				Females			
	0	5	50	500	0	5	50	500
Number of animals examined	10	5	5	10	10	5	5	10
Cross section of nasal cavity level 1	0	0	0	0	0	0	0	0
Cross section of nasal cavity level 2	0	0	0	7	0	0	0	3
Minimal	-	-	-	1	-	-	-	-
Mild	-	-	-	6	-	-	-	3
Cross section of nasal cavity level 3	0	0	2	6	0	0	3	7
Minimal	-	-	1	-	-	-	2	-
Mild	-	-	1	6	-	-	1	7
Cross section of nasal cavity level 4	0	0	0	6	0	0	1	5
Minimal	-	-	-	-	-	-	1	-
Mild	-	-	-	6	-	-	-	5

A NOAEL of 5 mg/kg bw/day is identified based on effects observed in the nasal cavity (olfactory epithelial degeneration) and in the liver (increase in absolute liver weight and increased incidence of periportal hepatocellular vacuolation) at 50 and 500 mg/kg bw/day. The dossier submitter notes that no difficulties with administration of the dose via gavage cannula were reported. In addition, no clinical signs after dosing were reported which would indicate reflux of the test material. The dossier submitter notes that, given the low vapour pressure of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate (-2 x 10^{-3} Pa) and the choice of vehicle (corn oil) in the study, it is considered unlikely that animals at 50 or 500 mg/kg bw/day were exposed to toxic or caustic vapours from the oral preparation. Therefore, while effects on nasal tissue following oral administration are relatively rare, the dossier submitter considers that based on the available information the effects observed on nasal tissue, which were not fully reversible after a 4 week recovery period, were treatment related.

In a 14-day oral repeated toxicity study conducted as a range finding study for the 90-day repeated dose toxicity study (Anonymous 2001, discussed above), 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate was administered via oral gavage to male and female rats at 0, 100, 500, 750 and 1000 mg/kg bw/day for 14 days. All animals survived to scheduled sacrifice. A non-statistically significant decrease in body weight was observed in males at ≥ 500 mg/kg bw/day and in females at 1000 mg/kg bw/day. Organ weights were not reported however; the study summary reports that absolute liver weights were increased in males at ≥ 100 mg/kg bw/day and females at ≥ 500 mg/kg bw/day, and relative liver weights were increased in males at ≥ 100 mg/kg bw/day and in females at ≥ 500 mg/kg bw/day.

Fine periportal hepatocellular vacuolation was observed in both sexes at ≥ 100 mg/kg bw/day. The study summary notes that the severity of the lesion appeared to be qualitatively and/or quantitatively greater at ≥

500 mg/kg bw/day, without providing details of the exact incidences. 1/10 males at 500 and 1000 mg/kg bw/day were reported to have small testes and epididymis. The same animals had mild to moderate seminiferous tubule degeneration of the testes and lumenal cellular debris and hypospermia of the epididymis. There was no indication in the study summary as to whether the nasal tissue was examined.

In a non-guideline dermal carcinogenicity study, 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate was applied undiluted to the skin of male mice at a single dose of between 4000 and 8000 mg/kg bw/day for 26 months. No organ weights or non-neoplastic histopathological examinations were performed. No increase in dermal tumour incidence was observed.

In a prenatal developmental toxicity study conducted in accordance with OECD 414, 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3-carboxylate was administered to female rats via oral gavage from gestation day (GD) 6 to 19 at 0, 5, 25, 125 and 500 mg/kg bw/day. All females survived to scheduled sacrifice. A significant decrease in mean body weight gain was observed between GD 6-20 at 500 mg/kg bw/day (94 g) compared with the control (115 g). Absolute kidney weights were statistically significantly decreased at ≥ 125 mg/kg bw/day. The reported weights were 2.09 g, 2.18 g, 2.15 g, 2.29 g and 2.34 g at 0, 5, 25, 125 and 500 mg/kg bw/day, respectively. No effect on liver weight was reported. No histopathological examination of kidney or liver were performed.

Due to the limited histopathological assessment performed in both the carcinogenicity study and the prenatal developmental toxicity study, these studies are not considered further in the weight of evidence assessment for classification for specific target organ toxicant following repeated exposure.

Table 23: Extrapolation of equivalent effective dose for toxicity studies of greater or lesser duration than 90 days

Study reference	Effective dose (mg/kg bw/day)	Length of exposure	Extrapolated guidance value for STOT RE 2	Classification supported by the study
OECD 408: repeated dose 90-day oral toxicity study in rodents (Anonymous, 2001).	Nasal cavity effects (epithelial degeneration) observed at ≥ 50 mg/kg bw/day. Liver effects (increase in absolute liver weight and increased incidence of periportal hepatocellular vacuolation) observed at ≥50 mg/kg bw/day.	90-days	10 < C ≤ 100 mg/kg bw/day	STOT RE 2
14-day repeated dose toxicity study (Anonymous, 2000. ECHA dissemination site, 2021.)	Liver effects (fine periportal hepatocellular vacuolation) at ≥ 100 mg/kg bw/day.	14 days	60 < C ≤ 600 mg/kg bw/day	STOT RE 2

10.12.2 Comparison with the CLP criteria

According to Annex I to the CLP Regulation, substances are classified as specific target organ toxicants following repeated exposure by the use of expert judgement, including the use of the recommended guidance values (as outlined in 3.9.2.9 of the CLP Regulation) and assigned to one of two categories:

Category 1:

"Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure. Substances are classified in category 1 for target organ toxicity (repeat exposure) on the basis of:

- reliable and good quality evidence from human cases or epidemiological studies; or

- observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose/ concentration values are provided below (see 3.9.2.9), to be used as part of a weight-of evidence evaluation."

The guidance value for STOT RE category 1 is C ≤ 10 mg/kg bw/day for an oral 90-day repeated dose toxicity study in rats.

Category 2:

"Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure. Substances are classified in category 2 for target organ toxicity (repeat exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) in order to help in classification. In exceptional cases human evidence can also be used to place a substance in Category 2 (see 3.9.2.6)."

The guidance value for STOT RE category 2 is 10 < C ≤ 100 mg/kg bw/day for an oral 90-day repeated dose toxicity study in rats.

No human repeated dose toxicity data are available for oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3- carboxylate.

Nasal cavity effects

In the available 90-day oral repeated toxicity study in rats with 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3- carboxylate, degeneration of the olfactory epithelium of the nasal tissue was observed in both sexes at ≥ 50 mg/kg bw/day. The degeneration was characterised by the loss of sustentacular cells, vacuolation and desquamation of neuroepithelial cells, which resulted in decreased height of the olfactory epithelium. These effects were not fully reversible after a 4 week recovery period. According to 3.9.2.7.3 (b) of Annex I of the CLP Regulation, *"effects on special senses (e.g. sight, hearing and smell)"* are considered to be indications of functional impairment and should be taken into consideration in the classification process. There is no data to indicate that this effect on the olfactory epithelium is not relevant for humans and therefore it should be considered for classification purposes.

The observed effect on the nasal tissue in the 90-day repeated dose toxicity study occurred at a dose (50 mg/kg bw/day) within the guidance value range for classification as STOT RE category 2 (10 < C ≤ 100 mg/kg bw/day). Therefore, classification in category 2 is warranted.

Liver effects

An increase in liver weight was observed in females at ≥ 50 mg/kg bw/day and males at 500 mg/kg bw/day. This was accompanied by alterations in clinical chemistry parameters at 500 mg/kg bw/day (decreased cholesterol and increase in direct bilirubin and sorbitol dehydrogenase) and an increased incidence of periportal hepatocellular vacuolation at ≥ 50 mg/kg bw/day. The effects observed in the liver were reversible

after a 4 week recovery period. Supporting evidence is provided from a 14-day repeated dose toxicity study were fine periportal hepatocellular vacuolation was observed at ≥ 100 mg/kg bw/day. According to 3.9.2.8.1 of Annex I of the CLP Regulation, classification is not justified for "*changes in organ weight with no evidence of organ dysfunction"* and *"adaptive responses that are not considered toxicologically relevant"*. Although some alterations of clinical chemistry parameters were observed, they did not indicate functional impairment of the liver. The only histopathological finding in the liver was hepatocellular vacuolation which may be an adaptive response rather than a significant toxic response. Therefore, although the observed effect on the liver in the 90-day repeated dose toxicity study occurred at a dose (50 mg/kg bw/day) within the guidance value range for classification as STOT RE category 2 (10 < C ≤ 100 mg/kg bw/day), the dossier submitter considers that this effect does not support classification for specific target organ toxicity following repeated exposure.

10.12.3 Conclusion on classification and labelling for STOT RE

Based on the available data, classification of 7-oxabicyclo[4.1.0]hept-3-ylmethyl 7-oxabicyclo[4.1.0]heptane-3- carboxylate as STOT RE category 2 is warranted. The hazard statement (H373) should specify the "nasal cavity" as the organ effected. As data is available from only one route of exposure (oral), it is proposed not to state the route in the hazard statement. Based on the available data, the assignment of a specific concentration limit is not warranted.

10.13 Aspiration hazard

Not evaluated as part of this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated as part of this dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated as part of this dossier.

13 ADDITIONAL LABELLING

Not applicable.

14 REFERENCES

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15 ANNEX I

Detailed study summaries for studies referenced in this report.