**Committee for Risk Assessment**

**RAC**

Annex 2

**Response to comments document (RCOM)**

to the Opinion proposing harmonised classification and labelling at EU level of

# iprovalicarb (ISO); isopropyl [(2S)-3-methyl-1-{[1-(4-methylphenyl)ethyl]amino}-1-oxobutan-2-yl]carbamate

**EC Number: -**

**CAS Number: 140923-17-7**

CLH-O-0000001412-86-237/F

**Adopted**

**30 November 2018**

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON IPROVALICARB (ISO); ISOPROPYL [(2S)-3-METHYL-1-{[1-(4-METHYLPHENYL)ETHYL]AMINO}-1-OXOBUTAN-2-YL]CARBAMATE**

## COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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**Substance name: iprovalicarb (ISO); isopropyl [(2S)-3-methyl-1-{[1-(4-methylphenyl)ethyl]amino}-1-oxobutan-2-yl]carbamate**
**EC number: -**
**CAS number: 140923-17-7**
**Dossier submitter: Ireland**

### GENERAL COMMENTS

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 15.03.2018 | France | | MemberState | 1 |
| Comment received | | | | |
| According to EFSA conclusion (Journal 2015;13(4):4060), the IUPAC name of the substance Iprovalicarb is isopropyl [(1S)-2-methyl-1-{[(1RS)-1-p-tolylethyl]carbamoyl}propyl]carbamate and the CAS name is 1-methylethyl N-[(1S)-2-methyl-1-[[[1-(4-methylphenyl)ethyl]amino]carbonyl]propyl]carbamate.<br><br>According to EFSA conclusion (Journal 2015;13(4):4060), toluene is considered as a relevant impurity with a limit at max.3g/kg. | | | | |
| Dossier Submitter's Response | | | | |
| Noted. The DS defers to the chemistry identification unit of ECHA to let them decide which is correct EFSA or ECHA.<br><br>The IUPAC name in all ECHA correspondence has been: isopropyl [(2S)-3-methyl-1-{[1-(4-methylphenyl)ethyl]amino}-1-oxobutan-2-yl]carbamate<br><br>The EFSA conclusion also states in the same sentence "Toluene was considered a relevant impurity from the toxicological point of view…although at the level found in the technical specification it is considered of of no concerm." The DS fails to see what point is being made in the above statement. | | | | |
| RAC's response | | | | |
| Thank you very much. Noted. The substance will be named according to opinion of the chemistry identification unit of ECHA. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 08.03.2018 | Germany | | MemberState | 2 |
| Comment received | | | | |
| Classification as Carc. 2, H351 requires labelling with signal word "Warning" instead of "Danger".<br>In addition, page numbering in the CLH report would be helpful for the commentary phase and follow-up discussions. | | | | |
| Dossier Submitter's Response | | | | |
| Noted and apologies for the oversight. The RAC opinion document will have the amended labelling indicated. | | | | |
| RAC's response | | | | |
| Thank you very much. Noted. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 19.03.2018 | Belgium | | MemberState | 3 |
| Comment received | | | | |
| BE CA welcomes this proposal for harmonized classification and labelling and would like to thank the PRCD DAFM Ireland for this well documented CLH proposal dossier. As a general comment, Iprovalicarb has a reported 95% degree of purity. We regret that the 5% impurities are reported as a confidential information.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment carcinogenic potential of iprovalicarb .docx | | | | |
| Dossier Submitter's Response | | | | |
| Noted. | | | | |
| RAC's response | | | | |
| Thank you very much. Noted. | | | | |

**CARCINOGENICITY**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 16.03.2018 | Spain | | MemberState | 4 |
| Comment received | | | | |
| An increased incidence of rare and uncommon tumours was recorded following chronic exposure of Wistar rats to iprovalicarb. The increased incidences at the high dose (20000 ppm) of malignant osteosarcoma (males) and benign transitional cell papillomas of the urinary bladder (females) and malignant mixed Muellerian tumours of the uterus from the intermediate dose (5000 ppm), were outside the concurrent controls and the historical control data ranges provided. The observed statistically significant trend towards an increase in thyroid follicular adenoma in females was outside the relevant historical control range given. There was no evidence of carcinogenicity in the long-term mouse study.<br><br>Iprovalicarb is not genotoxic. There is no evidence of pre-neoplastic change in any of the tumour-bearing organs and although some mechanistic data suggest that iprovalicarb is not a tumour initiator, no mode of action could be established for induction of any tumour type.<br><br>Although incidences of these tumours were low and confined to a single species at high | | | | |

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| doses, not otherwise considered excessively toxic, none of these tumour types was seen in control animals and they are either rare or uncommon in this strain of rat.<br><br>On overall, the Spanish CA agrees with the dossier submitter that, a possible relationship to treatment cannot be discounted and therefore it can´t be ruled out their relevance to humans. Therefore, classification with category 2 (H351) for carcinogenic is the most appropriate in this case. |
| Dossier Submitter's Response |
| Noted. Thank you for your support. |
| RAC's response |
| Thank you very much. Noted. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 15.03.2018 | France | | MemberState | 5 |
| Comment received | | | | |
| The classification proposal Carc 2 based on the low incidences of rare and uncommon tumours in the rat is supported. | | | | |
| Dossier Submitter's Response | | | | |
| Noted. Thank you for your support. | | | | |
| RAC's response | | | | |
| Thank you very much. Noted. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 08.03.2018 | Germany | | MemberState | 6 |
| Comment received | | | | |
| Upon analysis of the CLH report, we support CA proposal for carcinogenicity classification category 2 based on increase in incidences of rare type of malignant tumours in male and female rats treated with Iprovalicarb.<br>In males, 6 % increase in combined incidences of osteosarcoma of femur and lower jaw. No tumours of this type were observed in control animals in this study. Importantly, the incidence rate observed in treated males exceeds in-house HCD (0.1 % average, range 0 -1.7 %) and the RITA historical database data (0.2 % average, range 0 – 4 %).<br>Increased/accelerated ossification in the sterneabrae 5 observed in developmental toxicity study in rabbits points towards dysregulation of the differentiation of osteoblast potentially induced by the Iprovalicarb. In analysis of the mechanistic study investigating proliferation in selected tissues (document number M-267627-01 cited in Ref. 1), PCNA labelling of target tissues from 104-week sacrifice does not address the question specifically, as staining was analysed for osteocytes which represent late-stage differentiated bone-forming cells deprived of proliferation function. Thus, the conclusion that there were no differences in DNA replication rate between control and treated tissues in this case might be misleading.<br>Supporting information: Increase in malignant tumours was reported for females in this study as well. An increase in incidences of mixed muellerian tumours was observed in 20 000 ppm (4 %, 2 incidences) and 5000 ppm (2 %, 1 incidence). This is a rare type of tumour, with highest historical control incidence rate of 0 % (in-house data) and 2 % (RITA database). In the mechanistic study, replication in uterine tissues in samples from 24-month sacrifice, showed 90 % increase (1.9-fold, $p < 0.05$) in high dose and 60 % (1.6-fold, $p < 0.05$) in mid-dose treated animals. | | | | |

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| Ref 1: Tier 2 Summary of KIIA5 Toxicological and Toxicokinetic Studies on the active substance for Iprovalicarb, available from https://cropscience-transparency.bayer.com/-/media/BCS.../M-430953-02-3.ashx |
| Dossier Submitter's Response |
| Agreed. Thank you for your support. |
| RAC's response |
| Thank you very much. Noted. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.03.2018 | Sweden | | MemberState | 7 |
| Comment received | | | | |
| The Swedish Chemicals Agency agrees with the proposed classification of Iprovalicarb as Carc 2. Exposure to the substance caused rare tumors that may be of human relevance. Perhaps an endocrine disrupting mechanism is involved since some of the tumors developed in hormone-sensitive tissues. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your support. There is no indication in the data from the available studies in the whole toxicological database for iprovalicarb to support an endocrine-disruption mediated mode of action. Lesions indicating an effect on the thyroid gland such as hypertrophy have not been reported for example. There were no reported effects on fertility in the 2-generation rat study nor any relevant findings in the rat/rabbit development studies. In rat, mouse and dog, the liver has been identified as the main target organ in repeat dose studies as indicated by higher liver weights associated with liver enzyme induction and/or hepatocellular hypertrophy in all 3 species. There was no evidence of endocrine disruption. Increases in relative adrenal weight observed in high-dose males (dog, 1 year study) were not accompanied by any related clinico-chemical or histopathological findings. Despite the fact that according to the material and methods, hormone levels were measured in the short-term and long-term toxicity studies in rats no final measurement was made on hormone levels in any of the studies submitted. There were no specific investigations or studies to determine evidence of potential endocrine-mediated effects, there is no data to determine if the observed pattern of tumour incidence could be due to an endocrine-mediated effect. | | | | |
| RAC's response | | | | |
| Thank you very much. Noted. RAC supports the DS's opinion about the lack of evidences for a potential mechanism of carcinogenicity based on endocrine disruption. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 19.03.2018 | Denmark | | MemberState | 8 |
| Comment received | | | | |
| DK support the proposed classification of iprovalicarb as Carc. 2; H351. We propose at slight change of wording as we find it a bit contradicting to conclude in 4.10.6 that the exposure were to significantly high doses, as it was concluded on p. 52 that the dosing was considered to be 'adequate for assessment of chronic toxicity and carcinogenicity' even though the dose was in excess of 1000 mg/kg bw/day. | | | | |
| Dossier Submitter's Response | | | | |
| Noted. | | | | |
| RAC's response | | | | |
| Thank you very much. Noted. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 19.03.2018 | Belgium | | MemberState | 9 |

Comment received

The carcinogenic potential of iprovalicarb has been assessed in rat and mouse.
In a combined chronic toxicity/carcinogenicity study in rat, various neoplastic findings have been reported without significant increase in general toxicity at the high dose level of 20.000 ppm (1109,6/1379,7 mg/kg bw/day) :
- Skeletal system : 3 males with osteosarcoma (6 %, out of HCD), and 1 male with a chondrosarcoma of the nasal cavity.
- Reproductive tract : Although non-statistically significant, a dose related-increase in malignant mixed Muellerian tumours was reported exceeding HCD (uterus, 1 female at mid dose, 2 at top dose, including metastases in one of the two animals). Moreover 2 females of top dose had a squamous cell carcinoma of the clitoral gland. Although infrequent in rats, the relevance of these last findings seem nevertheless difficult to assess.
- Urinary tract : Benign transitional cell papillomas were found in the urinary bladder of 2 top dose females (4%, non-statistically significant, exceeding HCD). To note, the absence of non-neoplastic findings in the bladder of males might be explained by differences in excretion routes between males and females (mainly faeces for males vs faeces and urine for female).
- Thyroid : Two types of neoplastics findings were reported in thyroid. First, an increase in follicular cell adenoma in female at mid and top dose (4% at 20.000 ppm, exceeding in-house HCD). Secondly, increased follicular cell carcinoma was reported in top dose females (2%, exceeding in-house HCD).
BE CA would appreciate further enlightenments regarding the number of animals intercurrently died or killed. Indeed, in Table 32 of the CLH proposal (Tumour-bearing animals dying intercurrently or killed at termination), the following numbers are presented :

Male Female
Dose (ppm) 0 500 5000 20000 0 500 5000 20000
Number examined 19 20 14* 12 17 20 14* 17
Animals with tumours 7 15 10* 9 15 14* 12 14

Whereas in Table 33 (same page, Occurrence of tumours over time), the following are stated regarding animals intercurrenty died or killed :

Male Female
Dose (ppm) 0 500 5000 20000 0 500 5000 20000
Number examined 19 20 15* 12 17 20 16* 17
Summed animals with tumours 7 15 11* 9 15 15* 12 14

Moreover, in Table 32, there is a discrepancy between the number of intercurrently died/killed males at 500 ppm (20) and at terminal kill (31) vs all males at same dose (50).
In conclusion, the incidence in rat of rare tumours (benign, malignant) in various sites, resulting in metastasis for some cases warrants a classification for carcinogenicity. The genotoxic potential of iprovalicarb remains uncertain (negative genotoxic studies but QSAR alert due to the isopropyl carbamate). Taking into consideration the absence of neoplastic findings in mouse, BE CA supports the DS proposal to classify iprovalicarb as Carc. 2.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment carcinogenic potential of iprovalicarb .docx

Dossier Submitter's Response

Noted. The DS welcomes the comments by BE in their attached document. Unfortunately we cannot fully clarify your questions about the number of animals intercurrently died or killed as the tables reported in the original study report are not well explained and the data in the original study (tables 18 and 19 of the original study report) is as reported in the amended tables below.
The typographical errors discovered are amended (in red/yellow).

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"BE CA would appreciate further enlightenments regarding the number of animals intercurrently died or killed. Indeed, in Table 32 of the CLH proposal (Tumour-bearing animals dying intercurrently or killed at termination), the following numbers are presented:

| | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| Dose (ppm) | 0 | 500 | 5000 | 20000 | 0 | 500 | 5000 | 20000 |
| Number examined | 19 | 20 | **14*** | 12 | 17 | 20 | **14*** | 17 |
| Animals with tumours | 7 | 15 | 10 | 9 | 15 | 14 | 12 | 14 |

Whereas in Table 33 (same page, Occurrence of tumours over time), the following are stated regarding animals intercurrenty died or killed :

| | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| Dose (ppm) | 0 | 500 | 5000 | 20000 | 0 | 500 | 5000 | 20000 |
| Number examined | 19 | 20 | **15*** | 12 | 17 | 20 | **16*** | 17 |
| Summed animals with tumours | 7 | 15 | 10 | 9 | 15 | 14 | 12 | 14 |

Moreover, in Table 32, there is a discrepancy between the number of intercurrently died/killed males at 500 ppm (20) and at terminal kill (31)

DS: typographical error, should be (30 at terminal kill) vs all males at same dose (50)."

RAC's response

Thank you very much. Noted.

**MUTAGENICITY**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.03.2018 | Sweden | | MemberState | 10 |

Comment received

The Swedish Chemicals Agency agrees with no classification of Iprovalicarb for germ cell mutagenicity.

| Dossier Submitter's Response |
|---|
| Agreed. Thank you for your support. |
| RAC's response |
| Thank you very much. Noted. |

**TOXICITY TO REPRODUCTION**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 08.03.2018 | Germany | | MemberState | 11 |
| Comment received | | | | |
| We agree with DS opinion that no classification is warranted. | | | | |
| Dossier Submitter's Response | | | | |
| Agreed. Thank you for your support. | | | | |
| RAC's response | | | | |
| Thank you very much. Noted. | | | | |

**OTHER HAZARDS AND ENDPOINTS – Acute Toxicity**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 08.03.2018 | Germany | | MemberState | 12 |
| Comment received | | | | |
| No classification is suggested/required due to low acute toxicity. | | | | |
| Dossier Submitter's Response | | | | |
| Agreed. Thank you for your support. | | | | |
| RAC's response | | | | |
| Thank you very much. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 19.03.2018 | Belgium | | MemberState | 13 |
| Comment received | | | | |
| BE CA agrees that no classification is warranted for acute toxicity.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment carcinogenic potential of iprovalicarb .docx | | | | |
| Dossier Submitter's Response | | | | |
| Agreed. Thank you for your support. | | | | |
| RAC's response | | | | |
| Thank you very much. Noted. | | | | |

**OTHER HAZARDS AND ENDPOINTS – Skin Hazard**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 08.03.2018 | Germany | | MemberState | 14 |
| Comment received | | | | |
| Based on the evaluation of skin irritation and eye irritation/corrosion study in rabbits by Krötlinger, F. (1992) as described in Volume 3 of the RAR (RMS IE, 2013), no classification for skin irritation is required. | | | | |

| Dossier Submitter's Response |
|---|
| Agreed. Thank you for your support. |
| RAC's response |
| Thank you very much. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 19.03.2018 | Belgium | | MemberState | 15 |
| Comment received | | | | |
| BE CA agrees that no classification is warranted for skin irritation.<br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment carcinogenic potential of iprovalicarb .docx | | | | |
| Dossier Submitter's Response | | | | |
| Agreed. Thank you for your support. | | | | |
| RAC's response | | | | |
| Thank you very much. | | | | |

**OTHER HAZARDS AND ENDPOINTS – Eye Hazard**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 08.03.2018 | Germany | | MemberState | 16 |
| Comment received | | | | |
| Non-persistent irritation of the conjuctivae was observed in one animal, in Krötlinger, F. (1992) as described in Volume 3 of the RAR (RMS IE, 2013). We agree with position of the DS that no classification is applicable. | | | | |
| Dossier Submitter's Response | | | | |
| Agreed. Thank you for your support. | | | | |
| RAC's response | | | | |
| Thank you very much. Noted. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 19.03.2018 | Belgium | | MemberState | 17 |
| Comment received | | | | |
| BE CA agrees that no classification is warranted for eye irritation.<br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment carcinogenic potential of iprovalicarb .docx | | | | |
| Dossier Submitter's Response | | | | |
| Agreed. Thank you for your support. | | | | |
| RAC's response | | | | |
| Thank you very much. Noted. | | | | |

**OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 08.03.2018 | Germany | | MemberState | 18 |
| Comment received | | | | |
| We agree with position of the DS that no classification is applicable. | | | | |

| Dossier Submitter's Response |
|---|
| Agreed. Thank you for your support. |
| RAC's response |
| Thank you very much. Noted. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 19.03.2018 | Belgium | | MemberState | 19 |
| Comment received | | | | |
| BE CA agrees that no classification is warranted for skin sensitization.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment carcinogenic potential of iprovalicarb .docx | | | | |
| Dossier Submitter's Response | | | | |
| Agreed. Thank you for your support. | | | | |
| RAC's response | | | | |
| Thank you very much. Noted. | | | | |

**OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 08.03.2018 | Germany | | MemberState | 20 |
| Comment received | | | | |
| We agree that STOT SE classification is not required. | | | | |
| Dossier Submitter's Response | | | | |
| Agreed. Thank you for your support. | | | | |
| RAC's response | | | | |
| Thank you very much. Noted. | | | | |

**OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 08.03.2018 | Germany | | MemberState | 21 |
| Comment received | | | | |
| Liver toxicity: In rats, mice and dogs, the liver was identified as a target organ in sub-chronic studies. In rat studies, the effect on liver would manifest in doses above recommended guidance values for Category 2 classification defined as 10 < C < 100 mg/kg bw/day for 90 days studies and 30 < C < 300 mg/kg bw/day for 28 days studies. However, dog was more sensitive species, with liver toxicity observed in moderate exposure concentrations. Relevant findings in clinical chemistry, changes in absolute and relative liver weight with concomitant histopathology indicative of adversity were observed in 1 year dog study in animals treated with doses of Iprovalicarb from 24.7 mg/kg bw/day for males and 28.1 mg/kg bw/day for females. When applying the guidance values of 10 < C < 100 mg/kg bw/day recommended for subchronic oral exposure, classification would be applicable. This remains the case when extrapolating the effect level by application of the subchronic-to-chronic factor of 2.<br>Thus, classification as STOT RE 2 should be considered. Notably, liver toxicity is not covered by other hazard classes, as classification for carcinogenicity suggested by the DS | | | | |

is based on tumours of skeletal system, uteri and thyroid in the rat study. No liver tumours were observed in rats exposed to the test substance for 2 years in combined chronic toxicity/carcinogenicity study.

Note: In Table 22 (page 34), presentation of data separately for males and females in spite of low number of animals in the groups might support interpretation.

Dossier Submitter's Response

Thank you for your comments. The DS disagrees with the proposal to consider STOT RE. The dog is the most sensitive species and the liver is the target organ. In the 53 week dog study there are a variety of effects seen at the 800ppm dose level (24.7 mg/kg bw/day for males and 28.1 mg/kg bw/day for females). The guidance cut-off value for a classification for STOT RE in category 2 under CLP in this case would be 2.5 < C ≤ 25 mg/kg.

Summary of the short term toxicity of iprovalicarb. Studies indicated in yellow show effects at or below the cut-off dose criteria for STOT RE 2.

| **Study (test substance purity)** | **Dose Levels Ppm (mg/kg bw)** | **NOAEL (equal to mg/kg bw)** | **Findings at the LOAEL** | **References** |
|---|---|---|---|---|
| 28 day feeding study, Wistar rat (99.4%) | 0, 2000, 6000, 20000 ppm<br><br>(195.8/198.7, 579.3/572.8, 1973.9/1934.4 mg/kg) | 2000 (196) | Clinical chemistry, enzyme induction and increased liver weight at 6000 ppm | Anon, 1995 B.6.3.1.1 |
| 13 week feeding study, Wistar rat (98.1 - 98.7%) | 0, 1250, 5000, 20000 ppm<br><br>(87.4/133.9, 372.7/561.4, 1524/2585.9 mg/kg) | 5000 (373) | Relative liver weights increased by > 10% at 20000 ppm | Anon, 1996 B.6.2.3.1 |
| 13 week feeding study, B6C3F$_1$ mouse (98.1 - 98.7%) | 0, 280, 1400, 7000, 14000 ppm<br><br>(63/125, 325/696.5, 1724.6/3599.5, 3473/6869 mg/kg) | 1400 (325) | Slight ↑ in MCV and cholesterol in males and females; slight↑ liver weight in females; slight ↑ water intake and ↓ kidney wt. in males | Anon, 1996 B.6.3.2.2 |
| 4 week feeding study, beagle (98.1%) | 0, 100, 1000, 10000, 50000 ppm<br><br>(3/3.4, 31.5/35, 280/269.5, | 100 (3.0) | Subtle ↑ in APh levels at 1000 ppm. Histopathological alterations in liver - enlarged hepatocytes with | Anon, 1993 B.6.3.1.2 |

| | | | | |
|---|---|---|---|---|
| | 1322/1164.5 mg/kg) | | a ground-glass appearance | |
| Supplementary 28 day feeding study, beagle (98.9%) | 0, 10, 20, 40, 80 ppm<br><br>(0.41, 0.77, 1.61, 3/2.93 mg/kg) | 20 (0.77) NOEL | ↑ N-demethylase activity, slight ↑ Cyt P450 | Anon, 1997 B.6.3.1.3 |
| 13 week feeding study, purebred beagle (95.8 - 98.5%) | 0, 250, 2500, 50000 ppm<br><br>(9.1, 62.5, 1250 mg/kg) | < 250 (9.1) not established | At 250 ppm: slight ↑ in abs. and rel. liver weight, liver enzyme induction, minimal hepatocellular cytoplasmic change. ↑ activity of AP at higher dose levels | Anon, 1995 B.6.3.2.3 |
| **53 week** feeding study, purebred beagle (98.7%) | 0, 80, 800, 8000 ppm<br><br>(2.6/2.68, 24.69/28, 256.86/262.41 mg/kg) | 80 (2.6) (for females only) | 80 ppm (males only): ↑ activity of serum ALAT and AP, ↑ liver wt, liver enzyme induction;<br><br>**800 ppm**: ↑ serum enzyme activities, ↑ liver wt, relevant histopath. findings | Anon, 1997 B.6.3.3.1 |
| 5 day inhalation study, Wistar rat (97.6%) | 0, 20.6, 102.9, 504.4 mg/m$^3$ | ≥ 504.4 mg/m$^3$ (≡181 mg/kg bw/day) | This was the max. technically feasible concentration | Anon, 1993 B.6.3.4.1 |
| 4 week subacute dermal toxicity study, HC:NZW rabbits (95.8%) | 0, 1000 mg/kg bw | ≥ 1000 mg/kg bw | No effects observed at the limit dose | Anon, 1995 B.6.3.4.2. |

**Summary of the findings in the 4-week dog feeding study (1993)**

Iprovalicarb was administered to 5 groups of 2 male and 2 female pure-bred beagle dogs in the diet. No deaths occurred and all animals appeared in good health through scheduled termination after 4 weeks. The two higher dose levels had an adverse effect on body weight as all animals at 50000 ppm and both females at 10000 ppm lost body weight during the 4-week course of the study. Food consumption was reduced for both sexes at dietary concentrations of 10000 and 50000 ppm.

**Table 6.3.1.2.1: 4-wk oral feed study in dogs - body weight gain (%) and mean feed intake**

| Findings (wk 4) | 0 ppm | 100 ppm | 1000 ppm | 10000 ppm | 50000 ppm |
|---|---|---|---|---|---|
| Body weight gain [kg] m | 0.2 | 0.3 | 0.2 | 0.0 | -0.7* |
| f | 0.0 | 0.2 | 0.2 | -0.4 | -0.5 |
| Avg feed intake m | 211.8 | 208.9 | 221.0 | 196.0 | 185.1 |
| [g/kg bw/wk] f | 227.8 | 239.0 | 243.1 | 188.4 | 163.1 |
| * *Significantly different from control at the 0.05 level (Dunnett's test)* | | | | | |

There was a mild dose-related decrease in activated partial thromboplastin time and an increase in Alkaline phosphatase (AP), statistically significant, for the 10,000 ppm dose group.

**Table 6.3.1.2.2: 4-wk oral feed study in dogs - haematology and clinico-chemical findings**

| Findings (wk 4) | 0 ppm | 100 ppm | 1000 ppm | 10000 ppm | 50000 ppm |
|---|---|---|---|---|---|
| APTT [sec] m | 9.4 | 9.2 | 9.1 | **8.5*** | **8.4*** |
| f | 10.1 | 9.5 | 9.5 | 8.7 | 8.6 |
| APh [U/l] m | 76.3 | 87.7 | 143.4 | 199.0 | **485.6*** |
| f | 81.3 | 92.3 | 123.8 | **290.1**** | **251.4**** |

Absolute and relative-liver weights were increased for males (not statistically significant) and markedly for females from 10000 ppm (not statistically significant). Hepatocytes appeared large and contained cytoplasm having a ground-glass appearance, indicative of increased proliferation of the smooth endoplasmic reticulum.

**Table 6.3.1.2.4: 4-wk oral feed study in dogs - organ weight and histopathological findings**

| Findings (wk 4) | 0 ppm | 100 ppm | 1000 ppm | 10000 ppm | 50000 ppm |
|---|---|---|---|---|---|
| Abs. liver wt. [g] m | 325.6 | 332.7 | 302.5 | 341.9 n.s. | 341.3 n.s. |
| f | 281.4 | 241.1 | 282.8 | 364.3 n.s. | 347.1 n.s. |
| Rel. liver wt. m | 31.48 | 31.76 | 31.08 | 38.25 n.s. | 36.58 n.s. |
| [g / kg bw] f | 31.33 | 31.18 | 32.30 | 46.22 n.s. | 42.96 n.s. |
| Hepat. hypertrophy m | none | none | mild | moderate | min.-mild |
| f | none | none | minimal | moderate | mild |
| Hepat. with ground- m | none | none | mild-mod. | mild | mild-mod. |
| glass appearance f | none | none | mild | mild | mild |
| Hepat. centr. m | none | none | none | none-mild | none-mild |
| inflamm. infiltration f | none | none | none | none | none-min. |
| * (**)*Significantly different from control at the 0.05 (0.01) level (Dunnett's test)* | | | | | |

**Summary of the findings in the 28-day supplementary dog feeding study (1997)**

Iprovalicarb was administered to 7 groups of 3 male and 3 female purebred (strain Bor. Beag) beagle dogs in the diet at concentrations of 0, 10, 20, 40 or 80 ppm over a period of 28 days, and 0 or 80 ppm in the two recovery groups (28 days with test substance administration followed by a further 28 days recovery period without test substance exposure).

All the animals survived to the end of the study period. There were no clinical signs attributable to test substance administration in any of the treatment groups. Haematology and clinical chemistry was unaffected. At necropsy, no test-substance related gross pathological findingswere recorded. There were no treatment-related alterations in liver weights. There was no histopathology of the liver.

The only effect was a reversible statistically significant increase in liver microsomal enzyme induction (O- and N-demethylase and Cytochrome P-450, 1.3 fold, 1.7 fold and 1.2 fold above controls respectively).

**Summary of the findings in the 13-week dog feeding study (1995)**

Iprovalicarb was administered to groups of 4 male and 4 female thoroughbred beagles each day in their feed at concentrations of 0, 250, 2500 (62.5 mg/kg bw/day) or 50000 ppm for 13 weeks.

All animals in all of the groups survived with the exception of one high dose female, who had to be sacrificed prematurely, due to its emaciated state. Body weight gain of the control and low and mid dose animals did not differ significantly.

Haematology and urinalysis was unaffected. Clinical chemistry showed increases in alkaline phosphatase at 62.5 mg/kg bw/day (1.8 fold greater than controls). There were markedly increased activities for all enzymes in the highest dose group (1250 mg/kg bw/day). Microsomal liver enzymes (N-demethylase and O-demethylase and cytochrome P-450) were induced by iprovalicarb treatment at 2500 ppm.

Relative liver weight was distinctly increased in the high dose female dogs as well as males from ≥ 2500 ppm and marginally so in mid-dose females and low dose males.

**Table 6.3.2.3.4: 53-week feeding study in dogs: Selected histopathological findings**

| **Findings (wk 13)** | **male + female** | | | |
|---|---|---|---|---|
| | **0 ppm** | **250 ppm** | **2500 ppm** | **50000 ppm** |
| Abs liver wt. | 320 | 360 | 426 | 419 |
| Rel. liver wt. [g/kg] | 36 | 43 | 50 | 61 |
| Abs. testes wt. | 12.6 | 16.2 | 15.0 | 4.4 |
| Rel. testes wt. [g/kg] | 1 | 2 | 2 | 1 |
| Abs. prostrate wt. | 2.3 | 2.1 | 1.8 | 0.8 |
| Abs. thymus wt. | 8.0 | 8.4 | 7.6 | 3.4 |
| Rel. thymus wt [g/kg] | 1 | 1 | 1 | 0 |

*Data was not subjected to statistical analysis due to the limited number of animals per group*

Treatment-related liver histopathology consisted of hepatocellular cytoplasmic change. Cytoplasmic change occurred in males and females of all treatment groups. At a dose level of 2500 ppm hepatocellular hypertrophy and multilamellar bodies were observed in one female out of four. Major histopathological findings were confined to the high dose group.

**Table 6.3.2.3.5: 13-wk oral feed study in dogs - histopathological findings**

| Findings (wk 13) | | 0 ppm | 250 ppm | 2500 ppm | 50000 ppm |
|---|---|---|---|---|---|
| **Liver, hepatocell. cytoplasmic change** | **m** | 0/4 | 3/4 | **3/4** | 4/4 |
| | **f** | 0/4 | 2/4 minimal | **4/4 slight** | 3/4 moderate |
| **Liver, hepatocell. vacuolation** | **m** | 0/4 | 0/4 | 0/4 | 1/4 |
| | **f** | 0/4 | 0/4 | 0/4 | 2/4 moderate or slight |
| **Liver, hepatocell. hypertrophy** | **m** | 0/4 | 0/4 | **0/4** | 2/4 |
| | **f** | 0/4 | 0/4 | **1/4 minimal** | 3/4 moderate |
| **Liver, multilamellar bodies** | **m** | 0/4 | 0/4 | **0/4** | 1/4 |
| | **f** | 0/4 | 0/4 | **1/4** | 2/4 |
| **Liver, focal necrosis** | **m** | 0/4 | 0/4 | 0/4 | 3/4 |
| | **f** | 0/4 | 1/4 moderate | 0/4 | 1/4 moderate (m) slight (f) |
| **Liver, single cell necrosis** | **m** | 0/4 | 0/4 | 0/4 | 4/4 |
| | **f** | 0/4 | 0/4 | 0/4 | 2/4 slight or moderate |
| **Liver, iron pigment in Kupffer cells** | **m** | 0/4 | 0/4 | 0/4 | 2/4 |
| | **f** | 0/4 | 0/4 | 0/4 | 3/4 |
| **Liver, iron pigment in periportal hepatocytes** | **m** | 0/4 | 0/4 | 0/4 | 3/4 |
| | **f** | 0/4 | 0/4 | 0/4 | 1/4 |
| **Liver, granulocytic infiltration** | **m** | 0/4 | 0/4 | 1/4 | 3/4 |
| | **f** | 0/4 | 0/4 | 0/4 | 1/4 |
| **Gallbladder, abnorm. content** | **m** | 0/4 | 0/4 | 0/4 | 3/4 |
| | **f** | 0/4 | 0/4 | 0/4 | 2/3 |
| **Gallbladder, edema wall** | | 0/4 | 1/4 | 1/4 | 4/4 |
| | | 1/4 | 1/4 | 1/4 | 3/3 |
| **Gallbladder, dilated lymphatic vessel** | **m** | 0/4 | 1/4 | 1/4 | 4/4 |
| | **f** | 0/4 | 0/4 | 1/4 | 2/3 |
| **Testes, juvenile** | **m** | 1/4 no data | 0/4 | 1/4 slight | 4/4 slight to massive |
| **Epididymides, juvenile** | **m** | 1/4 no data | 0/4 | 1/4 slight | 4/4 moderate to massive |
| **Prostrate, juvenile** | **m** | 1/4 no data | 1/4 no data | 1/4 slight | 4/4 marked to massive |
| **Thymus, atrophy** | **m** | 0/4 | 0/4 | 0/4 | 4/4 |
| | **f** | 0/4 | 0/4 | 0/4 | 2/3 |
| **Bone marrow, serous atrophy** | **m** | 0/4 | 0/4 | 0/4 | 3/4 |
| | **f** | 0/4 | 0/4 | 0/4 | 1/4 |

*Data was not subjected to statistical analysis due to the limited number of animals per group*

**Summary of the findings in the 53 week dog study.**

Groups of 4 male and 4 female pure-bred beagle dogs were treated orally over a period of 53 weeks with dietary concentrations of 0, 80, 800, or 8000 ppm iprovalicarb (98.7% purity). Test article intake was calculated at averages of 0, 2.62, 24.69 and 256.86 mg/kg/day for males and 0, 2.68, 28.10 and 262.41 mg/kg/day for females.

No treatment-related mortalities occurred during the study. Observations on reflexes, body temperatures, pulse rates, blood pressures or ECGs reveal no relevant changes in these measurements. There was no detectable difference in the food consumption between control animals and that of animals up to and including those in group II (800 ppm). No abnormal ophthalmoscopic findings were reported during the study. Body weight gains were unaffected in animals of the 80 and 800 ppm groups. At 8000 ppm, mean body weigh gain in males only was reduced.

**Table 6.3.3.1.1: 53-week feeding study in dogs: Body weight changes**

| Dose level (ppm) | 0 | 80 | 800 | 8000 |
|---|---|---|---|---|
| **Body weight (kg)** | | | | |
| Male | 12.83 | 12.58 | 13.08 | 10.65 |
| Female | 11.20 | 12.00 | 10.93 | 11.90 |
| Male + female | 12.01 | 12.29 | 12.00 | 11.28 |
| **Body weight gain (kg)** | | | | |
| Male | + 1.00 | + 1.08 | + 0.73 | - 1.30 |
| Female | + 0.75 | + 1.27 | + 0.13 | + 0.92 |
| Male + female | + 0.87 | + 1.18 | + 0.42 | - 0.18 |

None of the haematological parameters measured were affected in any of the treatment groups. Differential blood counts were recorded. There were no major differences observed between controls and treatment groups.

Clinical-chemical investigations revealed increased activities of ALAT and AP at 800 ppm and above. In addition, at 8000 ppm, ASAT, GLDH, and GGT were increased. Plasma albumin values were decreased in 8000 ppm animals, and while this may be resulting directly from emaciation, it may also be treatment-related.

**Table 6.3.3.1.2: 53-week feeding study in dogs: Clinical chemistry findings**

| | | 0 ppm | | 80 ppm | | 800 ppm | | 8000 ppm | |
|---|---|---|---|---|---|---|---|---|---|
| Week | | -3 | 52 | -3 | 52 | -3 | 52 | -3 | 52 |
| ASAT [U/l] | m | 13.3 | 18.8 | 15.9 | 16.4 | 14.1 | 16.1 | 11.6 | 43.5 |
| | f | 11.2 | 17.1 | 13.7 | 15.8 | 13.3 | 16.6 | 14.3 | 20.4 |
| ALAT [U/l] | m | 16.7 | 27.7 | 26.5 | 34.9 | 18.0 | 38.7 | 27.6 | 271 |
| | f | 19.7 | 27.0 | 19.2 | 24.7 | 26.0 | 38.2 | 19.6 | 103.1 |
| AP [U/l] | m | 148 | 92 | 147 | 160 | 172 | 235 | 136 | 1629 |
| | f | 198 | 179 | 147 | 154 | 129 | 217 | 107 | 589 |
| GLDH [U/l] | m | 2.7 | 3.6 | 2.4 | 2.2 | 2.5 | 3.7 | 2.7 | 104.5 |
| | f | 1.4 | 2.9 | 2.7 | 2.7 | 2.6 | 2.8 | 2.9 | 31.1 |
| GGT [U/l] | m | 2 | 0 | 2 | 0 | 2 | 1 | 2 | 16 |
| | f | 2 | 0 | 2 | 0 | 2 | 1 | 2 | 4 |
| ALB [g/l] | m | 30.9 | 32.4 | 30.5 | 30.2 | 33.6 | 31.3 | 33.4 | 22.1 |
| | f | 31.4 | 33.8 | 31.5 | 32.6 | 32.2 | 28.6 | 33.6 | 26.3 |

There was a dose-dependent increase in N- and O-demethylase and Cyt P450 activities from 80 ppm and upwards. This is indicative of an enzyme induction in the liver, considered an adaptive process.

Urinalysis results revealed no abnormalities at dose levels up to and including 8000 ppm.

Absolute and relative liver weights were increased in mid-dose group males and above and in high-dose group females. A slight increase in the mean relative liver weight (15%) was also seen in males of the low-dose group, which was caused by marked increases in liver weight of two dogs (+27%), while the remaining two dogs showed liver weights that were within or even below control ranges.

**Table 6.3.3.1.4: 53-week feeding study in dogs: Organ weight changes**

| Findings (wk 53) | | 0 ppm | 80 ppm | 800 ppm | 8000 ppm |
|---|---|---|---|---|---|
| Abs liver wt. [g] | males | 428.0 | 471.8 | 533.5 | 573.5 |
| | females | 432.5 | 470.5 | 481.8 | 610.0 |
| Rel. liver wt. [g/kg] | males | 33.93 | 39.08 | 41.65 | 54.40 |
| | females | 39.20 | 40.20 | 44.93 | 51.30 |
| Rel. adrenal wt. [g/kg] | males | 0.116 | 0.130 | 0.143 | 0.176 |
| *Data was not subjected to statistical analysis due to the limited number of animals per group* | | | | | |

Treatment-related findings were reported from the histopathological examination. Relevant effects in the liver consisted of cytoplasmic change and hypertrophy, fatty change, and increased intrahepatocellular iron storage at 800 ppm and above. In the highest dose group (8000ppm), there were also focal necroses and an increased number of binucleated hepatocytes.

**Table 6.3.3.1.5: 53-week feeding study in dogs: Selected histopathological findings**

| Selected findings | | 0 ppm | 80 ppm | 800 ppm | 8000 ppm |
|---|---|---|---|---|---|
| **LIVER** | | | | | |
| **Hepatocellular cytoplasmic change** | m | 0/4 | 0/4 | 4/4 (min-sli)[1] | 4/4 (mod) |
| | f | 0/4 | 0/4 | 4/5 (sli) | 4/4 (mod) |
| **Hepatocellular hypertrophy** | m | 0/4 | 0/4 | 4/4 (min) | 4/4 (sli-mod) |
| | f | 0/4 | 0/4 | 4/5 (min-sli) | 4/4 (sli-mod) |
| **Hepatocellular multilamellar inclusions** | m | 0/4 | 0/4 | 0/4 | 1/4 (min) |
| | f | 0/4 | 0/4 | 0/5 | 3/4 (sli-mod) |
| **Periportal fatty change** | m | 0/4 | 1/4 (sli) | 3/4 (min-sli) | 2/4 (mod) |
| | f | 0/4 | 0/4 | 3/5 (min-sli) | 1/4 (min) |
| **Binucleated hepatocytes** | m | 0/4 | 0/4 | 0/4 | 3/4 (min-sli) |
| | f | 0/4 | 0/4 | 0/5 | 2/4 (min-sli) |
| **Focal necrosis** | m | 0/4 | 0/4 | 0/4 | 2/4 (min-sli) |
| | f | 0/4 | 0/4 | 0/5 | 0/4 |
| **Single cell necrosis** | m | 1/4 (min) | 0/4 | 0/4 | 1/4 (min) |
| | f | 1/4 (min) | 0/4 | 0/5 | 4/4 (min |
| **Iron pigment in hepatocytes** | m | 1/4 (min) | 0/4 | 0/4 | 4/4 (min-mod) |
| | f | 0/4 | 1/4 (min) | 3/5 (min-sli) | 1/4 (mod) |
| **Interstitial fibrosis** | m | 0/4 | 0/4 | 0/4 | 2/4 (sli-mod) |
| | f | 0/4 | 0/4 | 0/5 | 1/4 (min) |
| **Nodulular hyperplasia** | m | 0/4 | 0/4 | 0/4 | 1/4 (mod) |
| | f | 0/4 | 0/4 | 0/5 | 0/4 |
| **GALLBLADDER** | | | | | |
| **Adhesive mucus** | m | 0/4 | 0/4 | 1/4 (min) | 3/4 (sli-mod) |
| | f | 0/4 | 0/4 | 2/5 (min-sli) | 3/4 (min-sli) |

| | | | | | |
|---|---|---|---|---|---|
| **Pseudogland formation** | **m**<br>**f** | 0/4<br>0/4 | 0/4<br>0/4 | 0/4<br>0/5 | 2/4 (sli-mod)<br>2/4 (min-sli) |
| **Increased lymphoid tissue** | **m**<br>**f** | 0/4<br>0/4 | 0/4<br>0/4 | 0/4<br>1/5 (sli) | 3/4 (min-sli)<br>3/4 (min-sli) |
| *Data was not subjected to statistical analysis due to the limited number of animals per group*<br>[1] *min = minimal; sli = slight; mod = moderate; mar = marked severity* | | | | | |

The effects at ≈ 26 mg/kg (800ppm) are evidence of some liver toxicity but are not sufficiently severe for classification because there was no indication of organ impairment or functional deficiency that impacted on the overall state of health of the animals.

In conclusion, STOT RE is assigned on the basis of findings of "significant" or "severe" toxicity. In this context 'significant' means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant. 'Severe' effects are generally more profound or serious and indicate changes that are of a considerably adverse nature with a significant impact on health. The dog is clearly the most sensitive species and one of the most sensitive markers is alkaline phosphatase. The DS notes that at high substance concentrations and those above the cut-off values for STOT RE2 there are clear indications of hepatotoxicity.

RAC's response

Thank you very much. Noted. RAC concurs with DS and understands that the hepatotoxicity found in dog studies at doses below the respective cut-off points were not severe enough for supporting a classification.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 19.03.2018 | Belgium | | MemberState | 22 |

Comment received

Oral repeated-dose toxicity of iprovalicarb has been assessed in rat, mouse and dog.
Three main studies are available for Beagle dog. In the 4 week feding study (0 - 3/3,4 – 31,5/35 – 280/269,5 – 1322/1164,5 mg/kg bw/day), effects in the liver were observed from the lowest dose with mild/minimal enlarged hepatocytes with a ground-glass appearance. At 280/269,5 mg/kg bw/day, observations include increased relative and absolute liver weight in male and female, associated with enlarged hepatocytes and alterations in blood chemistry (increase in AP in females and decreased cholesterol in males).
In a 53 weeks feeding study (0 - 2,6/2,7 – 24,7/28 – 256,9/262,4 mg/kg bw/day), changes in absolute and relative liver weight are observed from 2,6 mg/kg bw/day, associated with periportal fatty change in one dog. Clinical chemistry showed increased AP, ALAT, N-DEM, O-DEM and P450. At mid dose, same observations are made in a dose-dependant way accompanied with hepatocellular hypertrophy. At higher dose, focal necrosis, binucleated hepatocytes, fibrosis of the liver parenchyma and nodular hyperplasia are reported for the liver.
Although there are some uncertainties (high gap between doses, no statistical analysis and data from sexes pooled) in the 13 week dog feeding study (0 – 9,1 – 62,5 – 1250 mg: kg bw/day), the observations support the findings of the two previous studies. No LOAEL could be derived and at 62,5 mg/kg bw/day, reporting include hepatocellular hypertrophy, liver discolouration, increase in absolute and relative liver weight. These findings are associated with blood chemistry alterations (decreased AP and protein/albumin and increased triglycerides) and also increased N-DEM, O-DEM and P-450.
In rat, a 28 days feeding study (LOAEL 579,3/572,8 mg/kg bw/day) and a 13 weeks feeding study (LOAEL 372,7/561,4 mg/kg bw/day) showed no effect warranting a

| |
|---|
| classification. In mouse, a 13 week feeding study (LOAEL 1724,6/3599,5 mg/kg bw/day) resulted in the same conclusion than for rat studies.<br>Overall, considering that the effects in dog liver include histopathological, blood chemistry and organ weight changes, BE CA is of the opinion that a classification STOT RE 2 for liver is warranted. Moreover, seeing the effects observed in the liver of mice and rats at higher doses, BE CA is of the opinion that the observations are relevant for human.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment carcinogenic potential of iprovalicarb .docx |
| Dossier Submitter's Response |
| Thank you for your comments. The DS does not propose STOT RE2. Please see comment 21. |
| RAC's response |
| Thank you very much. Noted. RAC concurs with DS and understands that the hepatotoxicity found in dog studies at doses below the respective cut-off points were not severe enough for supporting a classification. |

**OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 15.03.2018 | France | | MemberState | 23 |
| Comment received | | | | |
| FR agrees with the proposal to not classify Iprovalicarb under CLP environmental criteria | | | | |
| Dossier Submitter's Response | | | | |
| Agreed. Thank you for your support. | | | | |
| RAC's response | | | | |
| Noted by RAC. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 08.03.2018 | Germany | | MemberState | 24 |
| Comment received | | | | |
| 5.4 Aquatic toxicity (table 58):<br>It would be helpful to add for all presented results (EC/LC50, NOEC) whether referring to nominal or mean measured concentrations. Actually, the LC50 for fish (Lepomis macrochirus) and EC50 for daphnia (Daphnia magna) were > 20.7 mg/L and > 19.8 mg/L instead off "≥".<br><br>5.4.1.1 Short-term toxicity to fish:<br>For both studies the single tested nominal concentration was 100 mg/L. The measured concentration was 22.7 mg/L at the study with rainbow trout and 20.7 mg/L at the study with bluegill sunfish. | | | | |
| Dossier Submitter's Response | | | | |
| Agreed. Thank you for your comments.<br><br>**Table 58: Amended summary of relevant information on aquatic toxicity** | | | | |

| Method | Results | Remarks | Reference |
|---|---|---|---|
| EG C.1, EPA 72-1, OECD 203 | $LC_{50}$ >22.7 mg/L | Static *Oncorhynchus* | RAR: Anon, |

| | | | |
|---|---|---|---|
| GLP (yes)<br>Iprovalicarb: 97.1% | (mean measured) | *mykiss* | (1995a) B9.2.1.1 |
| EG C.1, EPA 72-1, OECD 203<br>GLP (yes)<br>Iprovalicarb: 97.1% | $LC_{50}$ > 20.7 mg/L<br>(mean measured) | Static *Lepomis macrochirus* | RAR: Anon, (1995b)<br>B9.2.1.2 |
| OECD 204, OECD draft TG\94.214, ISO 10229<br>GLP (yes)<br>Iprovalicarb: 98.9% | NOEC mg/L ≥ 9.89 mg/L<br>(all measured concentrations ranged from 84 to 99 % of nominal). Mean measured. | Semi-static: *Oncorhynchus mykiss* | RAR: Anon, (1997) B9.2.2.1 |
| OPPTS number 850.1400; ASTM StanRARd E1241-88a<br>GLP (yes)<br>Iprovalicarb: 97.6% | ELS NOEC = 5.0 mg/L<br>(mean measured) | Flow-through: *Oncorhynchus mykiss* | RAR: Anon, (2000) B9.2.2.2 |
| OECD 202, EPA 72-2<br>GLP (yes)<br>Iprovalicarb: 97.5% | $EC_{50}$ > 19.8 mg/L<br>(mean measured) | Static: *Daphnia magna* | RAR: Heimbach, (1996) B9.2.4.1 |
| OECD 202, EPA 72-4, EEC XI/681/86<br>GLP (yes)<br>Iprovalicarb: 97.0% | $NOEC_{paternal}$ = 1.89 mg/L<br>(mean measured)<br><br>$NOEC_{repr}$ = 5.81 mg/L<br>(mean measured) | Static renewal: *Daphnia magna* | RAR: Heimbach, (1996) B9.2.5.1 |
| OECD 201, EEC Directive 79/831/E, EPA 738-R-94-035, ISO 8692<br>GLP (yes)<br>Iprovalicarb: 97.0% | $E_rC_{50}$ > 10 mg/L<br>$NOE_rC$ ≥ 10 mg/L<br>(Quantitative analysis at day 0 showed 103% of nominal concentrations. All results are expressed in nominal terms). | Static: *Selenastrum capricornutum* | RAR: Anderson, (1996) B9.2.6.1 |
| OECD Guideline 218,<br>GLP (yes)<br>Iprovalicarb: 97.5% | $EC_{15emerg}$ > 128mg/kg<br>NOEC = 125 mg/kg<br>(nominal). | Spiked sediment: *Chironomus riparius* | RAR: Bruns, (2010) B9.2.8.1 |

RAC's response

Agreed. Thank you for your comments.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 19.03.2018 | Belgium | | MemberState | 25 |

Comment received

Based on the information reported in the CLH report, BE CA supports the conclusion that no classification is warranted for the environment.

Some editorial or/and minor comments :
- Daphnia magna : short term toxicity : in table 58: static regime, in study description (5.4.2.1.) : semi-static regime
- Please mention the study dates - it is not clear whether it concerns old or recent studies; as well as the purity of the tested substance and the reliability score of the

| |
|---|
| studies<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment carcinogenic potential of iprovalicarb .docx |
| Dossier Submitter's Response |
| Agreed. Thank you for your comments.<br>Please see amended table 58 in comment 24.<br>There were no reliability scores reported, all studies were guideline and GLP compliant. |
| RAC's response |
| Noted by RAC. |

PUBLIC ATTACHMENTS
1. carcinogenic potential of iprovalicarb .docx [Please refer to comment No. 3, 9, 13, 15, 17, 19, 22, 25]