# Committee for Risk Assessment

# RAC

Annex 2

**Response to comments document (RCOM)**

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

**tetra(sodium/potassium) 7-[(*E*)-{2-acetamido-4-[(*E*)-(4-{[4-chloro-6-({2-[(4-fluoro-6-{[4-(vinylsulfonyl)phenyl]amino}-1,3,5-triazine-2-yl)amino]propyl}amino)-1,3,5-triazine-2-yl]amino}-5-sulfonato-1-naphthyl)diazenyl]-5-methoxyphenyl}diazenyl]-1,3,6-naphthalenetrisulfonate;[substance having a complex composition with <80% of the above constituents and other reaction side products]; Reactive Brown 51**

**EC Number: 466-490-7**
**CAS Number: -**

CLH-O-0000007375-70-01/F

**Adopted**

**30 November 2023**

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**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON TETRA(SODIUM/POTASSIUM)7-[(*E*)-{2-ACETAMIDO-4-[(*E*)-(4-{[4-CHLORO-6-({2-[(4-FLUORO-6-{[4-(VINYLSULFONYL)PHENYL]AMINO}-1,3,5-TRIAZINE-2-YL)AMINO]PROPYL}AMINO)-1,3,5-TRIAZINE-2-YL]AMINO}-5-SULFONATO-1-NAPHTHYL)DIAZENYL]-5-METHOXYPHENYL}DIAZENYL]-1,3,6-NAPHTHALENETRISULFONATE; [SUBSTANCE HAVING A COMPLEX COMPOSITION WITH <80% OF THE ABOVE CONSTITUENTS AND OTHER REACTION SIDE PRODUCTS]; REACTIVE BROWN 51**

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

Comments provided during 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 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 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. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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**Substance name: tetra(sodium/potassium)7-[(E)-{2-acetamido-4-[(E)-(4-{[4-chloro-6-({2-[(4-fluoro-6-{[4-(vinylsulfonyl)phenyl]amino}-1,3,5-triazine-2-yl)amino]propyl}amino)-1,3,5-triazine-2-yl]amino}-5-sulfonato-1-naphthyl)diazenyl]-5-methoxyphenyl}diazenyl]-1,3,6-naphthalenetrisulfonate; [substance having a complex composition with <80% of the above constituents and other reaction side products]; Reactive Brown 51**
**EC number: 466-490-7**
**CAS number: -**
**Dossier submitter: Sweden**

## TOXICITY TO REPRODUCTION

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 14.03.2023 | Germany | | MemberState | 1 |
| Comment received | | | | |
| DE CA agrees that a classification as Repr. 1B (H360F) is warranted. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your support. | | | | |
| RAC's response | | | | |
| Noted. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 30.03.2023 | France | | MemberState | 2 |
| Comment received | | | | |
| FR agrees with the proposed classification for effects on sexual function and fertility as Repr. 1B – H360F based on a clear effect on females in high dose (1000 mg/kg bw/day) in the OECD 421 study. Effects are characterised by a decreased numbers of corpora lutea and implantation sites and no pups delivered in the females treated at 1000 mg/kg bw/day. | | | | |

No general toxicity was noted in the parental animals in the CLH report. But, it is mentioned in the Annex I of the CLH report, some clinical effects on salivation, body weight gain, haemotology and clinical biochemistry parameters and on behaviour at 1000 mg/kg bw/day in the OECD 407 study. The lack of details (such as incidence, amplitude of the effects…) makes difficult to conclude if they constitute or not general toxicity effects. Can you provide further information? Do you have access to the study report?

In the OECD 421 study, can you describe the minor deviations from OECD guideline mentioned?

No adverse effects on development is identified in the OECD 421 study. FR agrees that no classification is justified based on the lack of effects.

There is no data to adequately assess effects on or via lactation. FR agrees that no classification is justified based on the lack of data.

Dossier Submitter's Response

Thank you of your support and your comments. The study reports were available to us.

For the OECD 407 study, please find the requested descriptions of effects on different parameters during treatment/ recovery.

Body weight:

**BODY WEIGHTS (GRAM) SUMMARY**
**MALES**

| TREATMENT | | GROUP 1 0 MG/KG | GROUP 2 50 MG/KG | GROUP 3 200 MG/KG | GROUP 4 1000 MG/KG |
|---|---|---|---|---|---|
| DAY 1 | MEAN | 189 | 200 | 191 | 192 |
| WEEK 1 | ST.DEV. | 8.6 | 10.7 | 8.1 | 10.8 |
| | N | 10 | 5 | 5 | 10 |
| DAY 8 | MEAN | 236 | 252 | 243 | 237 |
| WEEK 2 | ST.DEV. | 10.7 | 14.3 | 10.0 | 12.7 |
| | N | 10 | 5 | 5 | 10 |
| DAY 15 | MEAN | 273 | 288 | 279 | 274 |
| WEEK 3 | ST.DEV. | 13.6 | 20.0 | 14.1 | 17.0 |
| | N | 10 | 5 | 5 | 10 |
| DAY 22 | MEAN | 303 | 321 | 311 | 301 |
| WEEK 4 | ST.DEV. | 18.5 | 29.2 | 16.5 | 23.5 |
| | N | 10 | 5 | 5 | 10 |
| DAY 28 | MEAN | 323 | 342 | 328 | 322 |
| WEEK 4 | ST.DEV. | 21.5 | 36.5 | 19.0 | 23.2 |
| | N | 10 | 5 | 5 | 10 |

## BODY WEIGHTS (GRAM) SUMMARY
**MALES**

| RECOVERY | | | GROUP 1 0 MG/KG | GROUP 2 50 MG/KG | GROUP 3 200 MG/KG | GROUP 4 1000 MG/KG |
|---|---|---|---|---|---|---|
| DAY 1 | | MEAN | 299 | --- | --- | 291 |
| WEEK 1 | | ST.DEV. | 20.9 | --- | --- | 21.5 |
| | | N | 5 | 0 | 0 | 5 |
| DAY 8 | | MEAN | 330 | --- | --- | 321 |
| WEEK 2 | | ST.DEV. | 22.7 | --- | --- | 25.9 |
| | | N | 5 | 0 | 0 | 5 |
| DAY 14 | | MEAN | 348 | --- | --- | 340 |
| WEEK 2 | | ST.DEV. | 23.5 | --- | --- | 32.2 |
| | | N | 5 | 0 | 0 | 5 |

## BODY WEIGHTS (GRAM) SUMMARY
**FEMALES**

| TREATMENT | | | GROUP 1 0 MG/KG | GROUP 2 50 MG/KG | GROUP 3 200 MG/KG | GROUP 4 1000 MG/KG |
|---|---|---|---|---|---|---|
| DAY 1 | | MEAN | 143 | 149 | 146 | 145 |
| WEEK 1 | | ST.DEV. | 6.5 | 8.1 | 6.9 | 5.1 |
| | | N | 10 | 5 | 5 | 10 |
| DAY 8 | | MEAN | 165 | 172 | 167 | 165 |
| WEEK 2 | | ST.DEV. | 9.4 | 9.2 | 5.0 | 7.8 |
| | | N | 10 | 5 | 5 | 10 |
| DAY 15 | | MEAN | 179 | 186 | 184 | 181 |
| WEEK 3 | | ST.DEV. | 9.4 | 13.2 | 6.5 | 8.1 |
| | | N | 10 | 5 | 5 | 10 |
| DAY 22 | | MEAN | 193 | 204 | 199 | 195 |
| WEEK 4 | | ST.DEV. | 12.5 | 14.0 | 9.6 | 10.6 |
| | | N | 10 | 5 | 5 | 10 |
| DAY 28 | | MEAN | 200 | 209 | 208 | 203 |
| WEEK 4 | | ST.DEV. | 12.2 | 17.8 | 9.0 | 12.2 |
| | | N | 10 | 5 | 5 | 10 |

## BODY WEIGHTS (GRAM) SUMMARY
**FEMALES**

| RECOVERY | | | GROUP 1 0 MG/KG | GROUP 2 50 MG/KG | GROUP 3 200 MG/KG | GROUP 4 1000 MG/KG |
|---|---|---|---|---|---|---|
| DAY 1 | | MEAN | 191 | --- | --- | 189 |
| WEEK 1 | | ST.DEV. | 11.3 | --- | --- | 6.4 |
| | | N | 5 | 0 | 0 | 5 |
| DAY 8 | | MEAN | 208 | --- | --- | 208 |
| WEEK 2 | | ST.DEV. | 9.7 | --- | --- | 8.8 |
| | | N | 5 | 0 | 0 | 5 |
| DAY 14 | | MEAN | 217 | --- | --- | 218 |
| WEEK 2 | | ST.DEV. | 12.0 | --- | --- | 9.2 |
| | | N | 5 | 0 | 0 | 5 |

Hematological measurements:

**HEMATOLOGY SUMMARY**
**MALES**

| | RBC T/l | HB mmol/l | HCT rel. 1 | MCV fl | RDW rel. 1 | MCH fmol | MCHC mmol/l |
|---|---|---|---|---|---|---|---|
| AFTER 4 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 8.39 | 9.9 | 0.43 | 51.3 | 0.128 | 1.18 | 23.04 |
| 2 (50 MG/KG) | 8.75 | 9.9 | 0.43 | 49.9 | 0.118 | 1.13 | 22.73 |
| 3 (200 MG/KG) | 8.21 | 9.9 | 0.43 | 52.9 | 0.122 | 1.21 | 22.84 |
| 4 (1000 MG/KG) | 8.62 | 9.9 | 0.43 | 50.0 | 0.132 | 1.15 | 23.00 |
| AFTER 6 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 8.65 | 9.9 | 0.46 | 53.4 | 0.161 | 1.14 | 21.42 |
| 4 (1000 MG/KG) | 9.23 * | 10.0 | 0.47 | 50.6 | 0.141 | 1.08 | 21.36 |

| | RETICULOCYTE COUNT | | | | | | |
|---|---|---|---|---|---|---|---|
| | HDW mmol/l | RETI rel. 1 | RETI G/l | L RETI rel. 1 | M RETI rel. 1 | H RETI rel. 1 | WBC G/l |
| AFTER 4 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 1.67 | 0.020 | 171 | 0.699 | 0.269 | 0.032 | 6.80 |
| 2 (50 MG/KG) | 1.60 | 0.020 | 173 | 0.743 | 0.231 | 0.025 | 7.40 |
| 3 (200 MG/KG) | 1.61 | 0.021 | 175 | 0.703 | 0.255 | 0.042 | 7.17 |
| 4 (1000 MG/KG) | 1.73 | 0.024 | 206 * | 0.696 | 0.275 | 0.029 | 7.83 |
| AFTER 6 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 1.89 | 0.025 | 215 | 0.667 | 0.299 | 0.034 | 5.88 |
| 4 (1000 MG/KG) | 1.87 | 0.022 | 206 | 0.743 | 0.234 | 0.022 | 6.02 |

| | DIFF.WBC COUNT (REL) | | | | | |
|---|---|---|---|---|---|---|
| | NEUT rel. 1 | EOS rel. 1 | BASO rel. 1 | LYMPH rel. 1 | MONO rel. 1 | LUC rel. 1 |
| AFTER 4 WEEKS | | | | | | |
| 1 (0 MG/KG) | 0.146 | 0.014 | 0.004 | 0.806 | 0.023 | 0.007 |
| 2 (50 MG/KG) | 0.198 | 0.016 | 0.004 | 0.758 | 0.020 | 0.004 |
| 3 (200 MG/KG) | 0.134 | 0.013 | 0.004 | 0.821 | 0.021 | 0.006 |
| 4 (1000 MG/KG) | 0.152 | 0.016 | 0.004 | 0.799 | 0.021 | 0.007 |
| AFTER 6 WEEKS | | | | | | |
| 1 (0 MG/KG) | 0.157 | 0.010 | 0.007 | 0.796 | 0.021 | 0.008 |
| 4 (1000 MG/KG) | 0.139 | 0.016 | 0.008 | 0.807 | 0.022 | 0.009 |

| | DIFF.WBC COUNT (ABS) | | | | | | |
|---|---|---|---|---|---|---|---|
| | NEUT G/l | EOS G/l | BASO G/l | LYMPH G/l | MONO G/l | LUC G/l | PLATELETS G/l |
| AFTER 4 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 0.99 | 0.10 | 0.03 | 5.48 | 0.16 | 0.05 | 1037 |
| 2 (50 MG/KG) | 1.51 | 0.12 | 0.03 | 5.57 | 0.15 | 0.03 | 1038 |
| 3 (200 MG/KG) | 0.97 | 0.09 | 0.03 | 5.88 | 0.16 | 0.04 | 1032 |
| 4 (1000 MG/KG) | 1.22 | 0.13 | 0.03 | 6.23 | 0.17 | 0.06 | 1084 |
| AFTER 6 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 0.91 | 0.05 | 0.04 | 4.71 | 0.12 | 0.05 | 1233 |
| 4 (1000 MG/KG) | 0.86 | 0.09 ** | 0.05 | 4.83 | 0.14 | 0.05 | 1035 |

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level. +: Steel-test sig. at 5% level.

**HEMATOLOGY SUMMARY**
**FEMALES**

| | RBC T/l | HB mmol/l | HCT rel. 1 | MCV fl | RDW rel. 1 | MCH fmol | MCHC mmol/l |
|---|---|---|---|---|---|---|---|
| AFTER 4 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 8.30 | 9.9 | 0.42 | 50.6 | 0.117 | 1.19 | 23.49 |
| 2 (50 MG/KG) | 8.20 | 9.8 | 0.41 | 50.7 | 0.139 | 1.20 | 23.63 |
| 3 (200 MG/KG) | 8.15 | 9.6 | 0.41 | 50.7 | 0.115 | 1.18 | 23.36 |
| 4 (1000 MG/KG) | 8.07 | 9.3 ** | 0.40 | 49.7 | 0.116 | 1.15 | 23.23 |
| AFTER 6 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 8.31 | 10.0 | 0.46 | 55.2 | 0.153 | 1.20 | 21.74 |
| 4 (1000 MG/KG) | 8.34 | 9.7 | 0.46 | 54.7 | 0.146 | 1.17 | 21.34 * |

| | | RETICULOCYTE COUNT | | | | | |
|---|---|---|---|---|---|---|---|
| | HDW mmol/l | RETI rel. 1 | RETI G/l | L RETI rel. 1 | M RETI rel. 1 | H RETI rel. 1 | WBC G/l |
| AFTER 4 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 1.54 | 0.024 | 194 | 0.646 | 0.318 | 0.037 | 6.08 |
| 2 (50 MG/KG) | 1.52 | 0.022 | 177 | 0.700 | 0.276 | 0.024 | 5.80 |
| 3 (200 MG/KG) | 1.51 | 0.022 | 178 | 0.673 | 0.295 | 0.032 | 5.45 |
| 4 (1000 MG/KG) | 1.53 | 0.027 | 216 | 0.642 | 0.321 | 0.037 | 5.17 |
| AFTER 6 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 1.63 | 0.024 | 196 | 0.659 | 0.309 | 0.032 | 3.81 |
| 4 (1000 MG/KG) | 1.56 | 0.023 | 194 | 0.664 | 0.302 | 0.034 | 3.77 |

| | DIFF.WBC COUNT (REL) | | | | | |
|---|---|---|---|---|---|---|
| | NEUT rel. 1 | EOS rel. 1 | BASO rel. 1 | LYMPH rel. 1 | MONO rel. 1 | LUC rel. 1 |
| AFTER 4 WEEKS | | | | | | |
| 1 (0 MG/KG) | 0.156 | 0.014 | 0.004 | 0.794 | 0.024 | 0.008 |
| 2 (50 MG/KG) | 0.187 | 0.014 | 0.003 | 0.765 | 0.025 | 0.006 |
| 3 (200 MG/KG) | 0.169 | 0.019 | 0.004 | 0.780 | 0.023 | 0.005 |
| 4 (1000 MG/KG) | 0.140 | 0.019 | 0.004 | 0.811 | 0.020 | 0.006 |
| AFTER 6 WEEKS | | | | | | |
| 1 (0 MG/KG) | 0.142 | 0.015 | 0.007 | 0.809 | 0.019 | 0.007 |
| 4 (1000 MG/KG) | 0.139 | 0.018 | 0.008 | 0.808 | 0.022 | 0.007 |

| | DIFF.WBC COUNT (ABS) | | | | | | |
|---|---|---|---|---|---|---|---|
| | NEUT G/l | EOS G/l | BASO G/l | LYMPH G/l | MONO G/l | LUC G/l | PLATELETS G/l |
| AFTER 4 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 0.95 | 0.09 | 0.03 | 4.82 | 0.15 | 0.05 | 1145 |
| 2 (50 MG/KG) | 1.23 | 0.07 | 0.02 | 4.29 | 0.15 | 0.03 | 1121 |
| 3 (200 MG/KG) | 0.92 | 0.10 | 0.02 | 4.26 | 0.12 | 0.03 | 1086 |
| 4 (1000 MG/KG) | 0.72 | 0.11 | 0.02 | 4.20 | 0.10 | 0.03 | 1155 |
| AFTER 6 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 0.53 | 0.06 | 0.03 | 3.09 | 0.07 | 0.03 | 1267 |
| 4 (1000 MG/KG) | 0.54 | 0.07 | 0.03 | 3.03 | 0.09 | 0.03 | 1150 |

*/**: Dunnett-test based on pooled variance sig. at 5% or 1% level. +: Steel-test sig. at 5% level.

**HEMATOLOGY SUMMARY**
**MALES**

| | | | COAGULATION | |
|---|---|---|---|---|
| | MET-HB rel. 1 | HEINZ BOD rel. 1 | PT rel. 1 | PTT sec |
| AFTER 4 WEEKS | | | | |
| 1 (0 MG/KG) | 0.009 | 0.000 | 0.88 | 21.4 |
| 2 (50 MG/KG) | 0.009 | 0.000 | 0.91 | 19.6 |
| 3 (200 MG/KG) | 0.010 | 0.000 | 0.93 | 20.3 |
| 4 (1000 MG/KG) | 0.010 | 0.000 | 0.98 | 21.7 |
| AFTER 6 WEEKS | | | | |
| 1 (0 MG/KG) | 0.011 | 0.000 | 0.83 | 21.1 |
| 4 (1000 MG/KG) | 0.011 | 0.000 | 0.82 | 23.1 |

**HEMATOLOGY SUMMARY**
**FEMALES**

| | | | COAGULATION | |
|---|---|---|---|---|
| | MET-HB rel. 1 | HEINZ BOD rel. 1 | PT rel. 1 | PTT sec |
| AFTER 4 WEEKS | | | | |
| 1 (0 MG/KG) | 0.009 | 0.000 | 1.00 | 21.0 |
| 2 (50 MG/KG) | 0.010 | 0.000 | 0.95 | 25.3 |
| 3 (200 MG/KG) | 0.008 | 0.000 | 0.93 | 23.6 |
| 4 (1000 MG/KG) | 0.010 + | 0.000 | 0.91 + | 23.1 |
| AFTER 6 WEEKS | | | | |
| 1 (0 MG/KG) | 0.011 | 0.000 | 0.82 | 21.3 |
| 4 (1000 MG/KG) | 0.011 | 0.000 | 0.86 | 22.9 |

Clinical biochemistry parameters:

**CLINICAL BIOCHEMISTRY SUMMARY**
**MALES**

| | GLUCOSE mmol/l | UREA mmol/l | CREAT µmol/l | BILI-T µmol/l | CHOLEST mmol/l | TRIGLY mmol/l | PHOS-LIP mmol/l |
|---|---|---|---|---|---|---|---|
| AFTER 4 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 4.32 | 5.24 | 24.5 | 1.26 | 1.71 | 0.48 | 1.55 |
| 2 (50 MG/KG) | 4.22 | 4.85 | 26.8 | 1.07 | 1.46 | 0.53 | 1.48 |
| 3 (200 MG/KG) | 4.27 | 5.56 | 26.6 | 0.83 + | 1.82 | 0.47 | 1.65 |
| 4 (1000 MG/KG) | 3.78 | 5.18 | 23.9 | 0.23 + | 2.20 * | 0.60 | 1.82 |
| AFTER 6 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 5.37 | 5.22 | 26.2 | 1.15 | 1.46 | 0.36 | 1.35 |
| 4 (1000 MG/KG) | 4.93 * | 4.64 | 25.5 | 1.14 | 1.71 | 0.43 | 1.45 |

| | ASAT U/l | ALAT U/l | LDH U/l | GLDH U/l | ALP U/l | GGT U/l | CK U/l |
|---|---|---|---|---|---|---|---|
| AFTER 4 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 74.5 | 29.0 | 281.4 | 5.7 | 114.2 | 0.0 | 241.2 |
| 2 (50 MG/KG) | 73.9 | 28.9 | 290.7 | 6.1 | 101.6 | 0.0 | 258.5 |
| 3 (200 MG/KG) | 82.8 | 28.8 | 177.3 | 5.4 | 98.2 | 0.0 | 210.9 |
| 4 (1000 MG/KG) | 84.2 | 28.9 | 420.8 | 4.8 * | 118.5 | 0.0 | 305.1 |
| AFTER 6 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 76.0 | 28.2 | 156.6 | 6.1 | 94.2 | 0.0 | 182.4 |
| 4 (1000 MG/KG) | 72.9 | 29.3 | 182.3 | 5.6 | 88.8 | 0.0 | 176.5 |

| | SODIUM mmol/l | POTASSIUM mmol/l | CHLORIDE mmol/l | CALCIUM mmol/l | PHOSPHORUS mmol/l | PROTEIN g/l | ALBUMIN g/l |
|---|---|---|---|---|---|---|---|
| AFTER 4 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 142.6 | 3.38 | 102.2 | 2.60 | 2.15 | 61.46 | 40.56 |
| 2 (50 MG/KG) | 142.8 | 3.50 | 102.6 | 2.65 | 2.24 | 62.88 | 40.48 |
| 3 (200 MG/KG) | 143.7 | 3.43 | 103.6 | 2.70 * | 2.20 | 63.24 | 41.35 |
| 4 (1000 MG/KG) | 146.2 ** | 3.48 | 103.6 | 2.66 | 2.40 * | 61.33 | 40.41 |
| AFTER 6 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 141.5 | 3.17 | 101.7 | 2.73 | 1.96 | 66.56 | 43.07 |
| 4 (1000 MG/KG) | 142.2 | 3.22 | 102.4 | 2.73 | 2.00 | 64.38 * | 43.21 |

| | GLOBULIN g/l | A/G RATIO |
|---|---|---|
| AFTER 4 WEEKS | | |
| 1 (0 MG/KG) | 20.90 | 1.95 |
| 2 (50 MG/KG) | 22.40 | 1.81 |
| 3 (200 MG/KG) | 21.89 | 1.91 |
| 4 (1000 MG/KG) | 20.91 | 1.94 |
| AFTER 6 WEEKS | | |
| 1 (0 MG/KG) | 23.50 | 1.84 |
| 4 (1000 MG/KG) | 21.17 * | 2.05 |

## CLINICAL BIOCHEMISTRY SUMMARY

**FEMALES**

| | GLUCOSE mmol/l | UREA mmol/l | CREAT µmol/l | BILI-T µmol/l | CHOLEST mmol/l | TRIGLY mmol/l | PHOS-LIP mmol/l |
|---|---|---|---|---|---|---|---|
| AFTER 4 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 3.90 | 5.79 | 27.3 | 1.57 | 1.41 | 0.30 | 1.56 |
| 2 (50 MG/KG) | 4.04 | 5.19 | 25.8 | 1.58 | 1.45 | 0.32 | 1.60 |
| 3 (200 MG/KG) | 4.20 | 6.34 | 29.0 | 1.68 | 1.23 | 0.32 | 1.40 |
| 4 (1000 MG/KG) | 3.68 | 5.59 | 28.9 | 1.04 | 1.74 | 0.35 | 1.76 |
| AFTER 6 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 5.17 | 6.32 | 33.2 | 1.56 | 1.25 | 0.36 | 1.32 |
| 4 (1000 MG/KG) | 4.85 | 7.12 | 34.5 | 1.46 | 1.66 | 0.34 | 1.60 |

| | ASAT U/l | ALAT U/l | LDH U/l | GLDH U/l | ALP U/l | GGT U/l | CK U/l |
|---|---|---|---|---|---|---|---|
| AFTER 4 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 68.5 | 25.6 | 216.4 | 5.3 | 51.1 | 0.0 | 203.0 |
| 2 (50 MG/KG) | 64.9 | 21.2 | 207.3 | 4.7 | 54.8 | 0.0 | 207.9 |
| 3 (200 MG/KG) | 69.1 | 21.7 | 261.1 | 5.9 | 47.2 | 0.0 | 197.5 |
| 4 (1000 MG/KG) | 72.2 | 23.0 | 274.8 | 7.0 | 55.1 | 0.0 | 210.0 |
| AFTER 6 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 64.6 | 21.2 | 203.9 | 4.7 | 41.5 | 0.0 | 148.4 |
| 4 (1000 MG/KG) | 61.1 | 24.8 | 213.1 | 7.3 | 39.3 | 0.0 | 164.2 |

| | SODIUM mmol/l | POTASSIUM mmol/l | CHLORIDE mmol/l | CALCIUM mmol/l | PHOSPHORUS mmol/l | PROTEIN g/l | ALBUMIN g/l |
|---|---|---|---|---|---|---|---|
| AFTER 4 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 144.4 | 3.18 | 104.9 | 2.70 | 2.11 | 65.82 | 45.92 |
| 2 (50 MG/KG) | 145.2 | 3.27 | 105.0 | 2.72 | 2.05 | 67.28 | 47.23 |
| 3 (200 MG/KG) | 145.6 | 3.27 | 105.0 | 2.68 | 2.09 | 66.54 | 46.92 |
| 4 (1000 MG/KG) | 144.6 | 3.02 | 103.9 | 2.62 | 2.12 | 65.72 | 45.75 |
| AFTER 6 WEEKS | | | | | | | |
| 1 (0 MG/KG) | 141.2 | 2.69 | 101.5 | 2.76 | 1.62 | 70.61 | 48.81 |
| 4 (1000 MG/KG) | 141.3 | 2.94 ** | 103.9 | 2.77 | 1.64 | 72.76 | 50.76 |

| | GLOBULIN g/l | A/G RATIO |
|---|---|---|
| AFTER 4 WEEKS | | |
| 1 (0 MG/KG) | 19.90 | 2.34 |
| 2 (50 MG/KG) | 20.05 | 2.36 |
| 3 (200 MG/KG) | 19.62 | 2.40 |
| 4 (1000 MG/KG) | 19.97 | 2.30 |
| AFTER 6 WEEKS | | |
| 1 (0 MG/KG) | 21.81 | 2.27 |
| 4 (1000 MG/KG) | 22.01 | 2.31 |

Locomotor activity:

**LOCOMOTOR ACTIVITY, SUMMARY DATA**

**MALES**

**BEAM COUNTS 4 WEEKS**

**GROUP 1**

**0 mg/kg**

| | 10 min | 20 min | 30 min | 40 min | 50 min | 60 min | Total |
|---|---|---|---|---|---|---|---|
| Mean | 446 | 316 | 208 | 220 | 150 | 77 | 1417 |
| St.dev. | 69 | 64 | 117 | 93 | 90 | 100 | 350 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**GROUP 2**

**50 mg/kg**

| | 10 min | 20 min | 30 min | 40 min | 50 min | 60 min | Total |
|---|---|---|---|---|---|---|---|
| Mean | 434 | 315 | 312 | 137 | 91 | 43 | 1332 |
| St.dev. | 84 | 55 | 104 | 122 | 116 | 61 | 343 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

**GROUP 3**

**200 mg/kg**

| | 10 min | 20 min | 30 min | 40 min | 50 min | 60 min | Total |
|---|---|---|---|---|---|---|---|
| Mean | 526 | 380 | 236 | 118 | 92 | 43 | 1396 |
| St.dev. | 130 | 100 | 31 | 146 | 143 | 73 | 431 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

**GROUP 4**

**1000 mg/kg**

| | 10 min | 20 min | 30 min | 40 min | 50 min | 60 min | Total |
|---|---|---|---|---|---|---|---|
| Mean | 554 * | 430 | 335 | 248 | 127 | 63 | 1757 |
| St.dev. | 95 | 113 | 121 | 112 | 114 | 87 | 340 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

*/** T-Test sig. at 5% or 1% level

**LOCOMOTOR ACTIVITY, SUMMARY DATA**

**FEMALES**

**BEAM COUNTS** **4 WEEKS**

**GROUP 1**

**0 mg/kg**

| | 10 min | 20 min | 30 min | 40 min | 50 min | 60 min | Total |
|---|---|---|---|---|---|---|---|
| Mean | 444 | 239 | 165 | 129 | 65 | 163 | 1203 |
| St.dev. | 108 | 100 | 81 | 142 | 115 | 85 | 452 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**GROUP 2**

**50 mg/kg**

| | 10 min | 20 min | 30 min | 40 min | 50 min | 60 min | Total |
|---|---|---|---|---|---|---|---|
| Mean | 539 | 256 | 125 | 64 * | 97 | 110 | 1192 |
| St.dev. | 49 | 75 | 104 | 87 | 106 | 104 | 259 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

**GROUP 3**

**200 mg/kg**

| | 10 min | 20 min | 30 min | 40 min | 50 min | 60 min | Total |
|---|---|---|---|---|---|---|---|
| Mean | 504 | 248 | 182 | 58 * | 89 | 169 | 1270 |
| St.dev. | 167 | 106 | 154 | 68 | 123 | 66 | 446 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

**GROUP 4**

**1000 mg/kg**

| | 10 min | 20 min | 30 min | 40 min | 50 min | 60 min | Total |
|---|---|---|---|---|---|---|---|
| Mean | 629 * | 323 | 230 | 144 | 52 | 77 | 1455 |
| St.dev. | 116 | 94 | 133 | 146 | 57 | 87 | 424 |
| N | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

*/** T-Test sig. at 5% or 1% level

We agree with the study author that any effects observed in the tables above were incidental or of such magnitude that these could be considered to be of low toxicological relevance. No effect on salivation was reported in the OECD 407 study, but in the OECD 421 study (there considered to be a physiological response rather than a systemic effect due to low severity and occurrence after dosing).

| |
|---|
| The minor deviations from the protocol in the OECD 421-study that was referred to were: formulation samples were not transferred ti the weighing room but dispatched directly to the test site (samples received in good order), lack of registration of the clinical observation on LD 3 for one pup, necropsy of a dam that failed to deliver was performed on day 28 post-coitum instead of day 25-27 post coitum, and a few (common) abnormalities of kidneys and liver that was not subjected to histopathology (three control animals, one low dose and one mid dose). We agree with the study author that these deviations did not significantly affect the integrity of the study. |
| RAC's response |
| Both the additional data from the OECD TG 407 study provided by the DS in the RCOM as well as more details on the minor deviations from the OECD TG 421 study protocol has been reflected in the opinion. |

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

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 14.03.2023 | Germany | | MemberState | 3 |
| Comment received | | | | |
| DE CA agrees with the dossier submitter that a classification as Skin Sens. 1A, H317 is warranted.<br><br>Proposed editorial changes:<br>Original text of Chapter 10.5.2 Comparison with the CLP criteria, 1st paragraph, 3rd (last) sentence:<br><br>"The CLP criteria state that a substance should be classified as a skin sensitiser in category 1A if EC3 is < 2% concentration of the substance (table 3.4.3 of the CLP regulation (EU, 2022)."<br><br>Please write "≤ 2% " as it is written in the table 3.4.3 of the CLP regulation (EU, 2022).<br>"The CLP criteria state that a substance should be classified as a skin sensitiser in category 1A if EC3 is ≤ 2% concentration of the substance …" | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your support and correction. This was a typographic error from our side. | | | | |
| RAC's response | | | | |
| Noted. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 30.03.2023 | France | | MemberState | 4 |
| Comment received | | | | |
| Skin sensitisation: FR agrees with the proposed classification as Skin Sens. 1A based on the very high probability that EC3 will occur ≤ 2% since a SI of 10.9 is found at 2.5%. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your support. | | | | |
| RAC's response | | | | |
| Noted. | | | | |