**Committee for Risk Assessment**

**RAC**

# Opinion

proposing harmonised classification and labelling
at EU level of

# Chloralose (INN); (R)-1,2-O-(2,2,2-trichloroethylidene)-α-D-gluco-furanose; glucochloralose; anhydroglucochloral

**EC number: 240-016-7**
**CAS number: 15879-93-3**

CLH-O-0000004852-71-03/F

**Adopted**
**12 September 2014**

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# OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonized classification and labelling (CLH) of:

**Chemicals name: Chloralose**
**Chloralose (INN); (R)-1,2-O-(2,2,2-trichloroethylidene)-α-D-gluco-furanose; glucochloralose; anhydroglucochloral**

**EC number: 240-016-7**

**CAS number: 15879-93-3**

The proposal was submitted by **Portugal** and received by the RAC on **28 January 2014**

In this opinion, all classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonized System (GHS). The classification notation for 67/548/EEC, the Dangerous Substances Directive (DSD) is no longer provided.

## PROCESS FOR ADOPTION OF THE OPINION

**Portugal** has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation on **11 February 2014**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **28 March 2013**.

### ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Marja Pronk**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation. The RAC opinion on the proposed harmonized classification and labelling was reached on **12 September 2014** and the comments received are compiled in Annex 2. The RAC Opinion was adopted by consensus.

**OPINION OF THE RAC**

The RAC adopted the opinion on **Chloralose** that should be classified and labelled as follows:

**Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)**

| | Index No | International Chemical Identification | EC No | CAS No | Classification | | Labelling | | | Specific Conc. Limits, M-factors | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Hazard Class and Category Code(s) | Hazard statement Code(s) | Pictogram, Signal Word Code(s) | Hazard state-ment Code(s) | Suppl. Hazard statement Code(s) | | |
| Current Annex VI entry | 605-013-00-0 | chloralose (INN); (R)-1,2-O-(2,2,2-trichloroethylidene)-α-D-glucofuranose; glucochloralose; anhydroglucochloral | 240-016-7 | 15879-93-3 | Acute Tox. 4*<br>Acute Tox. 4* | H332<br>H302 | GHS07<br>Wng | H332<br>H302 | | | |
| Dossier submitters proposal | 605-013-00-0 | chloralose (INN); (R)-1,2-O-(2,2,2-trichloroethylidene)-α-D-glucofuranose; glucochloralose; anhydroglucochloral | 240-016-7 | 15879-93-3 | **Maintain**<br>Acute Tox. 4*<br>**Confirm**<br>Acute Tox. 4<br>**Add**<br>STOT SE 3<br>Aquatic Acute 1<br>Aquatic Chronic 1 | H332<br>H302<br>H336<br>H400<br>H410 | GHS07<br>GHS09<br>Wng | H332<br>H302<br>H336<br>H410 | | M=10 (acute)<br>M=10 (chronic) | C |
| RAC opinion | 605-013-00-0 | chloralose (INN); (R)-1,2-O-(2,2,2-trichloroethylidene)-α-D-glucofuranose; glucochloralose; anhydroglucochloral | 240-016-7 | 15879-93-3 | ***No recommendation***<br>*Acute Tox. 4*([1])*<br>**Modify**<br>Acute Tox. 3<br>**Add**<br>STOT SE 3<br>Aquatic Acute 1<br>Aquatic Chronic 1 | *H332*<br>H301<br>H336<br>H400<br>H410 | GHS06<br>GHS09<br>Dgr | *H332*<br>H301<br>H336<br>H410 | | M=10 (acute)<br>M=10 (chronic) | C |

**([1])** Note to Commission: There are no adequate data for RAC to conclude on this endpoint from a scientific point of view. Please see text in opinion.

**OPINION OF THE RAC**

The RAC adopted the opinion on **Chloralose** that should be classified and labelled as follows:

**Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Resulting Annex VI entry if agreed by COM | 605-013-00-0 | chloralose (INN); (R)-1,2-O-(2,2,2-trichloroethylidene)-α-D-glucofuranose; glucochloralose; anhydroglucochloral | 240-016-7 | 15879-93-3 | ***No recommendation***<br>*Acute Tox. 4** ***(1)***<br>Acute Tox. 3<br>STOT SE 3<br>Aquatic Acute 1<br>Aquatic Chronic 1 | <br>*H332*<br>H301<br>H336<br>H400<br>H410 | GHS06<br>GHS09<br>Dgr | <br>*H332*<br>H301<br>H336<br>H410 | <br><br><br>M=10<br>M=10 | C |

**(1)** Note to Commission: There are no adequate data for RAC to conclude on this endpoint from a scientific point of view. Please see text in opinion.

## RAC evaluation of acute toxicity

## Summary of the Dossier submitter's proposal

Currently, chloralose has a minimum classification for acute oral and inhalation toxicity as Acute Tox. 4 * – H302 and Acute Tox. 4 * – H332, respectively. For acute oral toxicity, the dossier submitter confirmed the current classification (and thus proposed removal of the asterisk) based on an oral $LD_{50}$ value of 341 mg/kg bw in rats, as this $LD_{50}$ is within the range of 300 < ATE ≤ 2000 mg/kg bw.

For acute inhalation toxicity, the dossier submitter did not consider it appropriate to withdraw the minimum classification (and thus proposed to maintain the asterisk in the Annex VI entry) because the results of the available study in rats were considered inconclusive for classification purposes. In this study, rats were exposed for 4 hours (nose-only) to mean achieved concentrations of 1.04, 1.99, or 4.55 mg/L, and mortality was 0/10, 1/10 and 1/10 animals, respectively. Whereas the study author concluded the $LC_{50}$ to be >4.55 mg/L, the dossier submitter concluded that the $LC_{50}$ value can only be ascertained as being >1.99 mg/L, as this is the highest concentration at which there were not significant fluctuations in the actual exposure. At the maximum attainable concentration of 4.55 mg/L on the other hand, the actual exposure was considered to be uncertain because the exposure concentration varied by more than 15% of the mean value and only 40.9% of particles were of respirable size (<4 µm).

## Comments received during public consultation

One Member State competent authority (MSCA) supported the classification proposal for both acute oral and acute inhalation toxicity. One MSCA supported the classification proposal for acute inhalation toxicity, but suggested that for the oral route Acute Tox. 3 – H301 should be considered in view of the high variability observed between males and females, and that therefore classification should be based on the $LD_{50}$ of 212 mg/kg bw for female rats rather than on the $LD_{50}$ of 341 mg/kg bw for males and females combined. The same comment on the acute oral toxicity was made by a third MSCA.

## Assessment and comparison with the classification criteria

There is one acute **oral** toxicity study available. In this study, groups of 5 male and 5 female rats were given a single dose of 125, 200, 320 or 2000 mg/kg bw chloralose by gavage. Mortality was 1/10, 1/10, 5/10 and 10/10 animals, respectively, resulting in $LD_{50}$ values of 212 mg/kg bw for females, 611 mg/kg bw for males and 341 mg/kg bw for males and females combined. Based on the combined value, the dossier submitter proposed chloralose to be classified as Acute Tox. 4 – H302. However, in general, classification is based on the lowest $LD_{50}$ value available. Hence, RAC concluded that chloralose should be classified as **Acute Tox. 3 – H301**, given that the lowest $LD_{50}$ value of 212 mg/kg bw for female rats falls within the range for category 3 (50 < $LD_{50}$ ≤ 300 mg/kg bw).

As to the only acute **inhalation** study available for chloralose, RAC supported the conclusion of the dossier submitter that its results were inconclusive for classification purposes. There was no information on whether this study was the basis for classifying chloralose originally with Xn; R20 under DSD, or whether it was based on other data. In the absence of adequate information it was not possible for RAC to determine whether this classification, which was translated into Acute Tox. 4* – H332 under CLP, is justified or not. Hence, a recommendation for keeping Acute Tox. 4* – H332 or not cannot be made from a scientific point of view.

## RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

### Summary of the Dossier submitter's proposal

Chloralose has been used as a sedative, hypnotic and anaesthetic agent in veterinary and human medicine. Its toxicological mode of action as an acute CNS depressant (causing sedation, ataxia and respiratory depressant effects) has also been observed in the acute toxicity studies with rats. In the oral study, sedation, lateral decubitus, coma, and dyspnoea were observed in all animals within 15 minutes following administration. At 125, 200 and 320 mg/kg bw, most effects were reversible after 60 minutes, but at 2000 mg/kg bw additionally tonic and clonic convulsions were seen before death (within 4 hours post-treatment). In the inhalation study, the effects observed included hunched posture, pilo-erection, red-brown staining, increased respiration rate, laboured respiration, (severe) ataxia, tonic or clonic convulsions, lethargy and prostration. All animals that survived in the three dose groups showed reversibility in the effects, at the latest from days 8 to 11 post-exposure. The mode of action is further supported by human data referring to poisoning cases and medical use as a sedative and anaesthetic.

As the narcotic effects were demonstrated to be acute and of transient nature, the dossier submitter proposed chloralose to be classified as STOT SE 3 – H336.

### Comments received during public consultation

Two MSCAs supported the classification proposal for STOT SE 3. No comments opposing the proposal were received.

### Assessment and comparison with the classification criteria

According to the CLH dossier, chloralose has been used as a sedative, hypnotic, anaesthetic agent in veterinary and human medicine and in management of alcohol withdrawal symptoms in humans, at a dose of 75-300 mg in humans (equivalent to 1.25-5 mg/kg bw for a 60 kg person). It is, however, no longer used in medical practice. Available human data are mostly from acute suicidal, homicidal and accidental intoxications with chloralose. Symptoms of acute poisonings reported in literature include coma, myoclonus, convulsions, respiratory failure, bronchial hypersecretion, hypo- and hyperthermia, vomiting, headache and ataxia. The oral toxic dose was reported to be about 1g for adults (equivalent to 17 mg/kg bw for a 60 kg person) and 20 mg/kg bw for children, with ingested doses ranging from 3-30 g. Chloralose poisoning is usually severe and life-threatening. Despite the clinical severity, the prognosis is good if adequate symptomatic treatment (such as mechanical ventilation, anticonvulsants) is applied rapidly. This might explain the observation that fatal cases are rare. Adverse effects following medical use are reported to include ataxia, coma, myoclonus, tachycardia and respiratory depression. The medical and acute poisoning cases confirm that chloralose is a CNS depressant in humans.

CNS depressant effects were also observed in the available acute toxicity studies with rats. They occurred in all animals at all doses tested, but were reversible within one day (oral study) or a couple of days (inhalation study; mostly within 1-4 days, but day 8-11 at the latest). The effects were observed at lethal or near lethal doses (mortality was seen at all doses in the oral study and at the mid and high dose in the inhalation study).

The CNS depressant effects observed in humans and rats are consistent with its (past) medical indications. They in principle meet the criteria for STOT SE 3. However, RAC noted that in rats these effects observed at the same or somewhat higher doses have led to its current classification for lethality. The rat data in themselves therefore do not warrant additional classification with STOT SE 3. As to the human data, there is very little detail available on actual doses ingested in the few fatal cases reported, or on what are life-threatening doses if not rapidly treated. The window between therapeutic and lethal doses is probably somewhere within a factor of 10-400 (75-300 mg vs 3-30 g). RAC considered this difference to warrant additional classification for the CNS depressant effects and, overall, therefore supported the dossier submitter proposal for classification of chloralose as **STOT SE 3 – H336**.

## RAC evaluation of environmental hazards

## Summary of the Dossier submitter's proposal

The current Annex VI entry for chloralose does not include an environmental classification. The dossier submitter proposed to add Aquatic Acute 1 – H400 and Aquatic Chronic 1 – H410 (both with an M-factor of 10) to the existing classification.

***Degradation***
Hydrolysis of chloralose was 3.3% at 50°C and pH 9 in the preliminary test (5 days). Degradation at pH 4 and 7 was not further investigated since at pH 9 degradation was <10%. Based on that result, the half-life ($DT_{50}$) at any pH is expected to be > 1 year at 25°C.

Photodegradation of chloralose was not tested. The US EPA Test Guideline OPPTS 835.2210 Direct Photolysis Rate in Water by Sunlight test method is applicable to all chemicals which have UV/absorption maxima in the range of 290-800 nm. As chloralose has a UV absorption maximum of 194.5 nm (no UV absorbance in the sunlight spectrum), it was considered to be not susceptible to direct phototransformation and was assumed to be stable against photolysis in water.

Ready biodegradation was tested in a 28-day Closed Bottle study in compliance with EC Method C.4-E. The testing was performed at 20 ± 2 ºC with sampling on days 0, 7, 14, 21 and 28. A maximum of 17% biodegradation was found after 28 days.

Inherent biodegradation was studied in the Modified Zahn-Wellens/EMPA study in compliance with OECD Guideline 302B. This test was performed at 20-25°C and pH 7.4. The sampling was performed at 0 and 3 hours and on days 1, 2, 3, 6, 8 10, 14, 16, 21, 23, 27 and 28. The test material reached 19% degradation after 28 days. The results obtained from the abiotic test vessel showed that 14% loss of DOC (dissolved organic carbon) occurred over the study period. Correction of the DOC degradation rate for abiotic loss showed that the test material achieved 5% biodegradation after 28 days.

Based on the above, the dossier submitter concluded that chloralose is not expected to undergo abiotic degradation by hydrolysis or by photolysis in water, is not rapidly degradable, and is neither readily nor inherently biodegradable.

***Bioaccumulation***
A log $K_{ow}$ of 0.85 was measured for chloralose using the EC Method A.8, the Shake Flask Method. The dossier submitter did not consider this value valid, as the Shake Flask Method is not suitable for surface active substances, which chloralose is based on its surface tension (50.076 mN/m is <60 mN/m). Although without actual data it is not possible to conclude on the aquatic bioaccumulation status of the substance, the dossier submitter stated that this endpoint does not affect the classification proposal.

***Acute toxicity***
Two acute toxicity studies in fish, two in invertebrates and two in algae were reported.

Both fish tests have been performed with the rainbow trout (*Oncorhynchus mykiss)*, according to EC Method C.1, under semi-static conditions (renewal of test solutions after 24h) over 96h. The reported $LC_{50}$ (96 h) values were 2.4 mg/L in the first test and 5.01 mg/L in the second test; both based on nominal concentrations. Stability of chloralose was monitored with a 100 mg/L solution (first test) or with 0.1 and 50 mg/L solutions (second test). The measured concentrations remained within the 80-120% range for all measured samples.

Two acute toxicity tests with *Daphnia magna* were performed according to EC Method C.2, under static conditions. The reported $EC_{50}$ (48 h) values were 0.027 mg/L in the first test and 0.36 mg/L in the second test; both were based on nominal concentrations. Stability of chloralose was

monitored with a 100 mg/L solution (first test) or with 0.001 and 10 mg/L solutions (second test). The measured concentrations remained within the 80-120% range for all measured samples.

Two Growth Inhibition Tests on Algae were performed with *Pseudokirchneriella subcapitata* according to EC Method C.3. The $ErC_{50}$, 72 h (50% reduction in growth rate) was 0.52 mg/L in the first test and 4.9 mg/L in the second test. The no observed effect concentration (NOEC, 72 h) was 0.02 mg/L in the first test and 0.13 mg/L in the second test. All values were based on nominal concentrations. Stability of chloralose was monitored with a 100 mg/L solution (first test) or with 0.01 and 6.25 mg/L solutions (second test). The measured concentrations remained within the 80-120% range with the exception of the 0.01 mg/L concentration in which at the end of the test (72h) was 77% of nominal.

The dossier submitter concluded that chloralose meets the criteria to be classified as Aquatic Acute category 1 (H400) and that, since the $EC_{50}$ (48 h) value for the most sensitive organism (*Daphnia magna*) is within the range 0.01-0.1 mg/L, an acute M-factor of 10 should be assigned.

***Chronic toxicity***
For the long-term aquatic hazard, data were available only for one trophic level. Therefore the dossier submitter used the surrogate approach. Considering that chloralose is not rapidly degradable and that the most stringent outcome is the $EC_{50}$ (48 h) of 0.027 mg/L for *Daphnia magna*, classification as Aquatic Chronic category 1 (H410) with a chronic M-factor of 10 (since the value is within the range 0.01-0.1 mg/L) was proposed by the dossier submitter.

## Comments received during public consultation

Four MSCAs supported the classification proposal for aquatic acute and chronic toxicity. No comments opposing the proposal were received.

## Assessment and comparison with the classification criteria

***Degradation***
The information provided showed that chloralose is hydrolytically stable at environmentally relevant pHs (pH5-9). In a ready biodegradability Closed Bottle test, chloralose did not degrade more than 17% after 28 days. In an inherent biodegradability test, chloralose did not degrade more than 19% after 28 days. Considering these results, RAC agreed with the dossier submitter that chloralose is not readily or inherently biodegradable and not rapidly degradable for the purposes of classification and labelling.

***Bioaccumulation***
The log $K_{ow}$ of 0.85 was measured in the shake flask method, which is not suitable for chloralose, as this is a surface-active substance. However, the log $K_{ow}$ value was in line with the measured water solubility of 4840 mg/L, therefore RAC considered that chloralose not likely to be a bioaccumulative substance.

***Acute toxicity***
Aquatic acute toxicity studies were available for all trophic levels. The lowest $L(E)C_{50}$ value obtained was 0.027 mg/L for immobilization of *Daphnia magna*. Even though this value was based on nominal concentrations, the additional data from this test and all other aquatic toxicity studies (measured concentrations from preliminary and main tests remaining within ca. 80 – 120% of nominal), RAC considered this study as valid for classification purposes.

This lowest $EC_{50}$ of 0.027 mg/L is below the cut-off value of 1 mg/L, therefore chloralose fulfils the criteria for **Aquatic Acute 1 – H400**, with an **M-factor of 10** ($EC_{50}$ value is within the range of 0.01-0.1 mg/L). RAC therefore supported the proposal of the dossier submitter.

***Chronic toxicity***

Chronic aquatic hazard data was available only for one trophic level, i.e. algae. This in principle justifies consideration of the surrogate approach for those trophic levels which have no chronic data available. The most sensitive species in the acute tests was *Daphnia magna*. Inherent to the use of the surrogate approach is the uncertainty as to whether other species, such as fish, might possibly be more sensitive than invertebrates to chronic exposure to chloralose. Acknowledging this, RAC supported the surrogate approach used by the dossier submitter, resulting in a classification proposal for chloralose as **Aquatic Chronic 1 – H410**, with an **M-factor of 10**.

## ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and rapporteurs' comments (excl. confidential information).