Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

octhilinone (ISO); 2-octyl-2*H*-isothiazol-3-one; [OIT]

EC Number: 247-761-7
CAS Number: 26530-20-1

CLH-O-0000001412-86-255/F

Adopted

30 November 2018

30 November 2018

CLH-O-0000001412-86-255/F

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 Regulation (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 harmonised classification and labelling (CLH) of:

Chemical name: **octhilinone (ISO); 2-octyl-2*H*-isothiazol-3-one; [OIT]**

EC Number: **247-761-7**

CAS Number: **26530-20-1**

The proposal was submitted by **United Kingdom** and received by RAC on **17 January 2018.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

United Kingdom 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 at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **12 March 2018**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **11 May 2018**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Anna Biró**

Co-Rapporteur, appointed by RAC: **Riitta Leinonen**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **30 November 2018** by **consensus**.

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	613-112-00-5	octhilinone (ISO); 2-octyl-2*H*-isothiazol-3-one	247-761-7	26530-20-1	Acute Tox. 3 * Acute Tox. 3 * Acute Tox. 4* Skin Corr. 1B Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H331 H311 H302 H314 H317 H400 H410	GHS06 GHS05 GHS09 Dgr	H331 H311 H302 H314 H317 H410		Skin Sens. 1; H317: C ≥ 0,05 %	
Dossier submitters proposal	613-112-00-5	octhilinone (ISO); 2-octyl-2*H*-isothiazol-3-one; [OIT]	247-761-7	26530-20-1	**Add** Eye Dam. 1 **Modify** Acute Tox. 2 Acute Tox. 3 Acute Tox. 3 Skin Sens. 1A **Retain** Skin Corr. 1B Aquatic Acute 1 Aquatic Chronic 1	**Add** H318 **Modify** H330 H301 **Retain** H311 H314 H317 H400 H410	**Retain** GHS06 GHS05 GHS09 Dgr	**Modify** H330 H301 **Retain** H311 H314 H317 H410	**Add** EUH071	**Modify** Skin Sens. 1A; H317: C ≥ 0,005 % **Add** M=100 M=100	
RAC opinion	613-112-00-5	octhilinone (ISO); 2-octyl-2*H*-isothiazol-3-one; [OIT]	247-761-7	26530-20-1	**Add** Eye Dam. 1 **Modify** Acute Tox. 2 Acute Tox. 3 Acute Tox. 3 Skin Corr. 1 Skin Sens. 1A **Retain** Aquatic Acute 1 Aquatic Chronic 1	**Add** H318 **Modify** H330 H301 **Retain** H311 H314 H317 H400 H410	**Retain** GHS06 GHS05 GHS09 Dgr	**Modify** H330 H301 **Retain** H311 H314 H317 H410	**Add** EUH071	**Add** inhalation: ATE = 0.27 mg/L (dusts and mists) oral: ATE = 125 mg/kg bw dermal : ATE = 311 mg/kg bw M=100 M=100 **Modify** Skin Sens. 1A; H317: C ≥ 0,0015 %	
Resulting Annex VI entry if agreed by COM	613-112-00-5	octhilinone (ISO); 2-octyl-2*H*-isothiazol-3-one; [OIT]	247-761-7	26530-20-1	Acute Tox. 2 Acute Tox. 3 Acute Tox. 3 Skin Corr. 1 Eye Dam. 1 Skin Sens. 1A Aquatic Acute 1 Aquatic Chronic 1	H330 H311 H301 H314 H318 H317 H400 H410	GHS06 GHS05 GHS09 Dgr	H330 H311 H301 H314 H317 H410	EUH071	inhalation: ATE = 0.27 mg/L (dusts and mists) oral: ATE = 125 mg/kg bw dermal : ATE = 311 mg/kg bw Skin Sens. 1A; H317: C ≥ 0,0015 % M=100 M=100	

GROUNDS FOR ADOPTION OF THE OPINION

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

The Dossier Submitter (DS) summarised eight acute toxicity studies on octhilinone (OIT) in the CLH report, covering oral (4 studies on rat), inhalation (2 studies on rat) and dermal (1 study on rabbit and 1 study on rat) routes of exposure. According to the DS, the existing harmonised classification of OIT was based on the LD_{50} or LC_{50} values derived in the oldest studies that were not dose-corrected for the dilution of OIT in propylene glycol (42 to 46.7 % w/w instead of 100 % w/w).

For **acute oral toxicity**, four studies were included in the CLH report. In the first study (Anonymous, 1987) according to OECD TG 401 and GLP, male and female Charles River CD rats were treated by oral gavage with OIT (42-46.7 %) in propylene glycol at dose levels of 0, 126, 210, 336, 504 and 840 mg OIT/kg bw. Most animals treated with doses ≥ 210 mg/kg bw died on days 0-2. Clinical signs observed were central nervous system (CNS) depression, distended stomachs, pale extremities, respiratory noise, cool-to-touch, lacrimation, scant droppings, diarrhoea, red-stained muzzle and stained anogenital area. Gross necropsy revealed the presence of redness of the stomach and intestinal mucosa and/or yellow or white fluid-filled stomach or intestines in the decedents. The reported LD_{50} values were 318 mg OIT/kg bw (males) and 324 mg OIT/kg bw (females).

The second study (non-guideline, non-GLP) in CF Nelson Albino rats (Anonymous, 1977) reported an LD_{50} value of 247 mg OIT/kg bw (males) and 292 mg/kg (females). According to the DS, the study could not be assessed properly due to missing information.

A third study was carried out in Sprague-Dawley rats (Anonymous, 1991b) according to EPA 81-1 guideline (c.f. OECD TG 401) and under GLP. OIT (45 %) in propylene glycol was administered to male and females rats at dose levels of 0, 90, 180 and 450 mg OIT/kg bw. The result of the study was a combined LD_{50} value of 125 mg OIT/kg bw for males and females. Clinical signs included CNS depression, decreased respiratory rate, pallor of the extremities and piloerection. There were no abnormal findings during gross necropsy of the decedents/sacrificed.

A fourth study (Anonymous, 2002a) according to OECD TG 423 and GLP investigated oral toxicity in Wistar rats after administration of OIT (96.4 %) in water at dose levels of 0, 200, 500 mg/kg bw in male and females and in males only at 2 000 mg/kg bw. The LD_{50} was found to be greater than 500 mg/kg bw but less than 2 000 mg/kg bw. Gross necropsy revealed lesions in the lungs, mottling of the liver, bleeds to the stomach, white foci of the spleen and congestion of the kidneys.

The DS concluded that 125 mg OIT/kg bw was the relevant LD_{50} for both males and females and proposed to classify OIT as Acute Tox. 3; H301 (toxic if swallowed).

For **acute inhalation toxicity,** two guideline studies in Sprague-Dawley rats were assessed in the CLH report.

In the first study, rats were exposed, nose-only, to an aerosol (MMAD = 1.7-2.6 µm) of OIT (42-46.7 %) in propylene glycol for 4 hours (Anonymous, 1986) according to OECD TG 403 and GLP. Concentrations administered were 0, 0.058, 0.095, 0.229 and 0.671 mg OIT/L. The resulting combined LC_{50} for males and females was calculated to be 0.58 mg OIT/L. As for the oral studies, originally the LC_{50} value had not been dose-corrected for 100 % OIT and had been reported to be 1.254 mg/L. Clinical signs included signs of sensory and upper respiratory tract irritation (dyspnoea, bradypnoea, rales and gasping), CNS depression (ataxia, listlessness and prostration) which was considered secondary to respiratory distress and nasal mucosal irritation. Pathology of the decedents revealed red/brown foci and brown areas on the lungs and oedematous tongues.

The second study was performed in rats with an aerosol (MMAD = 1.58 µm) of OIT (45 %) in propylene glycol using whole-body exposure (Anonymous, 1992) according to OECD TG 403 and GLP. Rats were exposed to 0 (air control), 0.115, 0.224 and 0.330 mg/L for 4 h. The combined LC_{50} for males and females was determined to be 0.27 mg OIT/L, with most deaths occurring during the first 24 h following exposure. Clinical signs included gasping, disturbed respiration (noisy and exaggerated), immobility and staining of the fur. Gross necropsy of the decedents revealed congestion of the lungs, gas-filled stomachs (thought to be caused by swallowing of air during attempts to breathe) and some incidences of increased lung weight (relative to body weight). There were no treatment-related abnormalities in surviving animals.

The DS argued that additional exposure from the grooming of contaminated fur could not be ruled out in the whole-body exposure study, but it was not clear whether this accounted entirely for inconsistent LC_{50} values obtained in the two studies. It was noted in the whole-body exposure study, that necropsy revealed gas-filled stomach in the decedents and that this finding was often seen in rats that died as a result of respiratory distress as they swallowed air during attempts to breath. The DS concluded that 0.27 mg/L was a relevant LC_{50} value and proposed to classify OIT as Acute Tox. 2; H330 (fatal if inhaled).

Since the mechanism of pulmonary toxicity was considered to be corrosivity (OIT has a harmonised classification as Skin Corr. 1, and also clinical signs of respiratory tract irritation were observed in both acute inhalation studies), the DS also proposed an additional labelling phrase EUH071 "corrosive to the respiratory tract".

For **acute dermal toxicity**, two studies were included in the CLH report. Both studies used methods similar to that of OECD TG 402. In the first study (Anonymous, 2004a– study date 1977), OIT (42-46.7 %) in propylene glycol was applied to the skin of male albino rabbits at dose levels of 146, 291, 582, 1 163 and 2 326 mg OIT/kg bw for 24 h under semi-occlusive conditions (5 males/group). All animals treated with doses of ≥ 582 mg/kg bw died. Clinical signs including lethargy, prostration, ataxia and partial paresis of hind limbs were observed in animals treated with ≥ 291 mg/kg bw. At the site of treatment, there were local signs of corrosion such as severe erythema and oedema followed by eschar formation, which preceded death. The dermal LC_{50} value was determined to be 311 mg OIT/kg bw. Previously, this had been given as 690 mg/kg bw, however this value had not been dose-corrected for pure OIT.

In the second dermal study (Anonymous (1991c), a single dose of 900 mg/kg bw of OIT (45 %) in propylene glycol was applied to the skin of male and female Sprague-Dawley rats (5/sex) for 24 h under occlusive conditions. There were no deaths, clinical signs of systemic toxicity or macroscopic abnormalities at necropsy. Oedema (slight to well-defined) was observed at application sites on day 2. Localised severe damage to the skin, associated with oedema (severe) and scabbing developed over the next few days. Therefore, the dermal LC_{50} was considered to be > 900 mg/kg bw.

The lowest dermal LD_{50} value in the studies was 311 mg OIT/kg bw. Therefore the DS proposed that OIT should be classified as Acute Tox. 3; H311 (toxic in contact with skin).

Comments received during public consultation

One MSCA supported the proposed classification for acute toxicity, but asked to determine harmonised ATE values.

Two Company-Manufacturers disagreed with the proposed Acute Tox. 3 classification for the oral route since the selected key study had been conducted on a formulated OIT product (Anonymous 1991b) and not on the technical grade active substance. They were of the opinion that the study conducted on the technical grade material consisting of 96.4 % OIT (Anonymous 2002a) was more appropriate and justified the retention of the current harmonised classification as Acute Tox. 4 for OIT considering the LD_{50} of 500-2 000 mg OIT/kg bw of this study.

They also questioned the relevance of data obtained on an aerosol in view of the low vapour pressure of the substance and of the intended and reasonably expected use and conditions of handling of the substance. They did not agree that classification was warranted for acute inhalation toxicity, or with the supplementary labelling with EUH071 (corrosive to the respiratory tract). The Company-Manufacturers also objected to the chosen key study, and found the study via nose-only exposure to be more appropriate, as whole–body exposure might lead to exposure both orally (due to grooming) and dermally.

Both Company-Manufacturers supported the proposed classification for acute toxicity via the dermal route.

Assessment and comparison with the classification criteria

Oral route

The four oral rat studies gave a wide range of LD_{50} values. The studies with OIT in propylene glycol gave LD_{50} values of 318 mg OIT/kg bw (males) and 324 mg OIT/kg bw (females) in the first study; 247 mg OIT/kg bw (males) and 292 mg/kg (females) in the second study; and 125 mg OIT/kg bw in the third study. In the study carried out with OIT (96.4 %) in water the obtained LD_{50} was between 500-2 000 mg OIT/kg bw.

The lowest oral LD_{50} value in rats was 125 mg OIT/kg bw combined for both males and females. Although this value was obtained in a study conducted on OIT formulated in propylene glycol and the LD_{50} in the study conducted on neat OIT was higher, it is considered that the results of the studies on OIT formulated in propylene glycol cannot be dismissed and are considered relevant for classification. The criteria for classification with acute oral toxicity category 3 are $50 < LD_{50} \leq 300$. Therefore, RAC supports the DS's proposal to classify OIT as **Acute Tox. 3 via the oral route (H301)**. RAC also concludes that an **ATE value of 125 mg/kg bw** is warranted for OIT in a mixture.

Inhalation route

Two acute inhalation toxicity studies according to OECD TG 403 and GLP were performed in rats. In both studies rats were exposed to aerosols of OIT. The LC_{50} value was 0.58 mg OIT/L in the nose-only exposure study, which would warrant category 3 ($0.5 < LC_{50} \leq 1.0$), and 0.27 mg OIT/L in the whole-body exposure study, which would warrant category 2 ($0.05 < LC_{50} \leq 0.5$). Although additional exposure via grooming cannot be ruled out in the whole-body exposure study, it is not clear whether this accounts entirely for the discrepancy in the LC_{50} values. In the whole-body exposure study, necropsy revealed gas-filled stomachs in the decedents, and it was noted in the study summary that this finding was often seen in rats that died as a result of

respiratory distress and was due to swallowing air during attempts to breathe. Therefore the results of the whole-body exposure study cannot be dismissed and are considered relevant for the classification. RAC supports the DS's proposal that the LC_{50} of 0.27 mg/L warrants classification as **Acute Tox. 2 via the inhalation route (H330)**. RAC also concludes that **an ATE value of 0.27 mg/L (dust and mist)** is warranted for OIT in a mixture.

Clinical signs observed during the acute inhalation studies were consistent with respiratory tract irritation/corrosion. These included dyspnoea, bradypnoea, rales and gasping. Pathology of decedents in the nose-only exposure study revealed red/brown foci on the lungs and oedematous tongues. In the whole-body exposure study, necropsy revealed congestion of the lungs, increased lung weight (relative to body weight) and gas-filled stomachs that could have been caused by swallowing air during attempts to breathe. Given the nature of the clinical signs observed following inhalation exposure, and that OIT is corrosive to skin and eyes, it is likely that at least one mechanism of toxicity is corrosion of the respiratory tract. Therefore RAC is of the opinion that an **additional labelling of OIT with EUH071 ("Corrosive to the respiratory tract") is warranted**.

Dermal route

Two studies were included in the CLH report. In the first study the dermal LC_{50} value was determined to be 311 mg OIT/kg bw in rabbits. In the second dermal study a single dose of 900 mg/kg was tested in Sprague-Dawley rats. As there were no mortalities, the dermal LC_{50} was considered to be > 900 mg/kg bw. The lowest dermal LD_{50} value in the studies was 311 mg OIT/kg bw. The criteria for classification with acute dermal toxicity category 3 are $200 < LD_{50} \leq 1\,000$. RAC agrees with the DS's proposal that OIT should be classified as **Acute Tox. 3 via the dermal route (H311)**. RAC also concludes that an **ATE of 311 mg/kg bw** is warranted for OIT in a mixture.

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

Summary of the Dossier Submitter's proposal

The DS concluded that were no indications of specific target organ toxicity in the available studies warranting a classification as STOT SE 1 or 2. The DS did not either propose a classification for STOT SE 3, which is reserved for substances causing narcotic effects (H336) or respiratory tract irritation (RTI, H335). No specific comparison with the CLP criteria was performed for narcotic effects. As regards respiratory tract irritation, the DS reported reversible clinical signs of irritation (dyspnoea, rhinitis) and histopathology (focal squamous metaplasia of the respiratory epithelium, acute inflammation of the nasal mucosa). However, since OIT had a harmonised classification as corrosive to the skin, and as the DS proposed to classify OIT as Acute Tox. 2; H330 with an additional labelling as corrosive to the respiratory tract (EUH071), the DS concluded that OIT should not be additionally classified with STOT SE 3 (respiratory tract irritant).

Comments received during public consultation

In relation to the inhalation route, two Company-Manufacturers questioned the relevance of data obtained on an aerosol in view of the low vapour pressure of the substance and of the intended and reasonably expected use and conditions of handling of the substance. They therefore agreed with the DS to not classify OIT for STOT SE 3 (transient respiratory tract irritation and narcotic effects). The DS responded that the low (lack of) potential for exposure to OIT during normal

use does not prevent OIT to be classified based on its inherent hazards, using the information available and in accordance with the CLP Regulation.

Assessment and comparison with the classification criteria

According to the criteria, specific target organ toxicity (single exposure, STOT SE 1 and 2) is defined as specific, non-lethal target organ toxicity arising from a single exposure to a substance or mixture. With the exception of the skin and the lungs, no clear evidence of non-lethal effects on a specific target organ or tissues was observed in the oral, dermal and inhalation acute toxicity studies and therefore classification as STOT SE 1 or 2 is not warranted.

The hazard category STOT SE 3 covers transient respiratory tract irritation and narcotic effects. After inhalation, clinical signs of respiratory tract irritation (disturbed respiration, rales, gasping, dyspnoea, bradypnoea, nasal mucosal irritation) occurred, accompanied by histopathological findings in the lungs (red and/or brown foci on the lungs) at lethal doses. The supplementary label EUH071 and the classification as Acute Tox 2; H330 by inhalation cover the lung as a target organ after single exposure to OIT. RAC also notes that since no narcotic effects were reported at non-lethal doses, the classification as STOT SE 3; H336 is not warranted.

RAC agrees with the DS that **classification and labelling for STOT SE is not warranted**.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

Two studies were included in the CLH report on skin irritation in rabbits. The first study (Anonymous, 1984) was considered by the TC C&L for the original harmonised classification in 1993. Both studies were in accordance with the OECD TG 404 and GLP (4-h application). OIT (45-50 %) in propylene glycol (0.5 mL) was tested in both studies.

In the first study (Anonymous, 1984), OIT (occlusive) produced visible destruction of dermal tissue in all animals and severe erythema and oedema was noted from 1 h onwards. Eschar and blanching persisted in all animals until the end of the study period (14 days).

In the second study (Anonymous, 1991e), OIT (semi-occlusive) produced a well-defined erythema with severe oedema at all treatment sites from 30 minutes of removal of the dressing. Necrosis and chemical burns, with slight to moderate oedema had developed at all sites at 24 h. Reactions persisted up to day 14 in all but one animal where reactions improved slightly by day 8. This animal had desquamation of the stratum corneum (sloughing) on days 7 and 8 and hyperkeratosis from day 9 to the end of the study period.

The DS concluded that OIT should be classified as corrosive. Although no data were available on reactions at exposure lengths < 4 hours to allow a direct assignment of the subcategory, the DS proposed to classify OIT in subcategory 1B in line with note 2 to table 1.1 in Annex VII of CLP.

Comments received during public consultation

One MSCA generally agreed with the DS's proposals for classification of OIT, but did not provide any specific comment for this endpoint. Two Company-Manufacturers agreed with the DS's classification proposal for skin and eye corrosion.

Assessment and comparison with the classification criteria

In two skin corrosion/irritation studies, both according to TG 404 and GLP, OIT was found to be corrosive to the skin causing irreversible necrosis of the dermal tissue, well-defined chemical burns, erythema and oedema until the end of the study. Exposure time was 4 hours in both studies, so there are no data on reactions at exposure lengths < 4 hours to allow a direct assignment of a subcategory. A substance tested for 4 hours only and where it is not possible to distinguish between Cat. 1C and Cat. 1B should not be subcategorised (Commission Regulation (EU) 2016/918).

Therefore RAC proposes classification of OIT as **Skin Corr. 1; H314** without sub-categorisation.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The DS stated that OIT was corrosive in the dermal studies, therefore, serious eye damage was considered implicit. The DS proposed to classify OIT as Eye Dam. 1; H318, based on the Skin Corr. 1; H314 classification, stating however, that the substances should not be labelled with H318 as the hazard statement H314 included the warning for eye damage.

Comments received during public consultation

One MSCA generally agreed with the DS's proposals for classification of OIT, but did not provide any specific comment for this endpoint. Two Company-Manufacturers agreed with the classification proposal for serious eye damage.

Assessment and comparison with the classification criteria

OIT is corrosive to the skin. As a consequence, and in accordance with the Technical Notes for Guidance on Data Requirements (chapter 2 section 6.1.4), OIT was not tested in rabbits for severe eye damage/irritation. OIT is classified as corrosive to skin and serious eye damage is thus implicit.

The Guidance on the application of the CLP Criteria (Version 5.0 – July 2017), section 3.3.2.4 states that a skin corrosive substance is also classified for serious eye damage which is indicated in the hazard statement for skin corrosion (H314: Causes severe skin burns and eye damage). However, although classification for both endpoints (Skin Corr. 1 and Eye Dam. 1) is required, the hazard statement H318 'Causes serious eye damage' is not indicated on the label because of redundancy (CLP Article 27).

Thus, RAC agrees with the DS that OIT should be classified as **Eye Dam. 1; H318**.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Non-human information

Five skin sensitisation studies were assessed in the CLH report; three local lymph node assays (LLNA), a Buehler test and a guinea pig maximisation test (GPMT).

The first LLNA (Anonymous, 2003) was performed according to the OECD TG 429 (originally adopted in 2002) and GLP. Induction concentrations of 0, 0.25, 0.5, 1, 2.5 and 5 % OIT in acetone: olive oil (4:1) were used. The SI value obtained at concentrations of 0.5 % and above was greater than three, indicating a positive result. The positive control responded appropriately and the EC3 value for OIT was calculated to be 0.46 %. Evidence of irritation in the form of erythema and oedema were observed at the site of application.

The second LLNA (Anonymous, 2004b) was conducted using induction concentrations of 0, 100.6, 320.4, 1 036.6, 3 062.1 and 11 250 ppm in acetone. According to the DS, it was conducted according to GLP but it had deficiencies as the response of the positive control was low (SI < 3). The results showed a clear sensitisation reaction with a SI > 3 at the highest OIT concentration tested (11 250 ppm). The EC3 value was 0.66 %.

The third LLNA (Anonymous, 2006b) was done under GLP, using induction concentrations of 100, 300, 1 000, 3 000 and 10 000 ppm OIT in acetone. The test also deviated from the OECD TG 429 as it lacked the positive control. OIT was shown to be positive for skin sensitisation, with an SI > 3 at concentrations of 3 000 ppm and above and an EC3 value of 0.24 %.

The Buehler test (Anonymous, 1983) was carried out with OIT (48 % in propylene glycol) following OECD TG 406. As a deviation from the guideline, a range of induction (0, 25, 50, 100, 500, 750, 1 200 and 2 400 ppm) and challenge (100, 750 and 1 200 ppm) concentrations were tested. The vehicle used for the induction was aqueous ethanol (80 %), and for the challenge it was acetone. 20 % of animals responded following induction at 50 ppm (0.005 %) and 60 % of the animals responded following induction at 100 ppm (0.01 %). No positive control was used in this study.

In the non-guideline GPMT (Anonymous, 1991f), OIT (45 % in propylene glycol) was tested. In the preliminary study a 1 % formulation in Alembicol D was found to be the maximum concentration that did not cause skin irritation. Intradermal injections of 1 % and topical applications of 2.5 % were tested for the induction, and concentrations of 0.5 and 1 % were tested for the topical challenge. Necrosis was observed following the intradermal injections at 1 % after the topical application of 2.5 %. Sensitisation reactions (slight to well-defined erythema and none to slight oedema) were observed in all animals following the challenge concentration of 1 %. Less severe or no reactions were observed after the challenge with 0.5 % OIT.

Human information

There were four studies (one 21-day cumulative insult patch test, and three human repeated insult patch tests, HRIPTs) summarised in the CLH report on the skin sensitisation potential of OIT in humans.

In the 21-day cumulative insult patch test six groups of adult volunteers were investigated (Emmet *et al*., 1988). Various concentrations of OIT in petroleum and Tween-85 were applied to the paraspinal area of the back in Finn chambers. Approximately 24 hours after each of the daily 21 applications, the patch was removed and the skin was left open to the air for 10 minutes to minimise maceration. Possible allergic reactions were noted. Any volunteer with suspected sensitisation reactions received a challenge patch test at a distant skin site. Challenge patches were left in place for 48 hours. Of the 9 volunteers with suspected sensitisation reactions, 6 were confirmed at challenge. Confirmed sensitisation reactions occurred in 1/20 subjects induced/challenged with 500 ppm (0.05 %) OIT and in 5/20 volunteers with 1 000 ppm (0.1 %) OIT.

In the first HRIPT (Frank, 2000a), OIT in Koralone™ 500 (50 ppm, 0.005 %, diluted with water) was tested in 103 adult subjects. Test material (0.2 mL) was applied by occluded patch to give a dose of 2.5 µg/cm^2 skin. In the induction phase, a fresh patch was applied to the same site 3 times per week for a period of 3 weeks. The patches were applied for 24 h and then removed

for a further 24 h for an interim rest period. After a two-week rest period following the ninth induction application, the subjects received a challenge application at an adjacent skin site. The challenge patch was removed after 24 hours and scored at 24, 48, 72 and 96 hours post application. No skin reactions were observed in either the induction or challenge phases. RAC notes that the CLH report mentions OIT in water for the Frank 2000a and Frank 2000b studies, but according to the original study reports, Koralone™ 500 was used as the test material. The composition of Koralone™ 500 is confidential.

In the second HRIPT (Frank, 2000b), 222 volunteers were treated with OIT in Koralone™ 500 (100 ppm, 0.01 %, diluted with water) in the same manner as above. The test material (0.2 mL) was applied by occluded patch to give a dose of 5 µg/cm^2 skin. A sensitisation reaction, confirmed by re-challenge, was observed in one volunteer (1/222).

The third HRIPT (Frank, 2001) was done using the same method as described above, in 207 volunteers. OIT in "body lotion" (composition not available) was tested at a dose of 5 µg/cm^2 skin (equivalent to 100 ppm, 0.01 %). Sensitisation reactions were reported at challenge in three volunteers. Re-challenge was conducted in one of these three subjects and sensitisation was confirmed. A second subject was found to have participated previously in OIT patch testing and was therefore not eligible for the HRIPT.

The DS proposed to classify OIT as a Skin Sens. 1A on the basis of the most reliable LLNA study (Anonymous, 2003), in which the stimulation index was greater than 3 for OIT at doses ≥ 0.5 % (EC3 of 0.46 % (w/v)). According to the DS, the two human repeat insult patch tests showing positive responses at a dose of 5 µg/cm^2 skin in some volunteers also provided evidence for classification in Category 1A (a positive response observed at ≤ 500 µg/cm^2 warrants Category 1A).

The DS concluded that the LLNA results indicated that OIT was a strong sensitiser (EC3 of 0.2-2 %), that the GPMT results indicated the same, and that the Buehler test indicated OIT as an extreme sensitiser (≥ 60 % of the animals showed a positive response to an induction concentration of ≥ 0.01 %).

The DS proposed to lower the current SCL of 0.05 % assigned to OIT as in one human study, sensitisation reactions were confirmed in 1/20 volunteers induced with 0.05 %. In subsequent studies, sensitisation reactions were confirmed in 1/222 and 3/207 volunteers induced with 0.01 % OIT, while no reactions were observed at an induction concentration of 0.005 %. In addition, topical inductions as low as 0.005 % had been shown to cause positive skin sensitisation reactions in guinea pigs. Based on the information in humans and in the Buehler study, the DS proposed to update the existing SCL to 0.005 % (50 ppm).

Comments received during public consultation

All commenting parties (2 Company-Manufacturers, 2 MSCAs, 1 NGO) supported the proposed classification Skin Sens. 1A.

Two Company-Manufacturers agreed to Skin Sens. 1A based on the results of the 3 LLNAs conducted on the technical grade OIT material.

A trade association argued against the setting of an SCL and the socio-economic issues it would pose for the industry, also arguing that to be effective, usually a dosage of at least 250 ppm of OIT was needed, which was significantly above the proposed SCL of 50 ppm (0.005 %). Another trade association stressed the importance of OIT in industry, and argued against an SCL of 50 ppm, as it would mean that products containing OIT could not be sold to the public. A third industry/trade association noted the proposed SCL for OIT would significantly reduce the biocidal

use of the substance. One downstream user argued that consumer paints containing the substance should be allowed to be sold if gloves were supplied with the product.

Two Company-Manufacturers in a jointly prepared document argue against setting an SCL of 0.005 % on the basis of the HRIPT results by Frank (2000a, 2000b and 2001), stating that in these studies, contrary to the CLH report, the test material was not aqueous OIT, but Koralone™ 500, as described in the original reports. Koralone™ 500 was a formulated product of OIT, and in accordance to Annex I CLP Section 3.4.3.1.1 'SCLs are set on the basis of testing of the substance and never on the basis of testing of a mixture containing the sensitising substance'. Thus, according to industry, the results obtained from the Frank studies should not be used for SCL setting. The joint paper also considered that HRIPT (the application of occlusion and exposure protocols) generally overestimated the hazard/potency associated with sensitisation. In their view, this was supported by the few reports of allergic contact dermatitis following exposure to OIT reported in the literature and was indicative that the current SCL of 0.05 % was protective.

One MSCA commented that lowering the SCL to 0.005 % needed further discussion, as the data represented a borderline case for a lower SCL limit, observing that no sensitised individuals were observed at the exposure level of 50 ppm (0.005 %), recognising however that the Buehler test showed a positive response at a 0.005 % topical induction dose.

Another MSCA supported classification of OIT as Skin Sens. 1A with a strong to extreme potency as well as the proposal to reduce the current SCL. The MSCA cited recent publications (Schwensen *et al*., 2017; Aalto-Korte and Suuronen, 2017) which supported cross-reactivity between MIT (2-methyl-2*H*-isothiazol-3-one (CAS 2682-20-4) and OIT. The Aalto-Korte and Suuronen (2017) publication found that allergic reactions to OIT had become common during the MIT allergy epidemic. Their data showed that between 2012 and 2017, 2.9 % of 647 consecutively tested patients reacted to OIT (0.1 % OIT in petroleum) and that patients showing (extreme) reactions to MIT also reacted to OIT. Therefore it could not be excluded that patients previously sensitised to MIT would react to products containing OIT. The MSCA argued that the sensitising capacity of OIT was similar to or even stronger than that of MIT. Based on potency data from animal tests MIT was considered a "strong" and OIT a "strong to extreme" sensitizer. For a strong sensitizer a GCL of 0.1 % applied, but RAC had decided in 2016 to apply a SCL of 0.0015 % (15 ppm) for MIT due to cross reactivity to CMI (5-chloro-2-methyl-2*H*-isothiazol-3-one (CAS 26172-55-4) based on an Scientific Committee on Consumer Safety (SCCS) Opinion. The MSCA stressed that as the chemical structure of OIT was closely related to other thiazolinones (especially MIT) the cross-reactivity should be considered in SCL-setting to reduce the likelihood of OIT contributing to the rise in thiazolinone allergy.

The European Environmental and Contact Dermatitis Research Group (EECDRG) expressed a concern that the proposed SCL of 0.005 % was not low enough to protect workers and consumers from skin sensitisation. EECDRG cited two case reports that implied that concentrations lower than the proposed limit of 50 ppm may sensitise consumers: 1) An 89-year-old woman had wide-spread dermatitis on skin areas that corresponded contact areas of a new leather armchair. Clinical investigations revealed OIT contact allergy and a leather sample of the chair contained 28 ppm OIT following chemical analysis. The patient tested negative to MIT and BIT (Raison-Peyron *et al*., 2017). 2) In a series of 8 OIT-allergic patients from a Finnish occupational clinic, one was a sewing machine operator who had handled OIT-containing textiles and developed hand dermatitis. Four textile samples from the workplace contained 2, 10, 40 and 50 ppm OIT following chemical analysis (Aalto-Korte *et al*., 2007).

EECDRG additionally stressed that cross-reactivity between OIT and MIT should be taken into account, citing several publications: A recent Danish study indicated cross-reactivity between OIT, MIT and BIT in a modified local lymph node assay (Schwensen *et al*., 2017). Three clinical studies analysing patterns of concomitant reactions to OIT and MIT in patch-tested patients

supported the cross-reactivity between OIT and MIT (Aerts *et al*., 2016; Craig *et al.*, 2017; Aalto-Korte and Suuronen, 2017). EECDRG also emphasised that MIT-sensitised patients need to be warned about the possibility to develop allergic contact dermatitis from OIT-containing products. Especially patients with extreme allergic patch test reactions to MIT were at risk (Aalto-Korte and Suuronen, 2017). As skin sensitization (delayed type cell-mediated contact allergy) was a life-long state, sensitised individuals continued living with the vulnerability to react not only to MIT but also to OIT. EECDRG proposed the same SCL as had been agreed for MIT, namely 0.0015 %, or if a SCL lower than 0.005 % could not be accepted, the limit for labelling of OIT in chemical products should be 0.00015 % to protect thousands of MIT-allergic individuals in the European population.

Assessment and comparison with the classification criteria

RAC agrees with the DS and all parties providing comments during the public consultation that OIT is a potent sensitiser. As shown in the following table, the animal studies on OIT provide results that meet the criteria for classification in sub-category 1A.

Animal test	Criteria for high potency (sub-category 1A)	OIT data	Conclusion
LLNA (Anonymous, 2003)	EC3 value ≤ 2 %	EC3 value = 0.46 %	The EC3 value meets the criteria for Cat. 1A
LLNA (Anonymous, 2004b)	EC3 value ≤ 2 %	EC3 value = 0.66 %.	The EC3 value meets the criteria for Cat. 1A
LLNA (Anonymous, 2006b)	EC3 value ≤ 2 %	EC3 value = 0.24 %	The EC3 value meets the criteria for Cat. 1A
Buehler test (Anonymous, 1983)	≥ 15 % responding at ≤0.2 % or ≥ 60 % responding at >0.2 % to ≤ 20 % topical induction concentration	20 % response at 0.005 % topical induction concentration	The response rate at a topical induction concentration of 0.005 % meets the criteria for Cat. 1A
GPMT (Anonymous, 1991f)	≥ 30 % responding at ≤ 0.1 % or ≥ 60 % responding at > 0.1 % to ≤ 1 % intradermal induction concentration	100 % response at 1 % intradermal induction concentration of OIT (observed at 1 % challenge concentration)	The response rate at an intradermal induction concentration of 1 % meets the criteria for Cat. 1A.

Human data also support the classification as in a 21-day cumulative insult patch test (Emmet *et al*., 1988), confirmed sensitisation reactions occurred in 1/20 and 5/20 subjects induced/challenged with 500 ppm (0.05 %) and 1 000 ppm (0.1 %) OIT, respectively. Also two human repeat insult patch tests, in which positive responses were observed in some volunteers at 5 µg/cm^2 skin, provide evidence for classification in Category 1A (a positive response observed at ≤ 500 µg/cm^2 warrants Category 1A). More recent publications (Aalto-Korte and Suuronen, 2017) show that 2.9 % of 647 consecutively tested patients reacted to OIT (0.1 % OIT in petrolatum, 40 µg/cm^2) between 2012 and 2017.

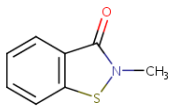
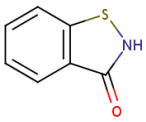
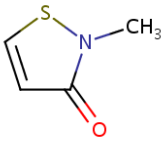
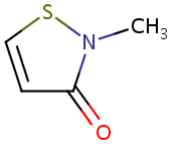
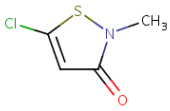
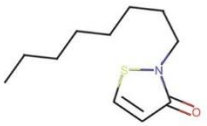
Based on the LLNA (Anonymous, 2003), which is a reliable study without restrictions, and the other animal and human studies as supportive evidence, RAC agrees with the DS that **classification as Skin Sens. 1A; H317 (may cause allergic skin reactions)** is warranted.

Specific Concentration Limit

The results of the LLNA studies indicate that OIT is a strong sensitiser (EC3 values were between 0.2 % and 2 %). In the GPMT 100 % of animals responded to an intradermal induction concentration of 1 %, meeting the criteria for a strong sensitiser (≥ 60 % animals responding to an intradermal induction concentration of > 0.1 - ≤ 1.0 %). Lower induction concentrations have not been tested to determine whether the criteria for extreme sensitiser would be met. In the Buehler test, 60 % of animals showed a response at a 0.01 % topical induction dose of OIT, therefore the result of this study met the criteria for an extreme sensitiser (≥ 60 % of animals showing a positive response to a topical induction concentration ≤ 0.2 %). Based on the results of the available animal studies, in accordance with section 3.4.2.2.5 of the Guidance on the application of the CLP criteria (Version 5.0, July 2017), OIT can be regarded as a strong to extreme sensitiser.

Based on the LLNA results (see table comparing related thiazolinones), the sensitising capacity of OIT is similar to or even stronger than that of MIT. RAC proposed to apply an SCL of 0.0015 % (15 ppm) for MIT. The chemical structure of OIT is closely related to other thiazolinones, especially to MIT. Schwensen *et al*. (2017) demonstrated in a modified local lymph node assay that cross-reactivity occurs between related thiazolinones OIT (2-octyl-2*H*-isothiazol-3-one, CAS 26530-20-1, MIT (2-methyl-2*H*-isothiazol-3-one, CAS 2682-20-4) and BIT (1,2-benzisothiazol-3(2*H*)-one, CAS 2634-33-5). Cross-reactivity between MIT and OIT as well as between MIT and BIT has been demonstrated in humans in several publications (Aerts, 2017, Aalto-Korte and Suuronen, 2017, Amsler *et al*., 2017). Aalto-Korte and Suuronen (2017) found that allergic reactions to OIT have become common during the MIT allergy epidemic. Their data show that between 2012 and 2017 2.9 % of 647 consecutively tested patients reacted to OIT (0.1 % OIT in petroleum) and that patients showing (extreme) reactions to MIT also reacted to OIT. Therefore it cannot be excluded that patients previously sensitised to MIT will also react to products containing OIT.

***Table**: Comparison of skin sensitising properties of several thiazolinones. Data taken from RAC opinions on MBIT (2018); MIT (2016); CMIT/MIT (2016) and OIT (this opinion). For BIT the LLNA information was taken from the public NICEATM LLNA databank.*

	MBIT (CAS 2527-66-4)	**BIT (CAS 2634-33-5)**	**MIT (CAS 2682-20-4)**	**CMIT/MIT (3:1) (CAS 55965-84-9)**	**OIT (CAS 26530-20-1)**
Chemical structure				 	
LLNA	EC3 = 1.04 % EC3 = 0.69 %	EC3 = 2.3 % EC3 = 32.4 % EC3 = 4.8 % EC3 = 10.4 %	EC3 = 0.86 %	EC3 = 0.003 % EC3 = 0.007 %	EC3 = 0.46 % EC3 = 0.66 % EC3 = 0.24 %
Classification	Skin Sens. 1A	Skin Sens. 1	Skin Sens. 1A	Skin Sens. 1A	Skin Sens. 1A (this opinion)
HRIPT	9/45 (20 %) volunteers showed dermal sensitization at 500 ppm	5/58 (9 %) at 725 ppm aq., 0/54 (0 %) at 360 ppm aq	1/116 (0.9 %) volunteers at 400 ppm and 1/210 (0.5 %) at 500 ppm	–	0/103 subjects at 50 ppm (0.005 %) 1/222 (0.45 %) subjects at 100 ppm (0.01 %)
SCL	0.0015 %	0.05 %	0.0015 %	0.0015 %	0.0015 % (this opinion)

There is an existing SCL for OIT of 0.05 % and the DS proposed a lower SCL of 0.005 %. The literature on OIT allergy in clinical patients is not very wide. Nevertheless, there are two case reports implying that concentrations lower than the proposed limit of 50 ppm may sensitise. In one case report, an 89-year-old woman had wide-spread dermatitis on skin areas that corresponded to contact areas of a new leather armchair. Clinical investigations revealed OIT contact allergy and a chemical analysis revealed that a leather sample of the chair contained 28 ppm OIT. The patient tested negative to MIT and BIT (Raison-Peyron *et al.*, 2017).

The second publication reports an OIT-allergic patient from a Finnish occupational clinic, who was a sewing machine operator who had handled OIT-containing textiles and developed hand dermatitis. A chemical analysis revealed that four textile samples from the workplace contained 2, 10, 40 and 50 ppm OIT (Aalto-Korte *et al.*, 2007).

Overall, taking into consideration that the animal tests indicate that OIT is a strong to extreme sensitiser, that there is cross-reactivity between OIT and MIT, and that there are case reports suggesting that concentrations lower than the proposed limit of 50 ppm may induce sensitisation, RAC is of the opinion that for OIT an SCL of 50 ppm is not low enough, and therefore proposes that **an SCL should be set at 15 ppm (0.0015 %).** This would also be in line with other thiazolinones.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Octhilinone (OIT) is a biocide approved for use in wood preservatives with approvals for other types of use ongoing. It is currently listed in Annex VI of the CLP Regulation with Aquatic Acute 1 and Aquatic Chronic 1 classification without M-factors. As the current entry in Annex VI does not include M-factors, the DS proposed to add an M-factor of 100 to Aquatic Acute 1 classification based on initially measured algae 48-hour E_rC_{50} values in the range 0.001 to 0.01 mg/L. The proposed M-factor of 10 for Aquatic Chronic 1 classification was based on initially measured 72-hour E_rC_{50} values in the range 0.001 to 0.01 mg/L for algae. The substance was considered not rapidly degradable and having a potential to bioaccumulate. After the Public Consultation (PC) the DS changed the proposal for chronic toxicity. The new proposal was based on the algae initial measured 48-h E_rC_{10} of 0.000224 mg/L. The value is in the range 0.0001 to 0.001 mg/L giving an M-factor of 100 for a not rapidly degradable substance.

OIT is anticipated to dissociate and be ionised at environmentally relevant pH due to pK_a values in the range 3.2-3.3. Aquatic toxicity studies were run at pH 5 or above reflecting environmental conditions where nearly all OIT would be in its ionised form.

Degradation

There are two GLP hydrolysis studies available following US EPA Guideline, Subsection N, Section 161-1. Both studies were performed at pH 5, 7 and 9 and showed no significant degradation. On this basis, the hydrolysis half-life was considered to be > 1 year and OIT was considered hydrolytically stable.

Two aqueous photolysis studies were available following GLP and US EPA Guideline Subsection N, section 161.2. In the test using ^{14}C radio-labelled OIT (10.0 mg/L), the photolytic DT_{50} was 15.3 days. Mineralisation accounted for 12.5 % AR (Applied Radioactivity) based on carbon dioxide (CO_2) at study termination (~ 30 days). Degradants observed were 2-(n-octyl)-4-thiazolin-2-one, a mixture of N-(n-octyl) malonamic acid (NNOMA) and oxamic acid, N-(n-octyl)acetamide (NNOA), and sulfoxide of OIT at concentrations 14.1, 12.5 and 11.2 % of AR at study termination and max. 10.1 % AR at 405 hours, respectively. The second study used ^{14}C radio-labelled OIT (0.5 mg/L) in two systems: sterile buffer solutions at pH 7 and sterile natural pond water at pH 8. OIT, decreased from 97.9 % AR and 98 % AR to 1.1 % AR and 2.5 % AR in the buffer and pond solutions respectively. The photolytic DT_{50} for the buffer solution system was 3.7 summer days at 50°N. The photolytic DT_{50} for the pond water system was 5.1 summer days at 50°N. The degradant identified in both buffer and pond solutions was NNOA at max 23.3 % AR and 25.1 % AR, respectively. The degradant 2-(*N*-octyl) ethyl amine was identified in buffer solutions at test termination (16.2 % AR). In both systems, unidentified degradants were observed. Mineralisation at test termination was 0.3 % AR and 7.9 % of AR in buffer and pond solutions, respectively.

A ready biodegradation study following GLP and OECD TG 301D (Closed Bottle) was available. Test solutions were prepared with 3 mg/L test item and 0.2 mL inoculum per 300 mL test vessel. The toxicity control (with 1.5 mg/L OIT and 5 mg/L sodium acetate) achieved 26 % degradation after 14 days and a maximum of 35 % degradation by day 21. While these values met the validity criteria of 25 % degradation by day 14, the CAR evaluation considered the test item may have led to a degree of microorganism inhibition. This was supported by an Activated Sludge

Respiration Inhibition Test (ASRIT) which determined an EC_{20} of 8.9 mg/L and 11 % inhibition observed at the lowest test concentration of 4 mg/L. A second ASRIT (Noack, 2001) also determined a similar EC_{20} of 7.3 mg/L. No degradation of OIT was observed in test item solutions during the OECD TG 301D test. Overall, the substance was considered not readily biodegradable although this might be influenced by a partially inhibitory test concentration.

Two aquatic biodegradation simulation studies are available using freshwater and seawater. Study 1 is a freshwater aquatic biodegradation simulation study following OECD TG 309 and GLP. The study used ^{14}C-OIT and surface water from the River Rhine in Switzerland. While OIT is anticipated to adsorb to organic matter, the suspended solid concentration in the test water is not known. Test vessels containing 0.0103 and 0.1029 mg/L OIT were maintained for 29 days under aerobic conditions at 20 ± 2 °C. Mean AR recoveries were 91.8 ± 5.6 % AR and 91.8 ± 5.6 % AR for low and high doses. The levels of AR in water decreased from 96.7 and 102 % on day 0 to 41.8 and 52.5 % on day 29 in the low and high dose systems, respectively. DT_{50} values of 0.6 and 1.2 days were calculated for OIT. After conversion to 12 °C, DT_{50} values were 1.1 and 2.3 days. Three degradants over 10 % were detected but could not be identified (M1 at 19 to 22.8 % AR; M5 at 14.7 to 15 % AR; and M6 at 9 to 10.5 % AR). The DT_{50} values calculated at 12°C were, for M1: 17.8 to 35.5 days, for M5: 19.3 to 30.9 days, and for M6: 8.3 to 22.9 days. A seawater aquatic biodegradation simulation study is available following OECD TG 309 and GLP. The study used ^{14}C-OIT and surface water from St. Margaret's Bay, Kent, UK with unknown suspended solid or organic carbon concentrations. Test vessels containing 0.0101 and 0.09986 mg/L OIT were maintained for 17 days under aerobic conditions at 20 ± 2°C. Mean AR recoveries were 91.4 ± 7.6 % AR and 92.1 ± 8.5 % AR for low and high doses. Levels of AR in water decreased from 100.7 and 102.6 % on day 0 to 40.4 and 47 % on day 17 in the low and high dose systems, respectively. The study calculated DT_{50} values of 1.6 and 2.1 days for OIT, indicating rapid primary degradation. These values were converted to 12 °C, resulting in DT_{50} values of 3 and 4 days. Various degradants were observed at concentrations less than 10 % AR. A sediment phase was not included in either test. In both tests, the decrease in water phase AR is considered to be due to primary degradation of OIT to degradants which were subsequently mineralised and some partitioning to dissolved organic solid matter.

Ready biodegradation studies are available for two degradants NNOA and NNOMA. Both studies followed OECD TG 301B (Modified Sturm test) and GLP. Both substances achieved over 60 % degradation meeting the 10-day window criterion. On this basis, both degradants are considered rapidly degradable. Aquatic toxicity data is available for NNOMA with the lowest acute toxicity value being a 72-hour E_rC_{50} of 0.44 mg/L for algae. The lowest chronic toxicity value is a 72-hour NOE_rC of 0.064 mg/L for algae. Both values are based on initially measured concentrations at 0-hour. Consequently, NNOMA fulfils the classification as Aquatic Acute Category 1 and Aquatic Chronic Category 2.

Given the available aquatic toxicity information for NNOMA and the lack of aquatic toxicity information for unidentified degradants, OIT degradants cannot be considered non-classifiable.

Overall, the degradation information did not provide sufficient data to show that OIT was ultimately degraded (mineralised) within 28 days (equivalent to a half-life < 16 days) or underwent primary degradation to non-classifiable products. Consequently, OIT was considered not rapidly degradable for the purpose of classification and labelling.

Bioaccumulation

OIT was considered surface active. Therefore, log K_{OW} studies determined using the HPLC method or the shake flask method were not considered reliable and not discussed further. Log K_{OW} based

on the solubility of OIT in *n*-octanol (> 524.8 g/L at 20 °C) and measured water solubilities at different pHs (pH 5, 7 and 9) and temperatures (10 °C, 20 °C and 30 °C) was calculated. As the solubility in water did not differ significantly, there was no significant effect on the log K_{OW} value, which was considered to be > 3.1. An experimental aquatic BCF study for OIT was available following GLP and OECD TG 305. The study used ^{14}C-OIT, a flow-through system with Rainbow Trout (*Oncorhynchus mykiss*) and two exposure concentrations; 0.0001 and 0.00048 mg/L. The exposure period ran for 14 days followed by a 14-day depuration period. The pH values ranged from 7.8 to 8.2. The parent compound accounted for 97-99 % of radioactivity. The study whole fish steady state BCFs were 507 ± 87 L/kg (high dose) to 538 ± 65 L/kg (low dose) wet weight. BCFs were not growth corrected although given the uptake duration; any corrections were likely to have little impact on BCF values. Lipid normalising the BCFs to 5 % lipid content increased BCFs to 843 to 886 L/kg wet weight. The BCF values were greater than the CLP trigger value of 500 for potentially bioaccumulative substances.

Aquatic toxicity

A summary of available valid information on the aquatic toxicity of OIT is presented in the following Table. According to the data in the CLH report under Annex 2, the identified degradants NNOMA and NNOA are relatively less toxic than the parent and are not discussed further in relation to toxicity.

The DS explained that OIT is a thiazolinone biocide. Algae are the most sensitive trophic level. Thiazolinones are rapidly taken up by algae where they react with enzymes to disrupt metabolism and inhibit growth (Williams, 2007) as a toxic response. During this process, cleavage of the isothiazole ring occurs and the parent substance is depleted. This mode of action in algae is rapid with uptake and enzyme effects in minutes affecting cell viability and resulting in cell death over hours. It also means that algal toxicity is dependent on initial substance concentration and algal cell density with greatest inhibition of algae resulting in slower degradation in test systems. However, given the rapid uptake and depletion of OIT by algal cells results in significant losses over a short period of time, initial measured concentrations are considered to reflect representative concentrations which induce toxic responses in algal studies. This is because mean measured concentrations would include a period of time when very little test item was available (generally below the analytical limit of detection) resulting in unrealistic calculated mean measured concentrations lower than those which induce the inhibition effect.

In the case of thiazolinones, the rapid knock-down of algal cells with depletion of the substance by uptake and metabolism means that shorter duration endpoints may be appropriate for consideration of acute toxicity to algae. This is suitable as multiple generations are not required and up to 48 hours accounts for the period of time before algal populations recover when the test item is depleted from solution. For the purpose of chronic classification, it was considered that the standard chronic time period of 72-96 hours for algal studies was appropriate to ensure multiple algal generations. It was noted that OECD TG 201 allows studies to be shortened to 48 hours if a 16-fold increase in cells is observed in controls indicating exponential growth and multiple generations. This was discussed for each study in the CLH Report.

***Table**: Summary of relevant information on aquatic toxicity for OIT*

Guideline/GLP	Species	Endpoint	Exposure		Results	
			Design	Duration	Endpoint	Toxicity mg/L
Fish						
Acute toxicity to fish US EPA FIFRA Guideline 72-1, GLP, purity: 98.5 % (1	Rainbow Trout (*Oncorhynchus mykiss*)	Mortality	Flow-through	96-h	LC_{50}	0.047 (mm) 86-101 % of nom.
Acute toxicity to fish US EPA FIFRA Guideline 72-1, GLP, purity: 98.5 % (1	Bluegill Sunfish (*Lepomis macrochirus*)	Mortality	Flow-through	96-h	LC_{50}	0.180 (mm) 84-106 % of nom.
Acute toxicity to fish US EPA FIFRA Guideline 72-1, GLP, purity: 98.5 % (1	Sheepshead Minnow (*Cyprinodon variegatus*)	Mortality	Flow-through	96-h	LC_{50}	0.160 (mm) 63-92 % of nom.
Acute toxicity to fish US EPA OPPTS Guideline 850.1075, GLP, purity: 99.2 % (2	Rainbow Trout (*Oncorhynchus mykiss*)	Mortality	Static	96-h	LC_{50}	0.036 (mm) 50-76 % of nom.
Acute toxicity to fish US EPA FIFRA OPPTS Guideline 72-1, GLP, purity: 96 % (3	Bluegill Sunfish (*Lepomis macrochirus*)	Mortality	Semi-static (renewal at 24-h intervals)	96-h	LC_{50}	0.16 (0-72h mm) 53-80 % of nom.
Fish Early Life-Stage (FELS) toxicity US EPA FIFRA Guideline 72-4, GLP, purity: 98.5 % (1	Fathead Minnow (*Pimephales promelas*)	Embryo survival and larval growth/ survival	Flow-through	35 days	NOEC egg hatchability, growth and survival	0.0085 (mm) 65-87 % of nom.
Invertebrates						
Daphnia sp. Acute Immobilisation US EPA FIFRA Guideline 72-2, GLP, purity: 98.5 % (1	*Daphnia magna*	Acute immobilisation	Semi-static	48-h	EC_{50}	0.32 (mm) 92-100 % of nom.
Daphnia sp. Acute Immobilisation US EPA FIFRA Guideline 72-2, GLP, purity: 99.2 %	Daphnia magna	Acute immobilisation	Semi-static	48-h	EC_{50}	0.42 (n) Fresh media: 89-112 % of nom. Expired media: 76-106 % of nom.
Daphnia sp. Acute Immobilisation OECD Guideline	Daphnia magna	Acute immobilisation	Semi-static	48-h	EC_{50}	0.1 (mm) 68-85 % of nom

Guideline/GLP	Species	Endpoint	Exposure		Results	
			Design	Duration	Endpoint	Toxicity mg/L
202 Part I, GLP, purity: 96 %						
Acute Toxicity US EPA FIFRA Guideline 72-3, GLP, purity: 98.5 % (1	Mysid Shrimp (*Mysidopsis bahia*)	Mortality	Flow-through	96-h	LC_{50}	0.071 (mm) 78-87 % of nom.
Acute Toxicity US EPA FIFRA Guideline 72-3, GLP, purity: 98.5 % (1	Oyster (*Crassostrea virginica*)	Shell growth	Flow-through	96-h	EC_{50}	0.013 (mm) 44-67 % of nom.
Daphnia magna Reproduction US EPA FIFRA Guideline 72-4, GLP, purity: 98.5 % (1	*Daphnia magna*	Survival; reproduction; growth	Flow-through	21 days	NOEC	0.074 (mm) 51-80 % of nom.
Daphnia magna Reproduction OECD TG 202, Part II, GLP, purity: 96 % (3	*Daphnia magna*	Survival; reproduction; growth	Semi-static	21 days	NOEC production of live juveniles	0.003 (n) 88-93 % of nom.
Algae and aquatic plants						
Freshwater Algal Growth Inhibition OECD TG 201, GLP, purity: 99.9 % (4	*Skeletonema costatum*	Cell multiplication inhibition	Static	24-h (b 48-h (a 72-h 96-h 96-h 48-h (a 72-h 96-h 96-h 48-h (a 72-h 96-h 96-h	 E_rC_{50} E_rC_{50} E_rC_{50} E_rC_{50} E_rC_{10} E_rC_{10} E_rC_{10} E_rC_{10} NOE_rC NOE_rC NOE_rC NOE_rC	- 0.00193 (im) 0.00161 (im) 0.00168 (im) 0.00029 (mm) 0.00118 (im) 0.00133 (im) 0.00138 (im) 0.000264 mm 0.00068 (im) 0.00068 (im) 0.00038 (im) 0.000184 (mm) 0-h: im 68-76 % of nom.
Freshwater Algal Growth Inhibition OECD TG 201, GLP, purity: 99.3 % (2	*Desmodesmus subspicatus**	Cell multiplication inhibition	Static	24-h 48-h 72-h 72-h 24-h 48-h 72-h 72-h	E_rC_{50} E_rC_{50} E_rC_{50} E_rC_{50} E_rC_{10} E_rC_{10} E_rC_{10} E_rC_{10}	>0.201 (im) 0.139 (im) 0.0979 (im) 0.076 (mm) 0.0208 (im) 0.0208 (im) 0.0239 (im) 0.0198 (mm)

Guideline/GLP	Species	Endpoint	Exposure		Results	
			Design	Duration	Endpoint	Toxicity mg/L
				24-h 48-h 72-h 72-h	 NOE_rC NOE_rC NOE_rC NOE_rC	0.0180 (im) 0.0180 (im) 0.0211 (im) 0.0156 (mm) 0 h: im 81-102 % on nom.
Freshwater Algal Growth Inhibition OECD TG 201, GLP, purity: 99.2 %	*Pseudokirchneriella subcapitata*	Cell multiplication inhibition	Static	24-h (c 48-h 72-h 72-h 48-h 72-h 72-h 96-h 72-h 72-h 96-h	 E_rC_{50} E_rC_{50} E_rC_{50} E_rC_{10} E_rC_{10} E_rC_{10} E_rC_{10} NOE_rC NOE_rC NOE_rC	0.0054 (im) 0.026 (im) 0.025 (mm) 0.0011 (im) 0.0059 (im) 0.0068 (mm) 0.0036 (im) 0.0011 (im) 0.00049 (mm) 0.031 (im) im 55-73 % of nom.
Freshwater Algal Growth Inhibition OECD TG 201, GLP, purity: 99.2 %	*Navicula pelliculosa*	Cell multiplication inhibition	Static	24-h 48-h 48-h 48-h	E_rC_{50} E_rC_{50} NOE_rC (* E_rC_{10} (*	0.00152 (im) **0.00129 (im)** 0.000071 (im) **0.000224 (im)**
Lemna sp. Growth Inhibition Test OECD TG 221 (draft), GLP, purity: 99.9 %	*Lemna gibba*	Growth	Static	7 days	E_rC_{50} E_rC_{10} NOE_rC	0.62 (mm) 0.041 (mm) 0.0087 (mm)

(1 solvent triethylene glycol (TEG) used; (2 ultrasonication; (3 direct addition; (4 intense stirring; (5 solvent dimethylformamide (DMF) used

(a 8.6 to 10.2 fold increase in algal cells was observed in controls at 48 hours which is below the 16-fold criteria indicating 48-hour endpoints are not suitable for chronic classification. No reliable cell count at 24-hour.

(b observations not available

(c initial cell density was 3 000 cells/mL which is below the guideline recommended value of 10 000 cells/mL

(d It is noted that mean measured endpoints are lower than initial measured endpoints which is unusual. This is due to a clearer distribution and dose response for the initial measured model. A reduced goodness of fit dose response model was observed using mean measured concentrations reflecting lower losses (less than 20 %) for higher treatments and greater losses (60-80 %) for lower treatments.

(im) initial measured; (mm) mean measured; (n) nominal

Bold values indicate most sensitive acute and chronic endpoints used for hazard classification

(* additional information in Public Consultation comments and Response to comments

Acute toxicity

There were five acute toxicity studies available on fish. *Oncorhynchus mykiss* is the most acutely sensitive fish species with LC_{50} values between 0.036 and 0.047 mg/L based on measured concentrations. There were five studies available on invertebrates, three for *Daphnia sp.*, one for *Mysidopsis bahia* and one for *Crassostrea virginica*. The marine oyster *Crassostrea virginica* was the most acutely sensitive invertebrate species with an acute EC_{50} of 0.013 mg/L based on measured concentrations.

Acute 24-hour endpoint data were only available for the *Navicula pelliculosa* study with an E_rC_{50} of 0.00152 mg/L based on initial measured concentrations. This was within the range 0.001-0.01 mg/L. A 16-fold growth increase in controls was observed at 72 and 96 hours indicating exponential growth meeting OECD TG 201 validity criteria. In addition, the controls met the coefficient of variation of average specific growth rates (detailed in OECD TG 201) over the study period indicating controls grew similarly over the study period. However, the coefficient of variation for section-by-section specific growth rates indicated significant variation in section-by-section growth rates over the study period with a low growth rate between 48 and 72 hours and negative growth rate between 72 and 96 hours. This indicates that while the controls appear valid for exponential growth (based on 16-fold control cell increase), from 48 hours exponential growth did not occur and the controls are not reliable. On this basis, only endpoints up to 48 hours are considered reliable. Acute 48-h E_rC_{50} data for three species (*S. costatum, P. subcapitata and N. pelliculosa*) lied within the range 0.001-0.01 mg/L based on initial measured concentrations. The lowest 48-hour E_rC_{50} was 0.00129 mg/L for the freshwater diatom *Navicula pelliculosa*. An additional species, *Desmodesmus subspicatus*, appears to be less acutely sensitive. There was also a 7-day aquatic plant toxicity study on *Lemna gibba* available. The 7-day E_rC_{50} value was 0.62 mg/L based on mean measured concentrations.

Chronic toxicity

There was one chronic study available on fish. The key endpoint was the 35-day NOEC of 0.0085 mg/L for *Pimephales promelas* based on measured concentrations.

There were two chronic studies on *Daphnia magna*; the most sensitive chronic endpoint is a 21-day NOEC of 0.003 mg/L based on verified nominal concentrations.

Four freshwater Algal and one aquatic plant study were included in the dossier. For the aquatic plants, the 7-day E_rC_{10} value was 0.041 mg/L (*L. gibba*) based on mean measured concentrations. Chronic 72-h E_rC_{10} data for two species (*S. costatum* and *P. subcapitata*) lied within the range 0.001-0.01 mg/L based on initial measured concentrations. The marine species *Skeletonema costatum* was the most chronically sensitive with a 72-h E_rC_{10} of 0.00133 mg/L based on initial measured concentrations. Valid chronic data were not available for the most acutely sensitive species *Navicula pelliculosa* – it is possible a valid chronic endpoint for this species could be lower.

There were aquatic toxicity data available for the degradants NNOMA and NNOA. The highest toxicity was derived from a 72-hour algal growth inhibition study with *Skeletonema costatum* for the degradant NNOMA (OECD TG 201, GLP). The study 72-hour E_rC_{50} was 0.44 mg/L and the 72-hour NOE_rC was 0.064 mg/L based on initial measured concentrations. Analytical concentrations were verified within 20 % of initial measured concentrations. At 72 hours, only a 3.7-fold increase was observed in control biomass compared to study initiation. At 96 hours a factor of 19, fulfilling the validity criteria of the test guideline, was observed. The study 96-hour E_rC_{50} was 0.47 mg/L and the 96-hour NOE_rC was 0.13 mg/L based on initial measured concentrations.

Comments received during public consultation

Comments were received from four MSCAs and from the biocide applicants. Two MSCAs agreed with the proposed classification. Two MSCAs preferred effect concentrations expressed as mean measured concentrations rather than initial measured concentrations when determining the test result. One of the MSCAs wanted to use the 72-hour E_rC_{50} values instead of a shorter period. An MSCA agreed with the acute classification but wanted to use *Navicula pelliculosa* data from the draft final CAR not mentioned in the CLH Report for chronic classification. The use of the NOEC 0.071 µg/L would change the M-factor from 10 to 1 000. The two biocide applicants provided comments on the rapid degradability of OIT. They made available a new OECD TG 309 study and a metabolite identification study demonstrating, in their opinion, rapid degradability of OIT. Consequently, they proposed a chronic M-factor of 10.

Regarding the mean measured concentrations the DS explained that OIT is a thiazolinone with a specific mode of action in algae. OIT is taken up by algal cells and transformed so it no longer exists. This process occurs rapidly and induces algal toxicity. Taking a non-standard approach to use initial measured concentrations is considered appropriate in this special case. This approach has been used by RAC before with other thiazolinones.

The DS answered that the *Navicula pelliculosa* 48-hour NOEC of 0.071 µg/L was not used because of the uncertainty concerning the use of shorter duration chronic endpoints in hazard classification. Considering that RAC concluded before in two isothiazolinone opinions that shorter duration chronic endpoints were relevant if validity criteria were met, the DS proposed to change the classification proposal and base the chronic classification on the 48-h E_rC_{10} of 0.000224 mg/L for *Navicula pelliculosa* resulting from the same study as the NOEC of 0.071 µg/L. The E_rC_{10} is based on statistical analysis and initial measured concentrations. OECD TG 201 (July 2011) validity criteria were met for 0-48 hours including exponential growth over this period. This value is in the M-factor range 0.0001 to 0.001 mg/L, which would result in a revised M-factor of 100 for a non-rapidly degradable substance.

In response to the biocide applicant's comments on rapid degradation, the DS explained that OIT undergoes rapid primary degradation in combination with some mineralisation. One of the degradation products NNOMA was observed during an aquatic photolysis study at 12.5 % AR as a mixture with oxamic acid. The aquatic toxicity and fate data for NNOMA indicate it would be classified as Aquatic Acute 1 and Aquatic Chronic 2. NNOMA was not confirmed in the two OECD TG 309 simulation studies, which were conducted in the dark indicating it may be formed under light conditions. The metabolite identification study identifies numerous degradants found in the former aerobic simulation studies in seawater and in river water in the dark. However, information on fate and aquatic toxicity data on the degradants are lacking. Consequently, it is not possible to evaluate if the degradants meet the classification criteria or not. The DS retained their conclusion that OIT is not rapidly degradable for classification purposes. The biocide applicants were of the opinion that the criteria for rapid degradability are fulfilled if not more than 30 % AR is left in the system after 28 days. However, CLP does not include such criteria or allow for such an interpretation. The identification and aquatic hazard classification of degradants is of importance when considering rapid degradation via primary degradation under CLP. The biocide applicants also proposed to consider non-extractable residue (NER) as irrelevant because it is not bioavailable. RAC agrees with the DS' conclusion that NER is under discussion in relation to persistency assessment and currently, unless there is data to the contrary, NER are not currently accounted for in the rate of removal.

Assessment and comparison with the classification criteria

Octhilinone was stable to hydrolysis, although it is susceptible to photodegradation. The experimental DT_{50} in sterile pure water was 3.7 days at 50°N in summer sunlight. The respective DT_{50} in pond water was 5.1 days. The photodegradation DT_{50} values reflect degradation to degradants and mineralisation to CO_2. No degradation of OIT was observed in an OECD TG 301D ready biodegradability test. Although this might have been influenced by a partially inhibitory test concentration, the substance is considered not readily biodegradable. In two aquatic biodegradation simulation studies using freshwater and seawater, the 12°C DT_{50} values were from 1.1 to 2.3 days and from 3 to 4 days, respectively. The decrease in water phase AR is considered due to primary biodegradation of OIT to degradants which were subsequently mineralised and some partitioning to dissolved organic solid matter. Three degradants over 10 % were detected but could not be identified in the freshwater study. In the seawater study, various degradants were observed at concentrations less than 10 % AR. Altogether, RAC does not agree to the biocide applicant's interpretation of the application of the CLP criteria. RAC agrees with the DS conclusion and reasoning on OIT being not rapidly degradable for classification purposes.

The Log K_{OW} based on the solubility of OIT in *n*-octanol and water at different pH and temperature was considered to be > 3.1. In the experimental aquatic BCF study with Rainbow Trout (*Oncorhynchus mykiss*), the whole fish steady state BCFs were 507 ± 87 L/kg (high dose) to 538 ± 65 L/kg (low dose) wet weight. Lipid normalising the BCFs to 5 % lipid content increased BCFs to 843 to 886 L/kg wet weight. The BCF values are greater than the trigger value of 500 for potentially bioaccumulative substances. Consequently, RAC agrees with the DS that OIT has a potential to bioaccumulate.

There were acute data available for fish, invertebrates, algae and aquatic plants. RAC is of the opinion that the lowest acute aquatic toxicity value is a 48-hour E_rC_{50} of 0.00129 mg/L for the algae *Navicula pelliculosa*. In this study, the controls appeared valid for exponential growth (based on 16-fold control cell increase), but from 48 hours exponential growth did not occur and the controls were not reliable. On this basis only, endpoints up to 48 hours are considered reliable. The 48-hour endpoint is chosen because thiazolinones are rapidly taken up by algae where they react with enzymes to disrupt metabolism and inhibit growth. During this process, the parent substance is degraded and depleted from solution. This mode of action is rapid with uptake and enzyme effects in minutes affecting cell viability and resulting in cell death over hours. The 48-hour E_rC_{50} values from tests with *Skeletonema costatum* and *Pseudokirchneriella subcapitata* are in the same range as the 48-hour *Navicula pelliculosa* value. Given the mode of action, algal study results based on initial measured concentrations are appropriate. The value of 0.00129 mg/L fulfils the criteria for Aquatic Acute 1, i.e. < 1 mg/L. The value is in the range of $0.001 < L(E)C_{50} \leq 0.01$, giving an M-factor of 100.

There were chronic data available for fish, invertebrates, algae and aquatic plants. RAC is of the opinion that the lowest value is a 48-h E_rC_{10} of 0.000224 mg/L for *Navicula pelliculosa*. OECD TG 201 (July 2011) validity criteria were met for 0-48 hours including exponential growth over this period. Therefore, the 48-h E_rC_{10} from the study is considered valid. Due to the specific mode of action of thiazolinones in algae, 48-hour test duration and use of initial measured concentrations are considered appropriate for chronic classification. In the other algae tests presented in Table xx, the initially measured E_rC_{10} values at 72 hours are already greater than at 48 hours reflecting the specific mode of action of OIT with the algae. The value of 0.000224 mg/L fulfils the criteria for Aquatic Chronic 1, i.e. ≤ 0.1 mg/L for a non-rapidly degradable substance. The value is in the range $0.0001 < NOEC \leq 0.001$, giving an M-factor of 100.

Overall, RAC agrees with the DS proposal to classify octhilinone as **Aquatic Acute 1; H400 (M=100) and Aquatic Chronic 1; H410 (M=100)**.

Additional references

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ANNEXES:

Annex 1 The 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 RAC (excluding confidential information).