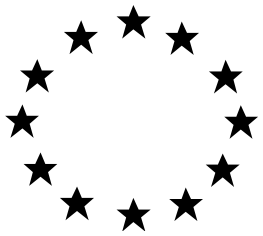
Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report
PUBLIC VERSION



Copper pyrithione

Product type 21

[Sept 2014, public version May 2015]

Rapporteur Member State: Sweden

Copper pyrithione (PT 21)
Assessment report

Finalised in the Standing Committee on Biocidal Products at its meeting on [May 2014]

CONTENTS

1. STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1 Principle of evaluation

This assessment report has been established as a result of the evaluation of copper pyrithione in product type 21(antifouling biocidal products), carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of biocidal products on the market[1] , with the original view to the possible approval of this substance under that directive.

The evaluation has therefore been conducted in the view to determine whether it may be expected, in light of the common principles laid down in Annex VI to Directive 98/8/EC, that there are products in product type 21 containing copper pyrithione that will fulfil the requirements laid down in Article 5(1) b), c) and d) of that directive.

1.2 Purpose of the assessment

The aim of the assessment report is to support a decision on the approval of copper pyrithione for product-type 21, and should it be approved, to facilitate the authorisation of individual biocidal products in product type 21 that contain copper pyrithione. In the evaluation of applications for product-authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, as well as the common principles laid down in Annex VI.

The conclusions of this report were reached within the framework of the uses that were proposed and supported by the applicants (see Appendix II). Extension of the use pattern beyond those described will require an evaluation at product authorisation level in order to establish whether the proposed extensions of use will satisfy the requirements of Regulation (EU) No 528/2012.

For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report shall be taken into account.

However, where conclusions of this assessment report are based on data protected under the provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of another applicant, unless access to these data has been granted.

1.3 Procedure followed

Copper pyrithione (CAS no. 14915-37-8) was notified as an existing active substance in product type 21 by Arch Chemicals Inc. (currently Lonza), and API Corporation Ltd. (currently Mitsubishi Chemical Corporation).

1 Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing biocidal products on the market. OJ L 123, 24.4.98, p.1

Commission Regulation (EC) No. 1451/2007 of 4 December 2007[2] lays down the detailed rules for the evaluation of dossiers and for the decision-making process in order to include or not an existing active substance into Annex I or IA to the Directive.

In accordance with the provisions of Article 7(1) of that Regulation, Sweden was designated as Rapporteur Member State (RMS) to carry out the assessment on the basis of the dossier submitted by the applicant. The deadline for submission of a complete dossier for copper pyrithione as an active substance in product type 21 was 30 April 2006 in accordance with Annex V of Regulation (EC) No. 2032/2003[3] .

The Swedish Chemicals Agency, the Competent Authority of Sweden, received on 30 April, 2006 two dossiers for the active substance copper pyrithione in PT 21 (antifouling products) from the applicants Arch Chemicals Inc. (bought by Lonza in 2011) and API Corporation Ltd. Some data gaps were identified in the latter dossier but the participant agreed to submit reports and study summaries to cover these gaps and the dossier was regarded as sufficiently complete to start the evaluation. The dossiers were accepted as complete on the 27th of October, 2006. During the evaluation of copper pyrithione, further information was requested for some endpoints whereupon new studies were submitted in January 2008 and December 2009.

On 28 January 2011, the Rapporteur Member State submitted, in accordance with the provisions of Article 10(5) and (7) of Regulation (EC) No. 2032/2003, to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report. The Commission made the report available to all Member States by electronic means on 7 February 2011. The competent authority report included a recommendation for the inclusion of copper pyrithione in Annex I to the Directive.

In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by the Commission. The first discussion took place at TM III in October 2011, and further discussions on technical level were held at TM IV in December 2011, TM I in March 2012, TM II in June 2012. Revisions agreed upon were presented at technical meetings and the competent authority report was amended accordingly til the version here presented for the Competent Authority Meeting (September 2013).

In accordance with Article 15(4) of Regulation (EC) No 1451/2007, the present assessment report contains the conclusions of the Standing Committee on Biocidal Products, as finalised during its meeting held on 22 May 2015.

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2 Commission Regulation (EC) No 1451/2007 of 4 December 2007 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. OJ L 325, 11.12.2007, p. 3

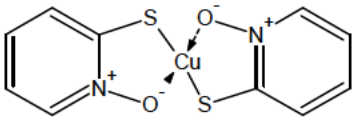
3 Commission Regulation (EC) No 2032/2003 of 4 November 2003 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/ 8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market, and amending Regulation (EC) No 1896/2000. OJ L307, 24.11.2003, p1

2. OVERALL SUMMARY AND CONCLUSIONS

2.1 Presentation of the Active Substance

2.1.1 Identity, Physico-Chemical Properties & Methods of Analysis

2.1.1.1 Identity

CAS-No.	14915-37-8
EINECS-No.	238-984-0
Other No. (CIPAC, ELINCS)	None
IUPAC Name	bis(1-hydroxy-1H-pyridine-2-thionato-O,S)copper
CA Name	copper, bis[1-hydroxy-2-(1H)-pyridinethionato-O,S]-
Common name, synonyms	No ISO-common name available Synonyms: copper pyrithione copper pyridinethione copper 2-pyridinethiol-1-oxide 2-pyridinethiol-1-oxide, copper salt copper *Omadine*® (registered trademark of Arch Chemicals, Inc.) Tomicide CPT (development code used by API corporation)
Structural formula	
Molecular formula	$C_{10}H_8N_2O_2S_2Cu$
Molecular weight (g/mol)	315.86
Purity of a.s.	Min: 95%w/w (supported by batch data from both manufacturers). Technical equivalence has been confirmed for the two manufacturers, see the confidential Appendix to Doc II-A* (i.e. equivalence has been confirmed despite the additional requirement for new 5-batch data as listed under impurities below)
Impurities	None of the impurities present in technical copper pyrithione are considered relevant. The information on impurities in the technical material are found in the respective Doc III A Confidential Annex for the two manufacturers. A new 5-batch analysis to confirm/revise the technical specification with respect to impurities for the applicant Arch

	is considered required (see further the Confidential Annex A for Arch).
Additives	No additives
Representative biocidal product(s)	[redacted] and [redacted] (viscous liquid antifouling paint formulations), Dummmy 4% and Dummy 2%.

* CAR_CuPT_CONFIDENTIAL_(to both Arch and API)_Doc_II_A_PT_21_Appendix_Technical_Equivalence

2.1.1.1 Physico-Chemical Properties

Technical copper pyrithione is a green odourless powder (>98% purity). Technical copper pyrithione decomposes upon melting at 273–279°C (>98% purity). The solubility of purified copper pyrithione (99% purity) in water was determined to be 49, 60 and 150 µg/L at 10, 20 and 30°C respectively (non-buffered distilled water, pH 5.9–7.1). In buffered solutions the solubility in water at 25°C was found to be 55, 102 and 109 µg/L at pH 5, 7 and 9 respectively (99% purity). The pH dependency of the water solubility is not considered significant and is not considered to be attributed to any dissociation of copper pyrithione under the conditions of the study. The formation constant of the complex copper pyrithione (log K >8.5 from published articles) indicates that copper pyrithione would not break even under highly acidic conditions. The pKa for free pyrithione is quoted as 4.67 in open literature, which means that the ionized dissociated form is mostly anticipated in the natural water compartment. Technical copper pyrithione (97.1% purity) was found to be sparingly soluble in organic solvents at 25°C (<0.2 mg/L in hexane, 176 mg/L in acetone, 8 mg/L in octane and 32 mg/L in xylene). The solubility of purified copper pyrithione (99.5% purity) in organic solvents was also tested (20 mg/L in methanol and 239 mg/L in acetone at 20°C). The log P_{ow} at 21-23°C was found to be 2.44 and 2.84 for purified grade (99% purity) and technical grade respectively (>98% purity) for non-buffered distilled water (pH 5.8-~7). The pH dependency has not been tested but given the findings for the water solubility a log P_{ow} of ~2.7 is expected at pH 5 (lowest water solubility) for the purified material, which does not indicate a risk for bioaccumulation. The vapour pressure for technical grade material (>98% purity) was determined as < 5.0 x 10^{-7} Pa and 4.3 x 10^{-17} Pa at 25°C by direct measurement and extrapolation respectively. The Henry's Law Constant was thus calculated as 3.48 x 10^{-13} Pa x mol/m^3 at 25°C using the extrapolated vapour pressure and a water solubility of 39 µg/l at 20°C and pH 6.3–6.8 (derived from a water solubility test not reported earlier). This indicates that volatilisation is not expected to significantly contribute to the dissipation of copper pyrithione in the environment. Furthermore, copper pyrithione should not be classified for flammability, explosivity or oxidizing properties.

2.1.1.2 Analytical methods

An acceptable HPLC-UV method, with respect to validation data, has been provided for the determination of copper pyrithione in the technical material. Following the submission of revalidation data for the determination of impurities in the technical material produced by Arch it is considered that these analytical methods are acceptable.

During the peer-review it was concluded that common moiety methods would in principle be acceptable for residue analytical methods in the case of copper pyrithione given that metal complexes are difficult to analyse as such and as they are not foreseen to remain as such in the different media where monitoring is required. Subsequently the RMS has proposed the following residue definitions for monitoring:

Water and soil (sediments):	Total pyrithione expressed as copper pyrithione
Air:	copper pyrithione (non-volatile, but used in spraying applications)
Body fluids and tissues:	2-pyridinethiol-1-oxide-S-glucuronide in urine (no residue in tissues)

For food of animal origin (fish and shell-fish) the TM-discussions were a bit inconclusive. In the tox-section it was concluded that there would not be any consumer risk not even with highest possible fish intake and maximum value of copper pyrithione in fish. However, the conclusion of the discussion in the general-section was that a method is not required if it can be shown that no residues will be present in fish and shell-fish. As the dossier does not contain sufficient data to demonstrate this, the following tentative residue definition is proposed (based on the fact that pyrithione is considered the toxicologically relevant residue which is likely to be present in water compartment available to fish and shell-fish):

Fish and shell-fish:	Total pyrithione expressed as copper pyrithione

With respect to the proposed residue definition, Arch has provided acceptable LC-MS/MS methods for sediment (LOQ 5 µg/kg), drinking and sea water (LOQ 0.1 µg/l) and fish (LOQ 0.5 µg/kg). Arch has also confirmed that they have been granted data access to the acceptable API-method for body fluids (see below).The LOQs of the methods are acceptable with respect to the relevant regulatory and scientific thresholds. No MRL is proposed for fish (or shell-fish) but the LOQ of the method is lower than the level used in the intake calculation showing no risk for consumers which means that the LOQ is considered sufficient. The methods are only validated for one ion-transition but this is considered acceptable given that at the time of the submission and evaluation of the data this was the common practice. For air: Arch provided a method for total pyrithione which is not appropriate with respect to the proposed residue definition and the LOQ (proven at 4.0 µg/m^3) is also not sufficient.

API has an acceptable RP-HPLC-UV method for the analysis of copper pyrithione in air which has a sufficient LOQ (0.58 µg/m^3) with respect to the short-term $AEL_{inhalative}$ of 0.002 mg/kg bw/day currently used in the risk assessment. The method is not highly specific but they have also provided an NP-HPLC-UV method for water analysis which is acceptable as such for the analysis of copper pyrithione and therefore accepted as a confirmatory method for the air analysis (i.e. not accepted for water; see below). API has also provided an acceptable method for monitoring 2-pyridinethiol-1-oxide-S-glucuronide in urine which is thus appropriate with respect to the proposed residue definition. The LOQ (47 µg/l) is also acceptable. As for the Arch-methods this LC-MS/MS method is only validated for one ion-transition but it is considered acceptable for the moment.

For the water compartment, API provided an acceptable method for the analysis of copper pyrithione as such but it is not considered appropriate with respect to the proposed residue definition. To address this further API submitted two methods from the open literature for the analysis of total pyrithione in water by HPLC-MS (LOQ 0.1–1 µg/L). However these published articles do not contain the level of validation data required by the TNsG on Analytical methods.

In conclusion therefore, acceptable methods are available for all required matrices. Given the uncertainties around the actual need for a monitoring method for fish and shell-fish at all no validation data for shell-fish is considered required at the moment. Arch will need to provide an acceptable method for analysis in air 6 months before the approval date of the active substance preferably to the original Rapporteur Member State. At the same point in time API will need to provide a method for sediment and water and possibly also for fish (and shell fish).

Furthermore, in order to evaluate the behaviour of the pyrithione complexes in the environmental compartments (see further section 2.2.2 below), especially the water compartment, the RMS has also performed an assessment of relevant analytical methods available in the open literature. In conclusion the published articles indicate that zinc pyrithione is easily trans-chelated to the more stable copper pyrithione complex and in the natural water compartment copper pyrithione is sufficiently stable to be extracted by organic solvents/sorbents and subsequently analysed by e.g. LC-MS/MS as the whole complex. The full evaluation in this respect is presented in document II-A section 1.4.3.

2.1.2 Intended Uses and Efficacy

The assessment of the biocidal activity of the active substance demonstrates that it has a sufficient level of efficacy against the target organism(s) (soft fouling organisms). The evaluation of the summary data provided in support of the efficacy of the accompanying paint products (against all target organisms including hard fouling organisms), establishes that the paint product may be expected to be efficacious.

In addition, in order to facilitate the work of granting or reviewing authorisations, the intended uses of the substance, as identified during the evaluation process, are listed in Appendix II: list of intended uses. Regarding which of these intended uses are supported (acceptable risk to human health and the environment), see Figure 2 (in List of Endpoint).

Six antifouling paint products (from five product formulators) have been evaluated, and these includes copper pyrithione as a **booster biocide** in the antifouling paint. A booster biocide is not the main biocide in the paint, but is ment to be effective against soft-fouling organisms, so its function is to increase the efficacy of the product in order to remove the most problematic fouling organisms, for example the common algae e.g. *Enteromorpha spp*. and *Amphora spp* which are tolerant of copper. (According to discussions with initiated EU colleagues the term “booster biocide” are more and more being replaced by the term “co-biocide”).

2.1.3 Classification and Labelling

Table 2.1.3-1 Proposed classification and labelling according to the criteria in Annex VI to Directive 67/548/EEC (so far no CLP dossier has been sent to ECHA)

Classification			
Category of danger	**R phrases**		**Concentration limits**
T+	R26	Very toxic by inhalation	N; R50: C ≥ 0.025 %
Xn	R21	Harmful in contact with skin	
Xn	R22	Harmful if swallowed	
Xi	R41	Risk of serious damage to eyes	
Xi	R37	Irritating to respiratory system	
T	R48/23/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed	
Xn	R63	Possible risk to unborn child	
N	R50	Very toxic to aquatic life	
Labelling			
Symbols/ Indication of danger	T+ N	Very toxic Dangerous for the environment	
R phrases	R26	Very toxic by inhalation	
	R21	Harmful in contact with skin	
	R22	Harmful if swallowed	
	R41	Risk of serious damage to eyes	
	R37	Irritating to respiratory system	
	R48/23/25	Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed	
	R63	Possible risk to unborn child	
	R50	Very toxic to aquatic life	
S phrases	S23	Do not breathe spray	
	S26	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice	
	S28	After contact with skin, wash immediately with plenty of water	
	S36/37/39	Wear suitable protective clothing, gloves and eye/face protection.	
	S38	In case of insufficient ventilation wear suitable respiratory equipment	
	S45	In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)	
	S63	In case of accident by inhalation: remove casualty to fresh air and keep at rest	
	S61	Avoid release to the environment. Refer to special instructions/safety data sheets	

Table 2.1.3-2 Proposed classification and labelling according to the criteria in Annex I to Regulation (EC) 1272/2008

Classification			
Hazard class	**Hazard statements**		**M-factor**
Acute Tox. 2	H330	Fatal if inhaled	
Acute Tox. 3	H301	Toxic if swallowed	
Acute Tox. 3	H311	Toxic in contact with skin	
Eye Dam. 1	H318	Causes serious eye damage	
STOT SE 3	H335	May cause respiratory irritation	
Repr Cat 2	H361	Suspected of damaging the unborn child	
STOT RE 1	H372	Causes damage to the nervous system through prolonged or repeated exposure	
Aquat. Acute 1	H400	Very toxic to aquatic life	100
Aquat. Chron. 1	H410	Very toxic to aquatic life with long lasting effects	100
Labelling			
Pictograms	GHS06; GHS05; GHS08; GHS09		
Signal word	Danger		
Hazard statements	H330	Fatal if inhaled	
	H301	Toxic if swallowed	
	H311	Toxic in contact with skin	
	H318	Causes serious eye damage	
	H335	May cause respiratory irritation	
	H361	Suspected of damaging the unborn child	
	H372	Causes damage to the nervous system through prolonged or repeated exposure	
	H400	Very toxic to aquatic life	
	H410	Very toxic to aquatic life with long lasting effects	
Pre-cautionary statements (professional use only)	P280	Wear protective gloves/protective clothing/eye protection/face protection.	
	P284	Wear respiratory protection.	
	P301 + P310	IF SWALLOWED: Immediately call a POISON CENTER or doctor/physician.	
	P302 + P352	IF ON SKIN: Wash with plenty of soap and water.	
	P361	Remove/Take off immediately all contaminated clothing.	
	P363	Wash contaminated clothing before reuse.	
	P304 + P340 + P310	IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing. Immediately call a POISON CENTER or doctor/physician.	
	P305 + P351 + P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.	
	P391	Collect spillage	
	P273	Avoid release to the environment.	

2.2 Summary of the Risk Assessment

Please refer to Figure 2 (in List of Endpoints) for an overview on what has been risk assessed.

2.2.1 Human Health Risk Assessment

2.2.1.1 Toxicokinetic, Metabolism and Read across

The toxicity studies have been conducted with copper pyrithione, zinc pyrithione and sodium pyrithione. Read across between these substances is considered acceptable by the RMS based on the mode of action and toxicokinetics of the three substances in addition to the similarities in toxic effects observed in the studies performed.

The pyrithiones are slowly but extensively absorbed from the gastrointestinal tract (oral absorption is >80 %), largely distributed, intensively metabolized, and almost completely eliminated, predominantly via the urine, within 96 hours. The major metabolite was found to be 2-pyridinethiol-1-oxide-S-glucuronide, excreted in the urine. No potential for accumulation was seen.

Dermal absorption was found to be 3 % in an *in vitro* study on human skin testing of copper pyrithione diluted in ethanol. An inhalation absorption study indicated that the absorption through this route is close to the default value of 100 %.

2.2.1.2 Acute toxicity

In the two studies performed, copper pyrithione exhibited moderate toxicity after oral exposure. In addition to mortality, clinical signs were observed as diarrhoea, mucoid stools, faecal staining around the anus, decrease in spontaneous activity, traces of reddish rhinorrhea, dirty lower belly, ataxia, hunched posture, lethargy, piloerection, ptosis, decreased respiratory rate and laboured respiration with additional signs or incidents of, emaciation, staining around the eyes, mouth or snout and high stepping or splayed gait. Reduced body weights were observed in high dose animals. Necropsy of animals that died showed dark reddish mucosa of the glandular stomach/surface of the forestomach, dark-reddish hemorrhage or atrophy of the thymus and/or atelectasis, haemorrhagic lungs, dark liver and dark kidneys. LD_{50} was 500 – 1000 mg/kg and 200 - 500 mg/kg bw, respectively, in the two studies.

Two copper pyrithione studies on dermal toxicity showed diverging results. At 2000 mg/kg bw no mortalities were observed in one study, while at the same dose level all tested animals were found dead or were sacrificed in extremis in a second study. Clinical signs included sluggishness, hunched posture, blepharospasm, ataxia, paralysis, few feces, a yellow nasal discharge, emaciation, prostration, rales, encrusted nose and body weight loss. Kidney and liver abnormalities were noted in one animal. Necropsy of these animals revealed inflammation of the abdominal organs. LD_{50} was found to be <2000 mg/kg bw and 400 - 2000 mg/kg bw respectively, in the two studies.

Copper pyrithione exhibited very high toxicity via the inhalation route with clinical signs including laboured breathing, tremors, increased salvation, lacrimation, changes in respiration rate, hypothermia, pallor of the extremities and abnormal gait. Necropsy showed abnormally dark lungs, haemorrhagic lung (one animal), and dark liver (one animal). LC_{50} was determined to be 0.07 mg/L and 0.14 mg/L in two studies, respectively.

Based on these studies, copper pyrithione is proposed to be classified as R21/22 Harmful by skin contact and if swallowed; R26 Very toxic by inhalation.

Copper pyrithione gave no irritation reaction after dermal application but was found to cause serious damage to eyes, with damage to the cornea, iris and conjunctiva being observed. The effects were not reversible and copper pyrithione thereby fulfils the requirements for classification with R 41 Risk of serious damage to eyes. No sensitising properties were observed in a maximisation test a test according to Buehler.

2.2.1.3 Short-term toxicity

Toxic effects have been investigated in rats, dogs and monkeys with rats and dogs showing higher sensitivity to the test substance.

The typical pyrithione effects observed in rats were mortality, hind limb weakness/paralysis, reduced body weight and gastric irritation. Pyrithione seems to be more toxic by the inhalation compared to the oral route and the sudden deaths seen are without any detectable explanation. However, a possible explanation could be the effect of pyrithione on intracellular Ca^{2+} levels which is known to be toxic in high concentrations and could probably result in sudden death of the animals once the Ca^{2+} gradient has collapsed in vital organs such as the heart. The mechanism of action of copper pyrithione has not yet been fully elucidated. Similar effects seen in the rats have also been observed in birds.

The dermal NOAEL was established at 100 mg/kg bw/day based on the 90 day rat study with zinc pyrithione.

The inhalation NOAELs are based on the 28-day rat inhalation study. The systemic NOAEL is 0.0015 mg/L (based on death that could not be explained); equal to 0.38 mg/kg bw/day and the local inhalation NOAEL is 0.0005 mg/L based on inflammation reaction.

Classification as Toxic with “R 48/23/25 Risk of serious damage to health after prolonged exposure through inhalation and if swallowed” as well as R 37 “Irritating to respiratory system” is proposed for copper pyrithione. R 48/23/25 is based on the 28 day inhalation study where mortality was observed at 0.005 mg/L and on an oral 28-day toxicity study with copper pyrithione where hind limb atrophy was observed and manifested as a lack of mobility in females at 5 mg/kg bw/day. R 37 is based on laboured breathing, increased salivation, noisy respiration, gasping, rales and increased or decreased respiratory rate which was seen in acute inhalation studies.

Two studies on monkeys were also included in the Arch dossier; one 28 day study with copper pyrithione, where the doses were given in gelatine capsules, and one 90 day study with zinc pyrithione.

In the monkey copper pyrithione study the NOAEL was 22 mg/kg bw/day and LOAEL was 44 mg/kg bw/day. No neurological effects were seen at LOAEL but diarrhoea, pale oral mucosa, decreased food consumption and body weight, decreased haematocrit count, haemoglobin, erythrocyte count, and increased liver weight and triglycerides and in the urine there was a decrease in chlorine, sodium and potassium concentration. Regarding neurological effects it is obvious that rat is a more sensitive animal than monkey. It is, however, not

considered suitable for reducing the interspecies assessment factor as the human sensitivity is unknown and no neurological effects have been seen in mice even though rats and mice is supposed to be similar (concluded at TM I 2012).

In monkeys dosed with zinc pyrithione the main effects observed were anaemia and gastrointestinal effects. However, in a study on monkeys performed with sodium pyrithione for one year no significant effects on haematology were observed. This might be explained by the fact that zinc toxicosis is known to be associated with haemolytic anaemia although the mechanism for this effect seems unclear. No significant effects on haematology were observed in rats. This could be explained by the fact that the dose levels used in monkeys were several times higher than those used in rats. It is possible that since rats were more sensitive to neurological effects they suffered from hind limb paralysis and death before any haematological effects occurred. The lack of haemotological effects in rats can therefore not be taken as evidence of lack of relevance of anaemia after repeated exposure to humans, although the effect in monkeys was not inconclusively shown.

According to a published study by Knox et al (2008) hind limb effects caused by sodium pyrithione are due to a reduced rate of axoplasmic transport and the resulting accumulation of tubulovesicular profiles at the distal nerve terminals of motor neurons leading to failure of synaptic transmission at neuro-muscular junctions. The study showed that sodium pyrithione evoked increased Ca^{2+} levels in motor neurons of both rats and monkeys, but with a significant difference in sensitivity (approximately 30 times higher for rats) between the two species.

In the API dossier a 90-day dog study was included. Four groups of four Beagle dogs/sex/dose were administered once daily with copper pyrithione. The only toxicologically relevant findings observed were the histopathological changes in the liver (slight pigment accumulation) of all four males and two females of the high dose group. Based on these changes, the NOAEL was established at 0.21 mg/kg bw/day.

2.2.1.4 Genotoxicity

In the studies submitted, copper pyrithione was found to be clastogenic in one chromosome aberration study *in vitro* with and without metabolic activation while two similar tests gave negative results. Copper pyrithione also tested positive for clastogenicity in one out of two *in vitro* gene mutation studies in mammalian cells with and without metabolic activation but was negative in two mutagenicity studies in bacteria (Ames test). However, no genotoxic hazard was identified in a well-performed zinc pyrithione micronucleus test in mice *in vivo,* submitted by Arch Chemicals. Thus, in spite of its clastogenic potential *in vitro*, copper pyrithione is probably metabolised *in vivo* to non-clastogenic metabolites and does not pose a genotoxic hazard *in vivo*.

For the present assessment of the genotoxic potential of copper pyrithione it is considered that sufficient data is available. The conclusion that copper pyrithione does not pose a genotoxic hazard *in vivo* is based on the micronucleus zinc pyrithione study submitted by Arch Chemicals. At product authorization level however, API Corporation must have access to data supporting this conclusion as the RMS does not consider the studies submitted by API

Corporation to be sufficient proof of lack of genotoxic hazard in vivo. At the WG II meeting in Mars 2014 it was agreed that there is no toxicological concern regarding the genotoxic potential of copper pyrithione due to the copper content.

2.2.1.5 Long-term toxicity and carcinogenicity

Read across to studies with sodium pyrithione has been accepted by RMS due to other existing data (TNsG on Data Requirements Principles for waiving, chapter 1.4).

A chronic NOAEL could not be established as effects were seen in the lowest dose level in both studies. The NOAEL is < 0.5 mg/kg bw/day based on increased incidences of hind leg wasting and spinal chord degradation.

Sodium pyrithione was not carcinogenic in the two studies performed with rats and mice.

Using studies on a different pyrithione compound raises the question of chronic toxicity and carcinogenicity of copper. The Swedish National Food Administration recommends a daily intake of 0.9-1.3 mg copper/day, which equals 0.015-0.022 mg/kg for a person who weighs 60 kg. The exposure levels to copper as copper pyrithione will fall below the recommended daily intake for copper and the lack of data on copper is therefore considered acceptable.

2.2.1.6 Reproduction toxicity

The overall NOAEL for developmental effects was 0.5 mg/kg bw/day based on the oral rabbit study with zinc pyrithione and the overall NOAEL for fertility was 0.7 mg/kg bw/day. It cannot be excluded that the pyrithione might cause reprotoxic effects even though the malformations observed occurred parallel to maternal toxicity. Examples of malformation occurring that is not considered to be due to maternal toxicity is; cleft plate, microglossia, malformed testis and bent limb bone. RMS therefore suggests a classification with Repro. R63 category 3. Moreover, similarly effects on pups were noted at doses which also resulted in parental toxicity. These effects were observed as reduced body weight gain and food consumption, atrophy of hind limb muscles with related hind limb paralysis/impairment of movement – all effects typically seen in the subchronic and chronic studies - as well as reduced kidney and epididymes weights and increased uterus and spleen weights.

2.2.1.7 Neurotoxicity

The pyrithiones seems to have a neurotoxic effect as ataxia and hind limb paralysis was seen in many studies. NOAEL was found to be 1.25 mg/kg bw/day based on toxic effects seen at 2.25 mg/kg bw/day in a 90 day neurotoxicity study with copper pyrithione on rat. The value was based on the sacrifice of one female in moribund condition, suffering from ataxia, muscle fibre atrophy and varying degrees of myositis, muscle fibre necrosis and muscle fibre degeneration.

Measurements of AChE activity was not done despite it would have been valuable since Copper pyrithione has been shown to cause decreases in the activity of this enzyme in fish.

In a single dose 14-day neurotoxicity study with zinc pyrithione and rats, mortality and reduced body weight and food consumption were noted in addition to clinical signs consisting

of dehydration, urine stained abdominal fur, soft or liquid faeces and a few incidences of chromorhinorrhea and localized alopecia on the underside. The major neurotoxic finding was an effect on movement. The motor activity measurements revealed significant decreases in the number of movements and the total time spent in movement for male and female rats at 75 and 150 mg/kg when tested one hour post dosage. Female rats at 25 mg/kg also exhibited a statistically significant decrease in both parameters at one hour post dosage. Clinical chemistry was not investigated but might have given valuable information. In spite of the apparent effect on movements seen in females, the RMS considers the NOAEL to be 25 mg/kg bw in the absence of other supporting information.

2.2.1.8 Medical data

Each employee in contact with copper pyrithione undergoes a detailed physical examination once every two years. During 30 years of manufacturing experience with pyrithiones, minor transient mucous membrane irritation has been noted but no neurological abnormalities have been identified.

2.2.1.9 Livestock and pets

Due to the expected use of copper pyrithione exposure to live stock and pets are not expected and has not been considered in this report.

2.2.1.10 Acceptable daily intake (ADI) and acute reference dose (ARfD)

ADI and ARfD needs to be established if the active substance will enter the food chain. Copper pyrithione is intended to be used in antifouling paints and in aquaculture for treatment of fishing nets. The latter field of use may result in exposure of copper pyrithione to fish and shellfish, and therefore ARfD and ADI has been established. The ARfD is 0.02 mg/kg bw/day based on early effects (after 2.5 hours); ataxia in hind limb and whole body tremor, seen at LOAEL in a 90 day oral rat study with sodium pyrithione and a safety factor of 100 (10 x 10 for inter-and intra-species variability). The ARfD was used for risk calculation of children licking the hand after having touched wet and dry antifouling paint on boats. The ADI is 0.0025 mg/kg bw/day based on two chronic oral rat studies with sodium pyrithione where LOAEL was 0.5 mg/kg bw/day based on nerve degeneration and muscle atrophy. An extra safety factor two was used to extrapolate from LOAEL to NOAEL together with a safety factor of 100 (10 x 10 for inter-and intra-species variability).

2.2.1.11 Acceptable Exposure Level (AEL)

At TM I 2012 it was decided that route-specific AELs should be set for copper pyrithione, i.e. one inhalation and one dermal AEL for short-term, medium-term and long-term exposure respectively. However, as it was impossible to estimate a dermal AEL due to lack of dermal absorption data the WG II-meeting in Mars 2014 decided that the dermal exposure should be covered by the oral AEL. The dermal short and medium term AEL is therefore set to 0.005 mg/kg bw/day based on all oral copper pyrithione, zinc pyrithione and sodium pyrithione subacute, subchronic, teratogenicity and 2-generation studies available to RMS, where the overall NOAEL was 0.005. The safety factor of 100 was used. The dermal short term AEL was decided to be the same as the dermal medium AEL, and thereby lower than the ARfD, as exposure directly into the bloodstream seems to be a more toxic exposure route than

the oral exposure that passes the liver before entering the bloodstream. The long term dermal AEL is considered to be the same as ADI which is 0.0025 mg/kg bw/day.

The short and medium term inhalation AEL is 0.002 mg/kg bw/day. The AEL derives from a NOAEL, 0.38 mg/kg bw/day, in a 28 day rat inhalation study were death of unexplained cause was seen at LOAEL, applying a safety factor of 200.

The inhalation long term AEL is based on the same study as the short and medium term AELs but an extra safety factor of 4 has been added to extrapolate from short to long time exposure, resulting in a long term inhalation AEL of 0.001 mg/kg bw/day. An external reference value (AEC) was derived from the local NOAEC of 0.0005 mg/mL in the 28 day rat inhalation study. The AF factor of 10 for intra species variation was used together with the factor for interspecies variation in toxicodynamics (2.5), resulting in a total safety factor 25 which gives a local AEC of 0.00002 mg/L (0.02 mg/m^3).

2.2.2 Human health exposure assessment

2.2.2.1 Exposure of manufacturers

Exposure of workers at the production/formulation plants is not considered in the risk assessment as it is assumed to be within the scope of other legislation on worker safety.

2.2.2.2 Exposure of professionals

Six antifouling products were evaluated in this report. The products are mainly intended to be used by professionals. The professional users can be divided into six sub-groups, each sub-group either forming part of the team applying paint to the surface or being workers removing paint during maintenance of a previously painted surface. The potentially exposed groups are the following:

- Sprayer; high-pressure spraying for surface coating.
- Painter using brush and roller.
- Potman; mixing and loading of antifoulant from supply container to high-pressure pump reservoir ensuring continuous supply to the spray gun.
- Ancillary worker; keeping paint lines free, manoeuvring mobile spray platforms as well as other tasks intended to aid the sprayer's job. The exposure risk for the ancillary worker is covered by the risk for the sprayer.
- Blast worker; performs a total or partial removal of the expired coating from the ship hull using abrasive or high-pressure water.
- Grit filler; mixing and loading of grit from supply container to high-pressure pump reservoir ensuring continuous supply to the spray gun.

One dummy product intended to be used in aquaculture has also been evaluated. Large woven nets are submerged into vessels containing the biocidal product. The net is allowed to dry before being lifted to a packing area where it is manually packed into plastic cover packing for despatch to the deployment area where the net normally is stretched out on a barge on the sea area and a team of up to six individuals manually deploy the net into the sea. The net is normally suspended from flotation buoys and anchored to the sea bed in the area designated

for the aquaculture. Bystanders are not supposed to come in contact with the nets. The use of copper pyrithione treated nets may result in exposure of copper pyrithione to fish and shellfish. RMS has done a rough calculation showing that the possible exposure from eating fish or oysters is well below the ADI for copper pyrithione.

The following six products have been evaluated in this rapport:

Antifouling paint	[redacted] 1.5 % Copper pyrithione
"	[redacted] 2.9 % Copper pyrithione
"	[redacted] 3.5 % Copper pyrithione
"	Dummy Product (Arch Chemicals Inc), 4 % Copper pyrithione
"	[redacted] 4.01 % Copper pyrithione
Net impregnation	Dummy Product (Arch Chemicals Inc.), 2 % Copper pyrithione

Table 2.2.2.2 The potential exposure to professional users

For a scenario to be accepted the total systemic exposure has to be ≤ 100% of dermal and inhalation AELs and also ≤ 100% of the local inhalation AEL. The values in the acceptable scenarios have been underlined.

[redacted]					
Exposure Scenario		**Exposure route**	**Estimated exposure**	**Exposure % of AEL**	**Total systemic exposure % of dermal and inhalation AELs**
Application by airless spray Risk assessment according to Model 3TNsG on Human Exposure, 2002.	**Tier 1** No PPE	Systemic via dermal route	0.4577 mg/kg bw/day	9153	**9964**
		Systemic via inhalation route	0.0162 mg/kg bw/day	811	
		Local inhalation concentration	0.260 mg/m³	**1298**	
	Tier 2 protective gloves double coverall (1 % penetration), respiratory mask with APF 40	Systemic via dermal route	0.00613 mg/kg bw/day	123	**143**
		Systemic via inhalation route	0.000405 mg/kg bw/day	20	
		Local inhalation concentration	0.00649 mg/m³	**32.4**	
Painter using brush and roller	**Tier 1** no PPE	Systemic via dermal route	0.0556 mg/kg bw/day	1111	**1505**
		Systemic via inhalation route	0.00788 mg/kg bw/day	394	

Risk assessment according to Links et at, 2007.		Local inhalation concentration	0.00420 mg/m^3	**21**	
	Tier 2 Safety shoes, one overall (Tyvek® or cotton) or sometimes normal clothing (e.g. trousers and a jumper), nitril rubber gloves, respiratory mask with APF 10	Systemic via dermal route	0.0000095 mg/kg bw/day	0.18900	**40**
		Systemic via inhalation route	0.000788 mg/kg bw/day	39	
		Local inhalation concentration	0.000420 mg/m^3	**2**	
Mixing and loading (pot-man) Risk assessment according to Model 4 Consumer product painting, TNsG on Human Exposure, 2002.	**Tier 1** no PPE	Systemic via dermal route	0.1647 mg/kg bw/day	3294	**3383**
		Systemic via inhalation route	0.00178 mg/kg bw/day	89	
		Local inhalation concentration	0.0285 mg/m^3	**143**	
	Tier 2a Protective gloves; single coverall (4 % penetration), Facial mask with APF 10	Systemic via dermal route	0.0160 mg/kg bw/day	321	**330**
		Systemic via inhalation route	0.000178 mg/kg bw/day	9	
		Local inhalation concentration	0.00285 mg/m^3	**14**	
	Tier 2b Protective gloves; double coverall (1 % penetration), Facial mask with APF 10	Systemic via dermal route	0.0123 mg/kg bw/day	246	**255**
		Systemic via inhalation route	0.000178 mg/kg bw/day	9	
		Local inhalation concentration	0.00285 mg/m^3	**14**	
	Tier2c Protective gloves; double coverall (1 % penetration), Facial mask with APF 40	Systemic via dermal route	0.0123 mg/kg bw/day	246	**248**
		Systemic via inhalation route	0.0000445 mg/kg bw/day	2	
		Local inhalation concentration	0.0007125 mg/m^3	**4**	

Removal paint Risk assessment according to "HEEG Opinion on the paper by Links et al. 2007 on occupational exposure during application and removal of antifouling paints" that was endorsed at TM IV 2012	**Tier 1** no PPE	Systemic via dermal route	0.05832 mg/kg bw/day	1166	**1941**
		Systemic via inhalation route	0.015491 mg/kg bw/day	775	
		Local inhalation concentration	0.24786 mg/m³	**1239**	
	Tier 2 waterproof overalls, strong protective gloves, Facial mask with APF 40	Systemic via dermal route	0.007203 mg/kg bw/day	144	**163**
		Systemic via inhalation route	0.000387 mg/kg bw/day	19	
		Local inhalation concentration	0.006197 mg/m³	**31**	
Grit fillers Risk assessment according to "HEEG Opinion on the paper by Links et al. 2007 on occupational exposure during application and removal of antifouling paints" that was endorsed at TM IV 2012	**Tier 1** no PPE	Systemic via dermal route	0.209223 mg/kg bw/day	4184	**5997**
		Systemic via inhalation route	0.036248 mg/kg bw/day	1812	
		Local inhalation concentration	0.57996 mg/m³	**2900**	
	Tier 2a Facial mask with APF 40	Systemic via dermal route	0.098852 mg/kg bw/day	1977	**2022**
		Systemic via inhalation route	0.000906 mg/kg bw/day	45	
		Local inhalation concentration	0.014499 mg/m³	**72**	
	Tier 2b The same exposure and type of PPE and RPE as the sand blasting worker	Systemic via dermal route	0.007203 mg/kg bw/day	144	**163**
		Systemic via inhalation route	0.000387 mg/kg bw/day	19	
		Local inhalation concentration	0.006197 mg/m³	**31**	

[redacted]				
Exposure Scenario	**Exposure route**	**Estimated exposure**	**Exposure % of AEL**	**Total exposure % of dermal and inhalation AELs**

Application by airless spray Risk assessment according to Model 3, TNsG on Human Exposure, 2002.	**Tier 1** No PPE	Systemic via dermal route	0.8848 mg/kg bw/day	17696	**19264**
		Systemic via inhalation route	0.0314 mg/kg bw/day	1568	
		Local inhalation concentration	0.5017 mg/m^3	**2509**	
	Tier 2 protective gloves double coverall (1 % penetration), respiratory mask with APF 40	Systemic via dermal route	0.0118 mg/kg bw/day	237	**276**
		Systemic via inhalation route	0.00078 mg/kg bw/day	39	
		Local inhalation concentration	0.0125425 mg/m^3	**62.7**	
Painter using brush and roller Risk assessment according to Links et at, 2007.	**Tier 1** no PPE	Systemic via dermal route	0.1074 mg/kg bw/day	2148	**2909**
		Systemic via inhalation route	0.015 mg/kg bw/day	761	
		Local inhalation concentration	0.00812 mg/m^3	**41**	
	Tier 2 Safety shoes, one overall (Tyvek® or cotton) or sometimes normal clothing (e.g. trousers and a jumper), nitril rubber gloves, respiratory mask with APF 10	Systemic via dermal route	0.0000183 mg/kg bw/day	0.36540	**<u>76</u>**
		Systemic via inhalation route	0.002 mg/kg bw/day	76	
		Local inhalation concentration	0.000812 mg/m^3	**<u>41</u>**	
Mixing and loading (pot-man) Risk assessment according to Model 4 Consumer product	**Tier 1** no PPE	Systemic via dermal route	0.3184 mg/kg bw/day	6368	**6541**
		Systemic via inhalation route	0.0034 mg/kg bw/day	172	
		Local inhalation concentration	0.0551 mg/m^3	**276**	
	Tier 2a	Systemic via dermal route	0.0310 mg/kg bw/day	620	**637**

painting,TNsG on Human Exposure, 2002.	Protective gloves; single coverall (4 % penetration), Facial mask with APF 10	Systemic via inhalation route	0.00034 mg/kg bw/day	17	
		Local inhalation concentration	0.00551 mg/m^3	**27.6**	
	Tier 2b Protective gloves; double coverall (1 % penetration), Facial mask with APF 10	Systemic via dermal route	0.0238 mg/kg bw/day	476	**493**
		Systemic via inhalation route	0.00034 mg/kg bw/day	17	
		Local inhalation concentration	0.00551 mg/m^3	**27.6**	
	Tier2c Protective gloves; double coverall (1 % penetration), Facial mask with APF 40	Systemic via dermal route	0.0238 mg/kg bw/day	476	**480**
		Systemic via inhalation route	0.00009 mg/kg bw/day	4	
		Local inhalation concentration	0.0013775 mg/m^3	**6.9**	
Removal paint Risk assessment according to "HEEG Opinion on the paper by Links et al. 2007 on occupational exposure during application and removal of antifouling paints" that was endorsed at TM IV 2012	**Tier 1** no PPE	Systemic via dermal route	0.11016 mg/kg bw/day	2203	**3666**
		Systemic via inhalation route	0.029261 mg/kg bw/day	1463	
		Local inhalation concentration	0.46818 mg/m^3	**2341**	
	Tier 2 waterproof overalls, strong protective gloves, Facial mask with APF 40	Systemic via dermal route	0.013605 mg/kg bw/day	272	**309**
		Systemic via inhalation route	0.000732 mg/kg bw/day	37	
		Local inhalation concentration	0.011705 mg/m^3	**59**	
Grit fillers Risk assessment according to "HEEG Opinion on the paper by Links et al. 2007 on occupational	**Tier 1** no PPE	Systemic via dermal route	0.395199 mg/kg bw/day	7904	**11327**
		Systemic via inhalation route	0.068468 mg/kg bw/day	3423	
		Local inhalation concentration	1.09548 mg/m^3	**5477**	
	Tier 2a	Systemic via dermal route	0.186721 mg/kg bw/day	3734	**3820**

exposure during application and removal of antifouling paints" that was endorsed at TM IV 2012	Facial mask with APF 40	Systemic via inhalation route	0.001712 mg/kg bw/day	86	
		Local inhalation concentration	0.027387 mg/m³	**137**	
	Tier 2b The same exposure and type of PPE and RPE as the sand blasting worker	Systemic via dermal route	0.013605 mg/kg bw/day	272	**309**
		Systemic via inhalation route	0.000732 mg/kg bw/day	37	
		Local inhalation concentration	0.011705 mg/m³	**59**	

[redacted]					
Exposure Scenario		**Exposure route**	**Estimated exposure**	**Exposure % of AEL**	**Total systemic exposure % of dermal and inhalation AELs**
Application by airless spray Risk assessment according to Model 3, TNsG on Human Exposure, 2002.	**Tier 1** No PPE	Systemic via dermal route	1.7798 mg/kg bw/day	35595	**37487**
		Systemic via inhalation route	0.0387 mg/kg bw/day	1934	
		Local inhalation concentration	0.6055 mg/m³	**3028**	
	Tier 2 protective gloves double coverall (1 % penetration), respiratory mask with APF 40	Systemic via dermal route	0.0238 mg/kg bw/day	477	**524**
		Systemic via inhalation route	0.000946 mg/kg bw/day	47	
		Local inhalation concentration	0.0151375 mg/m³	**76**	
Painter using brush and roller Risk assessment according to	**Tier 1** no PPE	Systemic via dermal route	0.2160 mg/kg bw/day	4321	**5240**
		Systemic via inhalation route	0.0184 mg/kg bw/day	920	
		Local inhalation concentration	0.0098mg/m³	**49**	

Links et at, 2007.	**Tier 2** Safety shoes, one overall (Tyvek® or cotton) or sometimes normal clothing (e.g. trousers and a jumper), nitril rubber gloves, respiratory mask with APF 10	Systemic via dermal route	0.0000368 mg/kg bw/day	0.73500	**93**
		Systemic via inhalation route	0.00184 mg/kg bw/day	92	
		Local inhalation concentration	0.00098 mg/m^3	**5**	
Mixing and loading (pot-man) Risk assessment according to Model 4 Consumer product painting,TNsG on Human Exposure, 2002.	**Tier 1** no PPE	Systemic via dermal route	0.6405 mg/kg bw/day	12810	**13018**
		Systemic via inhalation route	0.00416 mg/kg bw/day	208	
		Local inhalation concentration	0.0665 mg/m^3	**333**	
	Tier 2a Protective gloves; single coverall (4 % penetration), Facial mask with APF 10	Systemic via dermal route	0.0624 mg/kg bw/day	1247	**1268**
		Systemic via inhalation route	0.000416 mg/kg bw/day	21	
		Local inhalation concentration	0.00665 mg/m^3	**33.3**	
	Tier 2b Protective gloves; double coverall (1 % penetration), Facial mask with APF 10	Systemic via dermal route	0.0479 mg/kg bw/day	958	**978**
		Systemic via inhalation route	0.000416 mg/kg bw/day	21	
		Local inhalation concentration	0.00665 mg/m^3	**33.3**	
	Tier2c Protective gloves; double coverall (1 % penetration), Facial mask with APF 40	Systemic via dermal route	0.0479 mg/kg bw/day	958	**963**
		Systemic via inhalation route	0.000104 mg/kg bw/day	**5**	
		Local inhalation concentration	0.0016625 mg/m^3	**8.3**	
Removal paint	**Tier 1** no PPE	Systemic via dermal route	0.2592 mg/kg bw/day	5184	**7250**

Risk assessment according to "HEEG Opinion on the paper by Links et al. 2007 on occupational exposure during application and removal of antifouling paints" that was endorsed at TM IV 2012		Systemic via inhalation route	0.04131 mg/kg bw/day	2065	
		Local inhalation concentration	0.66096 mg/m³	**3305**	
	Tier 2 waterproof overalls, strong protective gloves, Facial mask with APF 40	Systemic via dermal route	0.032011 mg/kg bw/day	640	**692**
		Systemic via inhalation route	0.001033 mg/kg bw/day	52	
		Local inhalation concentration	0.016524 mg/m³	**83**	
Grit fillers Risk assessment according to "HEEG Opinion on the paper by Links et al. 2007 on occupational exposure during application and removal of antifouling paints" that was endorsed at TM IV 2012	**Tier 1** no PPE	Systemic via dermal route	0.92988 mg/kg bw/day	18598	**23431**
		Systemic via inhalation route	0.09666 mg/kg bw/day	4833	
		Local inhalation concentration	1.54656 mg/m³	**7733**	
	Tier 2a Facial mask with APF 40	Systemic via dermal route	0.439344 mg/kg bw/day	8787	**8908**
		Systemic via inhalation route	0.002417 mg/kg bw/day	121	
		Local inhalation concentration	0.038664 mg/m³	**193**	
	Tier 2b The same exposure and type of PPE and RPE as the sand blasting worker	Systemic via dermal route	0.032011 mg/kg bw/day	640	**692**
		Systemic via inhalation route	0.001033 mg/kg bw/day	52	
		Local inhalation concentration	0.016524 mg/m³	**83**	

Arch, Dummy product 4%				
Exposure Scenario	**Exposure route**	**Estimated exposure**	**Exposure % of AEL**	**Total systemic exposure % of dermal and inhalation AELs**

Application by airless spray Risk assessment according to Model 3, TNsG on Human Exposure, 2002. **Assuming 1% dermal absorption**	**Tier 1** No PPE	Systemic via dermal route	0.4068 mg/kg bw/day	8136	**10299**
		Systemic via inhalation route	0.04325 mg/kg bw/day	2163	
		Local inhalation concentration	0.692 mg/m^3	**3460**	
	Tier 2 protective gloves double coverall (1 % penetration), respiratory mask with APF 40	Systemic via dermal route	0.0054 mg/kg bw/day	109	**163**
		Systemic via inhalation route	0.00108 mg/kg bw/day	54	
		Local inhalation concentration	0.0173 mg/m^3	**87**	
Application by airless spray Risk assessment according to TNsG on Human Exposure, 2002. **Assuming 0.5% dermal absorption**	**Tier 1** No PPE	Systemic via dermal route	0.2034 mg/kg bw/day	4068	**6231**
		Systemic via inhalation route	0,04325 mg/kg bw/day	2163	
		Local inhalation concentration	0.692 mg/m^3	**3460**	
	Tier 2 protective gloves double coverall (1 % penetration), respiratory mask with APF 40	Systemic via dermal route	0.0027 mg/kg bw/day	54	**109**
		Systemic via inhalation route	0.00108 mg/kg bw/day	54	
		Local inhalation concentration	0.0173 mg/m^3	**87**	
Painter using brush and roller Risk assessment according to Links et at, 2007. **Assuming 1% dermal absorption**	**Tier 1** no PPE	Systemic via dermal route	0.0494 mg/kg bw/day	988	**2038**
		Systemic via inhalation route	0.0210 mg/kg bw/day	1050	
		Local inhalation concentration	0.0112 mg/m^3	**56**	
	Tier 2a Safety shoes, one overall (Tyvek® or cotton) or sometimes normal clothing	Systemic via dermal route	0.0000084 mg/kg bw/day	0.16800	**105**
		Systemic via inhalation route	0.00210 mg/kg bw/day	105	

	(e.g. trousers and a jumper), nitrile rubber gloves, respiratory mask with APF 10	Local inhalation concentration	0.00112 mg/m^3	**6**	
	Tier 2b Safety shoes, one overall (Tyvek® or cotton) or sometimes normal clothing (e.g. trousers and a jumper), nitrile rubber gloves, respiratory mask with APF 40	Systemic via dermal route	0.0000084 mg/kg bw/day	0.16800	**<u>26</u>**
		Systemic via inhalation route	0.000525 mg/kg bw/day	26	
		Local inhalation concentration	0.000280mg/m^3	**<u>1</u>**	
Mixing and loading (pot-man) Risk assessment according to Model 4 Consumer product painting,TNsG on Human Exposure, 2002. **Assuming 1% dermal absorption**	**Tier 1** no PPE	Systemic via dermal route	0.1464 mg/kg bw/day	2928	**3166**
		Systemic via inhalation route	0.00475 mg/kg bw/day	238	
		Local inhalation concentration	0.076 mg/m^3	**380**	
	Tier 2a Protective gloves; single coverall (4 % penetration), Facial mask with APF 10	Systemic via dermal route	0.0143 mg/kg bw/day	285	**309**
		Systemic via inhalation route	0.000475 mg/kg bw/day	24	
		Local inhalation concentration	0.0076 mg/m^3	**38**	
	Tier 2b Protective gloves; double coverall (1 % penetration), Facial mask with APF 10	Systemic via dermal route	0.011209 mg/kg bw/day	219	**243**
		Systemic via inhalation route	0.000475 mg/kg bw/day	24	
		Local inhalation concentration	0.0076 mg/m^3	**38**	
	Tier2c	Systemic via dermal route	0.0109 mg/kg bw/day	219	**225**

	Protective gloves; double coverall (1 % penetration), Facial mask with APF 40	Systemic via inhalation route	0.000119 mg/kg bw/day	6	
		Local inhalation concentration	0.0019 mg/m^3	**10**	
Mixing and loading (pot-man) Risk assessment according to Model 4 Consumer product painting,TNsG on Human Exposure, 2002. **Assuming 0.5% dermal absorption**	**Tier 1** no PPE	Systemic via dermal route	0.0732 mg/kg bw/day	1464	**1702**
		Systemic via inhalation route	0.00475 mg/kg bw/day	238	
		Local inhalation concentration	0.076 mg/m^3	**380**	
	Tier 2a Protective gloves; single coverall (4 % penetration), Facial mask with APF 10	Systemic via dermal route	0.0071 mg/kg bw/day	143	**166**
		Systemic via inhalation route	0.000475 mg/kg bw/day	24	
		Local inhalation concentration	0.0076 mg/m^3	**38**	
	Tier 2b Protective gloves; double coverall (1 % penetration), Facial mask with APF 10	Systemic via dermal route	0.0055 mg/kg bw/day	109	**133**
		Systemic via inhalation route	0.000475 mg/kg bw/day	24	
		Local inhalation concentration	0.0076 mg/m^3	**38**	
	Tier2c Protective gloves; double coverall (1 % penetration), Facial mask with APF 40	Systemic via dermal route	0.0055 mg/kg bw/day	109	**115**
		Systemic via inhalation route	0.000119 mg/kg bw/day	6	
		Local inhalation concentration	0.0019 mg/m^3	**10**	
Removal paint Risk assessment according to "HEEG Opinion on the paper by Links et al. 2007 on occupational exposure during application and removal of	**Tier 1** no PPE	Systemic via dermal route	0.0540 mg/kg bw/day	1080	**3232**
		Systemic via inhalation route	0.043031 mg/kg bw/day	2152	
		Local inhalation concentration	0.6885 mg/m^3	**3443**	
	Tier 2 waterproof overalls, strong protective gloves,	Systemic via dermal route	0.006669 mg/kg bw/day	133	**187**
		Systemic via inhalation route	0.001076 mg/kg bw/day	54	
		Local inhalation concentration	0.017213 mg/m^3	**86**	

antifouling paints" that was endorsed at TM IV 2012 **Assuming 1% dermal absorption**	Facial mask with APF 40				
Removal paint Risk assessment according to "HEEG Opinion on the paper by Links et al. 2007 on occupational exposure during application and removal of antifouling paints" that was endorsed at TM IV 2012 **Assuming 0.5% dermal absorption**	**Tier 1** no PPE	Systemic via dermal route	0.0270 mg/kg bw/day	540	**2692**
		Systemic via inhalation route	0.043031 mg/kg bw/day	2152	
		Local inhalation concentration	0.6885 mg/m^3	**3443**	
	Tier 2 waterproof overalls, strong protective gloves, Facial mask with APF 40	Systemic via dermal route	0.003335 mg/kg bw/day	67	**120**
		Systemic via inhalation route	0.001076 mg/kg bw/day	54	
		Local inhalation concentration	0.017213 mg/m^3	**86**	
Grit fillers Risk assessment according to "HEEG Opinion on the paper by Links et al. 2007 on occupational exposure during application and removal of antifouling paints" that was endorsed at TM IV 2012	**Tier 1** no PPE	Systemic via dermal route	0.193725 mg/kg bw/day	3875	**8909**
		Systemic via inhalation route	0.1006875 mg/kg bw/day	5034	
		Local inhalation concentration	1.611 mg/m^3	**8055**	
	Tier 2a Facial mask with APF 40	Systemic via dermal route	0.09153 mg/kg bw/day	1831	**1956**
		Systemic via inhalation route	0.00251719 mg/kg bw/day	126	
		Local inhalation concentration	0.040275 mg/m^3	**201**	
	Tier 2b The same exposure and type of PPE	Systemic via dermal route	0.006669 mg/kg bw/day	133	**187**
		Systemic via inhalation route	0.001076 mg/kg bw/day	54	

Assuming 1% dermal absorption	and RPE as the sand blasting worker	Local inhalation concentration	0.017213 mg/m³	**86**	
Grit fillers Risk assessment according to "HEEG Opinion on the paper by Links et al. 2007 on occupational exposure during application and removal of antifouling paints" that was endorsed at TM IV 2012 **Assuming 0.5% dermal absorption**	**Tier 1** no PPE	Systemic via dermal route	0.0968625 mg/kg bw/day	1937	**6972**
		Systemic via inhalation route	0.1006875 mg/kg bw/day	5034	
		Local inhalation concentration	1.611 mg/m³	**8055**	
	Tier 2a Facial mask with APF 40	Systemic via dermal route	0.045765 mg/kg bw/day	915	**1041**
		Systemic via inhalation route	0.00251719 mg/kg bw/day	126	
		Local inhalation concentration	0.040275 mg/m³	**201**	
	Tier 2b The same exposure and type of PPE and RPE as the sand blasting worker	Systemic via dermal route	0.003335 mg/kg bw/day	67	**120**
		Systemic via inhalation route	0.001076 mg/kg bw/day	54	
		Local inhalation concentration	0.017213 mg/m³	**86**	

[redacted]				
Exposure Scenario	**Exposure route**	**Estimated exposure**	**Exposure % of AEL**	**Total systemic exposure % of dermal and inhalation AELs**

Application by airless spray Risk assessment according to Model 3, TNsG on Human Exposure, 2002.	**Tier 1** No PPE	Systemic via dermal route	0.2447 mg/kg bw/day	4894	**7062**
		Systemic via inhalation route	0.0434 mg/kg bw/day	2218	
		Local inhalation concentration	0.69373 mg/m^3	**3469**	
	Tier 2 protective gloves double coverall (1 % penetration), respiratory mask with APF 40	Systemic via dermal route	0.0033 mg/kg bw/day	66	**120**
		Systemic via inhalation route	0.00108 mg/kg bw/day	54	
		Local inhalation concentration	0.017343 mg/m^3	**86.7**	
Painter using brush and roller Risk assessment according to Links et at, 2007.	**Tier 1** no PPE	Systemic via dermal route	0.0297 mg/kg bw/day	594	**1647**
		Systemic via inhalation route	0.02105 mg/kg bw/day	1053	
		Local inhalation concentration	0.011228 mg/m^3	**56**	
	Tier 2 Safety shoes, one overall (Tyvek® or cotton) or sometimes normal clothing (e.g. trousers and a jumper), nitril rubber gloves, respiratory mask with APF 10	Systemic via dermal route	0.0000051 mg/kg bw/day	0.1	**105**
		Systemic via inhalation route	0.002105 mg/kg bw/day	105	
		Local inhalation concentration	0.0011228 mg/m^3	**5.6**	
	Tier 2b Safety shoes, one overall (Tyvek® or cotton) or sometimes normal	Systemic via dermal route	0.0000051mg/kg bw/day	0.1	**<u>26</u>**
		Systemic via inhalation route	0.000526 mg/kg bw/day	26	

	clothing (e.g. trousers and a jumper), nitril rubber gloves), respiratory mask with APF 40	Local inhalation concentration	0.000281 mg/m^3	**1.4**	
Mixing and loading (pot-man) Risk assessment according to Model 4 Consumer product painting,TNsG on Human Exposure, 2002.	**Tier 1** no PPE	Systemic via dermal route	0.0881 mg/kg bw/day	1761	**999**
		Systemic via inhalation route	0.008 mg/kg bw/day	238	
		Local inhalation concentration	0.07619 mg/m^3	**381**	
	Tier 2a Protective gloves; single coverall (4 % penetration), Facial mask with APF 10	Systemic via dermal route	0.0086 mg/kg bw/day	171	**195**
		Systemic via inhalation route	0.00048 mg/kg bw/day	24	
		Local inhalation concentration	0.007619 mg/m^3	**38.1**	
	Tier 2b Protective gloves; double coverall (1 % penetration), Facial mask with APF 10	Systemic via dermal route	0.0066 mg/kg bw/day	132	**155**
		Systemic via inhalation route	0.00048 mg/kg bw/day	24	
		Local inhalation concentration	0.007619 mg/m^3	**38.1**	
	Tier2c Protective gloves; double coverall (1 % penetration), Facial mask with APF 40	Systemic via dermal route	0.0066 mg/kg bw/day	132	**138**
		Systemic via inhalation route	0.00012 mg/kg bw/day	6	
		Local inhalation concentration	0.00190475 mg/m^3	**9.5**	
Removal paint Risk assessment according to "HEEG Opinion on the paper by Links	**Tier 1** no PPE	Systemic via dermal route	0.032724 mg/kg bw/day	654	**2828**
		Systemic via inhalation route	0.043462 mg/kg bw/day	2173	
		Local inhalation concentration	0.695385 mg/m^3	**3477**	
	Tier 2	Systemic via dermal route	0.004041 mg/kg bw/day	81	**135**

et al. 2007 on occupational exposure during application and removal of antifouling paints" that was endorsed at TM IV 2012	waterproof overalls, strong protective gloves, Facial mask with APF 40	Systemic via inhalation route	0.001087 mg/kg bw/day	53.4	
		Local inhalation concentration	0.017385 mg/m³	**87**	
Grit fillers Risk assessment according to "HEEG Opinion on the paper by Links et al. 2007 on occupational exposure during application and removal of antifouling paints" that was endorsed at TM IV 2012	**Tier 1** no PPE	Systemic via dermal route	0.117397 mg/kg bw/day	2348	**7433**
		Systemic via inhalation route	0.101694 mg/kg bw/day	5085	
		Local inhalation concentration	1.62711 mg/m³	**8136**	
	Tier 2a Facial mask with APF 40	Systemic via dermal route	0.055467 mg/kg bw/day	1109	**1236**
		Systemic via inhalation route	0.002542 mg/kg bw/day	127	
		Local inhalation concentration	0.040678 mg/m³	**203**	
	Tier 2b The same exposure and type of PPE and RPE as the sand blasting worker	Systemic via dermal route	0.004041 mg/kg bw/day	0.81	**135**
		Systemic via inhalation route	0.001087 mg/kg bw/day	53.4	
		Local inhalation concentration	0.017385 mg/m³	**87**	

Arch, Dummy product 2%					
Exposure Scenario		**Exposure route**	**Estimated exposure**	**Exposure % of AEL**	**Total systemic exposure % of dermal and inhalation AELs**
Net coating	**Tier 2a**	Systemic via dermal route	0.0475 mg/kg bw/day	951	**955**

Risk assessment according to Model 4 – Professionals: Aquaculture (TNsG, 2002) **Assuming 1% dermal absorption**	Protective gloves	Systemic via inhalation route	0.00008 mg/kg bw/day	4	
		Local inhalation concentration	0.004 mg/m^3	**20**	
	Tier 2b (protective gloves, single coverall (4 % penetration)	Systemic via dermal route	0.0051 mg/kg bw/day	102	**106**
		Systemic via inhalation route	0.00008 mg/kg bw/day	4	
		Local inhalation concentration	0.004 mg/m^3	**0.8**	
	Tier 2c (protective gloves, double coverall (1 % penetration)	Systemic via dermal route	0.0038 mg/kg bw/day	76	**80**
		Systemic via inhalation route	0.00008 mg/kg bw/day	4	
		Local inhalation concentration	0.004 mg/m^3	**0.8**	
Net deployment Risk assessment according to Model 2 – Professionals: installing fish cages… (TNsG, 2002) **Assuming 1% dermal absorption**	**Tier 2a** Protective gloves	Systemic via dermal route	0.0078 mg/kg bw/day	155	**155**
		Systemic via inhalation route	---		
		Local inhalation concentration	---		
	Tier 2b (protective gloves, single coverall (4 % penetration)	Systemic via dermal route	0.0005 mg/kg bw/day	10	**10**
		Systemic via inhalation route	---		
		Local inhalation concentration	---		

Products for antifouling paint.
With none of the four products - [redacted] ([redacted] [redacted]
([redacted] [redacted] [redacted] or [redacted] ([redacted] – is the exposure acceptable from spray application but the risk for painting with brush and roller is acceptable for all four products when relevant protective equipment is used. However, a risk is identified for removal of these paints based on the current data and calculations.

When RMS evaluated the dummy product, containing 4% copper pyrithione, the assumption was that the dermal absorption was 0.5 or 1 %. When 0.5 % dermal absorption was assumed,

the brush and roller scenario gave acceptable risks if relevant protection equipment was used but there was a risk for removal of the paint. The exposure during spray application exceeded the AELs but to a small extent (109 %), so with a lower percentage of copper pyrithione in the product it would probably be no risk for spray application. It should be noted that RMS has followed the HEEG recommendations. In some scenarios the use of the 75th percentile was recommended. However, as only the 90th percentile values were available to RMS these values have been used which is a conservative way of doing the calculation. Moreover, HEEG recommended that values from different studies should be pooled before the values were used. This has not been done in this report due to lack of time. When the products are evaluated at the product authorisation stage the outcome might therefore be different and more products and scenarios might be acceptable.

The ancillary worker work together with the sprayer and as the spraying scenario was found to be unacceptable the ancillary worker scenario has not been included in this table. However the calculations can be found in the Documents II BC for the different products. There would not be any risk for the ancillary worker as long as the paint spraying scenario is without risk and the ancillary worker wears the same type of protection as the paint sprayer.

Duration and frequency of the tasks performed by the potman are directly correlated to the tasks done by the sprayer. However the potman will get a higher dermal exposure than the sprayer.
It can be assumed that the grit filler get the same exposure as the sand blasting person if he uses the same type of PPE and thereby the grit filler scenario is covered by the sand blasting scenario.

Dummy product 2% for net coating
The two scenarios; net coating and deployment of the treated nets gave acceptable risk if relevant protection equipment was used and provided that the dermal absorption for the product does not exceed 1%.

2.2.2.3 Exposure of non-professionals

Table 2.2.2.3 The potential exposure to non-professional users

For a scenario to be accepted the total systemic exposure has to be ≤ 100% of dermal and inhalation AELs and also ≤ 100% of the local inhalation AEL. The values in the acceptable scenarios have been underlined.

Arch, Dummy product 4 %					
Exposure Scenario		**Exposure route**	**Estimated exposure**	**Exposure % of AEL**	**Total systemic exposure % of dermal and inhalation AELs**
	Tier 1 no PPE	Systemic via dermal route	0.0644 mg/kg bw/day	1288	**1291**

Painter using brush and roller Risk assessment according to Links et at, 2007. **Assuming 1% dermal absorption**		Systemic via inhalation route	0.0000625 mg/kg bw/day	3	
		Local inhalation concentration	0.002 mg/m^3	**10**	
	Tier 2a long-sleeved shirt and trousers or skirt and shoes	Systemic via dermal route	0.0552 mg/kg bw/day	1103	**1107**
		Systemic via inhalation route	0.0000625 mg/kg bw/day	3	
		Local inhalation concentration	0.002 mg/m^3	**10**	
	Tier 2b long-sleeved shirt and trousers or skirt and shoes and rudimentary/ household gloves	Systemic via dermal route	0.0203 mg/kg bw/day	406	**409**
		Systemic via inhalation route	0.0000625 mg/kg bw/day	3	
		Local inhalation concentration	0.002 mg/m^3	**10**	
Painter using brush and roller Risk assessment according to Links et at, 2007. **Assuming 0.5% dermal absorption**	**Tier 1** no PPE	Systemic via dermal route	0.0322 mg/kg bw/day	644	**647**
		Systemic via inhalation route	0.0000625 mg/kg bw/day	3	
		Local inhalation concentration	0.002 mg/m^3	**10**	
	Tier 2a long-sleeved shirt and trousers or skirt and shoes	Systemic via dermal route	0.0276 mg/kg bw/day	552	**555**
		Systemic via inhalation route	0.0000625 mg/kg bw/day	3	

		Local inhalation concentration	0.002 mg/m³	**10**	
	Tier 2b long-sleeved shirt and trousers or skirt and shoes and rudimentary/ household gloves	Systemic via dermal route	0.0,0102 mg/kg bw/day	203	**206**
		Systemic via inhalation route	0.0000625 mg/kg bw/day	3	
		Local inhalation concentration	0.002 mg/m³	**10**	
Removal paint Risk assessment according to "HEEG Opinion on the paper by Links et al. 2007 on occupational exposure during application and removal of antifouling paints" that was endorsed at TM IV 2012	**Tier 1** No PPE	Systemic via dermal route	Not expected		**94**
		Systemic via inhalation route	0.001875 mg/kg bw/day	94	
		Local inhalation concentration	Not expected		

[redacted]					
Exposure Scenario		**Exposure route**	**Estimated exposure**	**Exposure % of AEL**	**Total systemic exposure % of dermal and inhalation AELs**
Painter using brush and roller Risk assessment according to	**Tier 1** no PPE	Systemic via dermal route	0.0387 mg/kg bw/day	774	**778**
		Systemic via inhalation route	0.0000627 mg/kg bw/day	3	
		Local inhalation concentration	0.002 mg/m³	**10**	

Links et at, 2007. **Assuming 1% dermal absorption**	**Tier 2a** long-sleeved shirt and trousers or skirt and shoes	Systemic via dermal route	0.0332 mg/kg bw/day	664	**667**
		Systemic via inhalation route	0.0000627 mg/kg bw/day	3	
		Local inhalation concentration	0.002 mg/m^3	**10**	
	Tier 2b long-sleeved shirt and trousers or skirt and shoes and rudimentary/ household gloves	Systemic via dermal route	0.0122 mg/kg bw/day	244	**247**
		Systemic via inhalation route	0.0000627 mg/kg bw/day	3	
		Local inhalation concentration	0.002 mg/m^3	**10**	
Removal paint Risk assessment according to "HEEG Opinion on the paper by Links et al. 2007 on occupational exposure during application and removal of antifouling paints" that was endorsed at TM IV 2012	**Tier 1** No PPE	Systemic via dermal route	Not expected		**<u>95</u>**
		Systemic via inhalation route	0.00189375 mg/kg bw/day	95	
		Local inhalation concentration	Not expected		

The applicant foresees a use of [redacted] by non-professionals using the product on private leisure craft. Due to the product's classification as corrosive to eyes (Xi; R41) and sensitising (Xi; R43) the product cannot in principle be authorized for non-professional use since this group of users is assumed to have no means of protection from exposure in the form of protective clothing or equipment (TNsG on Annex I inclusion, 3.1.1, p 19). However, as risk assessments indicate that most antifoulant substances will cause too high risk for use by amateurs (with no PPE) and we need to have some antifouling paints for amateur use, it has

been decided to generally make an exception for antifouling substances and allow the use of products containing this type of substance if the products are sold with suitable gloves that decrease the risk to an acceptable level. When amateurs use gloves, the risk for sensitization can also be ignored, at least when the substance isn't volatile. However, both [redacted] and the dummy product containing 4% copper pyrithione caused a risk by exceeding the acceptable exposure (short term dermal AEL0 0.005 mg/kg bw/day) during application with brush and roller, even when light clothing with 50 % penetration and household gloves were used and therefore these products do not fulfil the conditions for authorisation even according to the exceptional conditions agreed between CAs.

2.2.2.4 Incidental exposure of non-professionals/bystanders

Secondary exposure to antifouling products, used by professional workers, is expected to occur to bystanders if individuals working in the dock yard were to pass by or stop to watch a spraying or blasting operation. However these bystanders are also expected to be professional workers and can therefore be expected to have some protecting clothes. It was decided at TM III 2011 that no quantitative risk assessment should be performed for this group but that the product should be labelled with the phrases "unprotected persons be kept out of treatment areas".

Table 2.2.2.4 The potential exposure to children touching wet or dry paint
For the exposure to be acceptable the values has to be ≤ 100% of ARfD or ≤ dermal short-term AEL

[redacted] **4.01 % copper pyrithione and 0.6 % dermal absorption**					
Exposure Scenario		**Exposure route**	**Estimated exposure**	**Exposure % of ARfD**	
Toddler touching wet paint on a boat	**Tier 1**	Systemic via dermal route	0.0254127 mg/kg bw/day	**508 %** of short-term dermal AEL (0.005 mg/kg bw/day)	
		Systemic via inhalation route	Negligible		
Toddler touching wet paint on a boat and then hand –to-mouth contact		Systemic via oral rout	0.423545	**2112 %** of ARfD (0.02 mg/kg bw/day)	
Toddler touching dry paint	**Tier 1**	Systemic via dermal rout	**0.00060994**	**12.2 %** of short-term dermal AEL (0.005 mg/kg bw/day)	

		Systemic via inhalation route	Negligible		
Toddler touching dry paint on a boat And then hand –to-mouth contact	**Tier I**	Systemic via oral route	0.05524778	**276 %** of ARfD (0.02 mg/kg bw/day)	
	Tier 2 Refinement based on leaching rate of copper pyrithione	Systemic via oral route	0.0014375 mg/kg bw/day	**7.2 %** of ARfD (0.02 mg/kg bw/day	

When [redacted] containing 4.01 % copper pyrithione is used by non-professionals there is a risk that small children touch the newly treated and still wet area on the boat or touch the dry paint and after that lick their hands. The risk assessment of toddlers touching wet paint with subsequent hand-to-mouth transfer indicated high risks and children must therefore not be allowed to touch the wet paint. Touching dry paint was found to be without risk. The Dummy product 4 % was also intended for non-professional use and at the product authorisation step a calculation has to be done with the dermal absorption and the copper pyrithione concentration for the specific product.

Bystanders are not supposed to come in contact with the nets used for aquaculture. The use of copper pyrithione treated nets may result in exposure of copper pyrithione to fish and shellfish. RMS has done a rough calculation showing that the possible exposure from eating fish or oysters is well below the ADI for copper pyrithione.

2.2.3 Environmental Risk Assessment

For the environment, we present a risk assessment for antifouling products which release copper pyrithione and which in turn gives rise to the relevant metabolite 2-pyridinesulfonic acid (PSA). Both copper pyrithione and PSA are risk assessed, but not the copper ion. Today, most antifouling paints on the market are based on copper ion as the major active substance, and an evaluation of this ion is certainly needed for a product authorisation. For copper ion we refer to ongoing EU work in the CAR for copper ion as biocide PT 8 and 21.

2.2.3.1 Fate and distribution in the environment

In water solutions, copper- and zinc pyrithione has the potential to appear as many different species of metal chelates with the pyrithione (Figure 2.2.3-1). This type of chemical speciation between ionic and neutral entities is not unique to pyrithiones (TGD, part II, Appendix XI), but has previously been studied for other organometal compounds, for instance tributyltin in which case it turned out that the understanding of fundamental properties such as the octanol–water partition coefficient (K_{OW}), and the particle–water distribution coefficient (K_d) was greatly improved by accounting for properties of the specific species present in the water.

The species pattern is a function of the concentrations of chelating metal ions (mainly from the transition metals copper, zinc, iron, manganese etc), the total concentration pyrithione, and the formation constant for the species. In natural waters where the total pyrithione concentration is much lower than the chelating metal ions, the species pattern is thereby potentially influenced by the background concentration of the chelating metals, and pH.

Theoretical calculations of the speciation pattern have been done by use of the software CHEAQS PRO (CAR CPT PT 21, API, Doc III A7.1.1.2.4/Kramer KJM, 2008). Free pyrithione (PT^-) was predicted to be the dominating species under essentially all scenarios representable to realistic conditions in the environment. The copper pyrithione complexes ($CuPT_2$, $CuPT^+$) were only significant under extreme conditions, for instance when the concentration of total Cu was above 6.4 mg/l and total pyrithione was above 7.9 µg/l, which probably represent conditions very close to a boat hull painted with copper- and pyrithione-containing antifouling paint, or even on/in the paint. There are, however, indications from the open research literature, that more ions than free pyrithione exist in significant amounts in marine water solutions even at low concentrations. This statement is based on results from experiments with pyrithione salts, where researchers were able to detect the intact $CuPT_2$ complex using LC-MS.

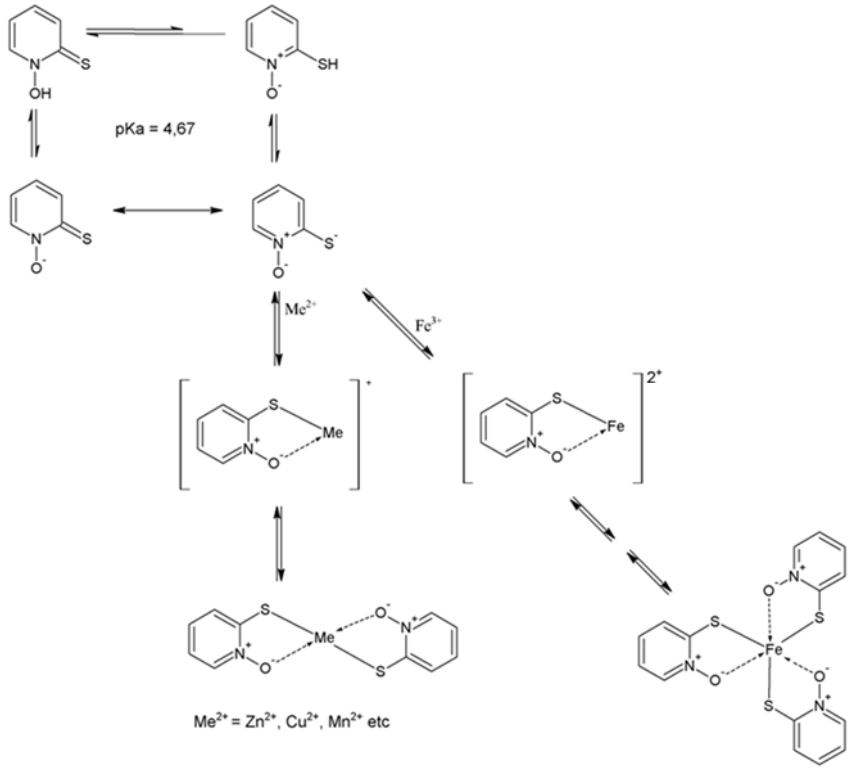


Figure 2.2.3-1. Speciation of pyrithione in aqueous solution. The tautomers of free pyrithione indicate it is has acid–base properties. Illustration and pK_a adopted from Doose (2003). Specific metabolites formed under aerobic and anaerobically conditions are not shown here.

Fate and distribution of zinc pyrithione, copper pyrithione, and sodium pyrithione is expected to be influenced by the properties of all pyrithione species which are formed in the environment. And since this species pattern is a function of the environmental conditions, it is

expected that all three pyrithione salts, when diluted, behave almost identically. The interpretation of all fate studies supports this expectation. For instance, in soil and sediment studies, the sorption strength (K_{OC}) was pH-dependent in similar ways for all three salts.

When testing the pyrithiones in various Ready biodegradability tests, copper pyrithione (OECD 301 B and C) and zinc pyrithione (OECD 301 B) were not readily biodegradable. This is due to the fact that suspensions of solid substances were tested, and the soluble (degradable) concentrations were too low to generate the requested amount of inorganic carbon within the time limits. The salts simply dissolve to slow. When sodium pyrithione which has much higher water solubility was tested (OECD 301 B) in comparable concentrations, but administered in the form of a solution, the test result was "readily biodegradable". Hence, we consider the pyrithione moiety as readily biodegradable. The relevant metabolite, 2-pyridine sulphonic acid (PSA), was also "readily biodegradable" in the tests. The test result that a substance is ready degradable does not mean that it is totally non-persistent. The degradation rate is still a finite value, perhaps corresponding to 15–150 d half-life in water as the TGD propose. Accumulation of PSA in significant amounts in all fate studies supports this.

Aerobic and anaerobic aquatic degradation studies using marine water and sediment and microcosm studies in both saltwater and freshwater systems gave further information. The conditions under which these studies were conducted simulate the environmental conditions and concentrations relating to the release of pyrithione from various types of use. Biodegradation was also assessed in a seawater die-away study with radiolabelled copper pyrithione at a low concentration. Anaerobic degradation rate is higher than the aerobic degradation rate, but overall pyrithione degrades fast in water and sediment, and the most stable metabolite is PSA. In some studies bound residues constituted 60–68% of the deposited dose in sediment, but never exceeded 70% of the added dose to the system, which would have triggered further studies (98/8/EC, Annex VI, §85). The CO_2 formation was typically below 0.9% in simulation tests with pyrithiones.

Other metabolites are formed, but these are more short-lived, and all lead to the formation of PSA. It seems reasonable to assume that the metabolites from pyrithione are ready biodegradable, and therefore pyrithiones should not be considered to be persistent (P) in a PBT assessment. Very rough 'two-point estimates' of the persistence of one such metabolite, (omadine disulfide, OMDS), can possibly be made from ecotoxicity tests where it was added as a single solute dose to the water. Such estimates indicate a single-first order dissipation half-life of 9–53 hours (0.4–2.2 days) in various aquatic ecotoxicity test systems (fish, invertebrates). The metal ion of copper pyrithione (or of zinc pyrithione and sodium pyrithione) is obviously persistent. Please refer to the CAR for copper as biocide PT 8 and 21. A typical PT 21 paint contains a higher percent copper ion than pyrithione (which is only added in low amounts as a booster biocide).

In the MAMPEC model there is no input for degradation activity of the active substance inside (sorbed to) suspended matter. It is, however, the case that PEC suspended matter is calculated from a partitioning coefficient multiplied by PEC water, so any degradation activity (rate) used for the water column will have influence on PEC suspended matter. It is

also the case that the current data set for pyrithiones (and most likely for any other chemicals) do not contain specific studies on degradation rate for the fraction biocide sorbed to suspended matter, other than that such a rate is already included (via the water column degradation activity). It can also be said that there are no guidelines to our knowledge that could be used to produce better data, in essence data that distinguish degradation activity of an active substance sorbed to suspended matter from degradation activity in the bulk water column.

In addition, a study on zinc pyrithione conducted according to the guideline OECD 303A (simulation test – activated sludge units) at a concentration of 4 µg/l in the influent also provides information on degradation. The results show that pyrithione was highly removed from the effluent water (approximately 98% removed compared to inflow) during biological wastewater treatment. Approximately 81% was shown to degrade (into CO_2, metabolites or bound residues). Based upon the levels of $^{14}CO_2$ production (39.2±5.8%) biodegradation appeared to be the major mechanism of removal.

Copper-, zinc and sodium pyrithione are hydrolytically stable in experiments with high concentrations. However, the rate is detectable but still slow in experiments with lower concentration. No clear conclusions on pH dependency was drawn since rates both increase and decrease with pH, in studies which appear to be comparable.

Pyrithione had considerable light absorptivity in the range of 290–400 nm, where photoactive solar radiation is available. Photolysis rate is faster at lower concentrations. Photolysis is very rapid in the laboratory, and probably also in the field, again leading to the final somewhat persistent degradant PSA. The quantum yield (Φ^c_E) for different pyrithione salts at 0.1–1.0 µg/l varied between 0.10 and 0.24.

Pyrithione is not expected to volatilise from waters or soils to any significant extent. Calculations according to the Atkinson calculation method indicate a half-life of 26–160 h of pyrithione in the atmosphere. The rates are based on the assumption of OH radical concentration in the TGD. The rates would be 3 times higher if based on the OH radical concentration which is given in the software used by the applicants (1.5×10^6 (radicals)/ml).

In the key study on adsorption K_{OC} for ^{14}C-pyrithione ranged from 780 to 11,000 l/kg$_{OC}$ (log K_{OC} of 2.9–4.0) (values at 1 mg/l), and typically increased with decreasing concentration (Freundlich $n < 1$), and the sorption data fitted reasonably well to the Freundlich isotherm, within the studied concentrations (0.5–4 mg/l). The adsorption and desorption log K_{OC} varied strongly with soil or sediment pH.

2.2.3.2 Effects assessment

Please refer to effects data in the tables of the LoEP.

Pyrithione

Effects were studied in both fresh- and marine organisms, and no clear difference could be seen in sensitivity, judged from a look at the summary tables in Doc II A. There was typically

a high variability in the effect data, and much of this is explained by the degree of degradation of the test substance, where the fresh active substance is the most toxic. An illustration of this was given from the 7-days tests with *Lemna gibba* where the EC50 values increased roughly by a factor of 10 when comparing three tests where the test solution was replaced, respectively: 7 times per day (lowest EC_{50}), once a day (intermediate EC50), and a static experiment (highest EC_{50}).

The key study for acute toxicity to fish was done with *Pimephalis promelas* and gave a LC_{50} mortality of 2.6 µg/l (TWA). The study set up was flow through, and used dechlorinated tap water.

The key study for acute toxicity to invertebrates was done with *Mysidopsis bahia*, and gave a 96-h LC_{50} mortality of 1.6 µg/l (TWA). The study set up was flow through (6.3 replacements per 24 h) and natural sea water diluted with tap water.

The key study for acute and chronic toxicity to algae was carried out with *Skeletonema costatum,* and a geometric mean of TWAs for NOECs from four *Skeletonema* studies was considered most relevant (0.176 µg/l). The study set up was static for all *Skeletonema* tests.

The **acute toxicity** tests gives EC/LC_{50} values for invertebrates and fish are within one order of magnitude (1.6–2.6 µg/l). Furthermore, the dose–response is typically steep, with NOEC values within a factor of two from the EC/LC_{50} value. The **long-term toxicity** was assessed from the multi generation algae test, which resulted in a NOEC of 0.176 µg/l (geomean of TWA from four studies). This NOEC was selected as the key endpoint for the risk assessment of aquatic pelagic organisms.

For assessment of risk to aquatic benthic organisms, the 10-days EC50 for the sediment dweller (*Hyalella azteca*) was 1.9 mg/kg ww sediment (8.5 mg/kg dw) (geomean of EC50 day 0 and day 10), and similar ECs were observed in two more sediment dweller tests.

Acute EC_{50} values were only a factor of 2 higher than the chronic LOEC for fish. This was seen both in studies from one applicant (which studied *Pimephales promelas*), and in studies with *Fundulus heteraclitus* from a (open literature. For invertebrates, the acute LC_{50} for the sea urchin *Arbacia punctulata* was very close to the chronic LOEC for the marine copepod *Acartia tonsa*. That acute and chronic effect concentrations are closely positioned can be concluded also from comparison of a single invertebrate species, since the applicants' studies with *Daphnia magna* gave a chronic LOEC of 4.9 µg/l, and an acute EC_{50} value of 22 µg/l (and acute NOEC 7.9 µg/l).

The effect of different pyrithione salts on aerobic biological sewage treatment processes was assessed in six studies, by determining inhibition of respiration of the **microorganisms** present in activated sludge following 30 minutes. The lowest EC_{50} observed was >0.32 mg/l, and the lowest NOEC was 0.032 mg/l. In a seventh study, exposure for 16 hours with pyrithione to the bacteria *Pseudomonas putida* gave an EC_{50} value of 0.22 mg/l and a NOEC of 0.063 mg/l, in essence values that are similar to the activated sludge tests.

Pyrithione tested for **terrestrial toxicity** on earthworms gave a 14-d NOEC mortality of 400 mg/kg dw (nominal). For plants, a seedling emergence test gave a NOEC of 100 mg/kg dw soil (nominal concentration), and EC_{50} was 280 mg/kg dw (nominal). The same NOEC value was also observed in for mortality of the soil dweller Collembola (*Folsomia candida*). A time-weighted average NOEC was estimated to 8.7 mg/kg dw soil (based on a subjectively selected 16 days averaging period and dissipation rate of 0.717 d^{-1}). The choice of time window for the TWA factor was based on considerations of that pyrithione has shown rapid effects in most ecotoxicity studies. Using a longer time would overestimate toxicity. In fact, the TWA factor approaches zero for longer values of time, and that is not reasonable.

For the bird Northern Bobwhite (*Colinus virginanus*) the 14-days LD_{50} was 60 mg/kg body weight, NOEC was 31.2 mg/kg body weight. The 8 days LC_{50} was 1110 mg/kg food, and no lethality (LC_0) was 492 mg/kg food. Effects on birds comprised signs of toxicity and abnormal behaviour which included: reduced reaction to external stimuli (sound and movement in reaction to the observer); ruffled appearance; lethargy; wing droop; loss of coordination; depression; prostrate posture; loss of righting reflex; reduced reaction; shallow and rapid respiration; and lower limb weakness. Similar effects as these are also seen for rats, and possibly also in fish where inflammatory masses in lateral fish muscle were observed.

PNECs were not derived for the **air compartment**, but reference data for inhalation toxicity to humans are available from the toxicological section. The physicochemical properties of pyrithione, and the expected emission routes from biocidal use, do not suggest that this substance will pose a risk to the atmosphere.

A very high BCF value which was observed in one of the API studies may be due to sorption of pyrithione (and/or bound residues or even inadvertently formed pyrithione disulfide) to fish food which according to BCF guidelines shall be removed within 30 minutes (which it probably was not).

A typical value for BCF in fish is 7.7 l/kg ww or log BCF = 0.88 log (l/kg ww). For BCF in invertebrates the typevalue is 8.0 l/kg ww or log BCF = 0.91 log (l/kg ww). These typevalues are one to two orders of magnitude lower than log BCF = 3.0, above which bioconcentration is generally considered to be of concern. It is also acceptable judged by the criteria of BCF > 2000 in the TNsG on Annex I inclusion into directive 98/8/EC.

The low BCF, combined with the relatively rapid degradation of pyrithione in natural aquatic systems (leading to lower exposure), and in vertebrates tested in the human toxicology data set indicates that the inherent properties of pyrithione makes it unlikely to reach high concentrations in aquatic species, either directly or through the food webs (**secondary poisoning**). This is further supported by the fact that in monitoring studies, so far it has not been possible to detect pyrithione in aquatic biota, in spite of the long historical use of pyrithiones.

For the derivation of PNECs, the assessment factor of 10 was used for aquatic pelagic organisms. This is motivated since long term chronic NOECs from 3 different trophic groups (fish, crustaceans, algae) are available, and short-term toxicity from additional species

(echinodermates, bivalve, tunicate) representing marine taxonomic groups does not indicate higher sensitivity:

PNEC marine = geomean of ^{TWA}NOEC (*Skeletonema*) / AF = (176 µg/l) / 10 = 17.6 ng/l.

For PNEC sediment a factor 1000 for benthic aquatic organisms (2 short term EC50s are available; three tests, but two are on the same species). The PNECsediment derived from tests with sediment living organisms, was a factor of 2 lower than that derived from the EPM (3.84 µg/kg ww) so in accordance with MOTA (version 6, appendix on PT 21, point 5.2) the test is used. Hence:

PNEC sediment = 1.9 mg/kg dw / 1000 = 1.9 µg/kg ww
PNEC sediment = 8.5 mg/kg dw / 1000 = 8.5 µg/kg dw.

For PNEC microorganisms, a factor 10 for microorganisms (motivation: NOEC values exists for OECD 209 test on respiration inhibition of STP organisms):

PNEC stp= (0.032 mg/l wet sludge) / 10 = 3.2 µg/l wet sludge.

For PNEC soil, a factor of 50 for terrestrial organisms (2 long term NOECs are available):

PNEC soil = (8.7 mg/kg dw soil) / 50 = 0.17 mg/kg dw (= 0.15 mg/kg ww).

Metabolites

For the metabolite PSA there are three acute LC_{50} for fish, *Pimephalis promelas*, *Cyprinodon variegates*, *Oncorhyncus mykiss*. The lowest LC_{50} was >46.9 mg/l (TWA). There are three acute LC_{50} for invertebrates, *Daphnia, Mysidopsis, Crassostrea*. The lowest LC_{50} was 71.6 mg/l (TWA) for *Mysidopsis*. There is one EC_{50} for acute/chronic freshwater algae *Selenastrum capricornutum* and this (120-h) EC_{50} was >32 mg/l, its NOEC was 5.46 mg/l (TWA). In this data set there are 4 taxonomic groups tested (fish, arthropods, bivalves, algae). To fulfil the TGD requirement, there should be 3 + 2 acute LC_{50} values from 5 taxonomic groups. Hence, there is one data point missing. But, in addition to the 4 taxonomic groups, there is the chronic fish NOEC which is only reported as >10 µg/l. An assessment factor of 1000 would generate a PNEC of 5.46 µg/l. This is below the NOEC from the chronic fish test (>10 µg/l). From this taken together it seems over conservative to use a higher assessment factor than 1000. The PNECmarine water for PSA is thereby 5.46 µg/l based on an assessment factor of 1000 and the algae NOEC (TWA).

^{PSA}PNEC marin = (5.46 mg/l) / 1000 = 5.46 µg/l.

For sediment, no tests with sediment organisms was available, so the equilibrium partitioning model was used to extrapolate toxitity from water to sediment

^{PSA}PNEC sediment = ^{EPM}PNEC sediment =
= (Ksediment_water / RHOsediment) × PNECwater × 1000

= (25.9 m^3 w/m^3 ww soil / 1150 kg ww soil/m^3 ww soil) × (5.46 µg/l) × 100
= 123 µg/kg dw (= 566 µg/kg dw).

For soil, no tests on soil living organisms was available, so the equilibrium partitioning model was used to extrapolate toxitity from water to soil.

^{PSA}PNEC soil = ^{EPM}PNEC = PNEC_soil
= (Ksoil_water / RHOsoil) × PNECwater × 1000
= (30.2 m^3 w/m^3 ww soil / 1700 kg ww soil/m^3 ww soil) × (5.46 µg/l) × 100
= 97 µg/kg dw (= 110 µg/kg dw).

For sewage treatment plants, no tests were available, so the same PNEC as for pyrithione was assumed.

^{PSA}PNEC stp = ^{Pyrithione}PNEC stp = 3.2 µg/l.

For the metabolite copper ion we refer to the CAR for copper as biocide PT 8. In the version (April 2008) the PNEC aquatic (fresh water) for copper ion (+II) is set to 2.68 µg/l. This was increased to 7.8 µg/l in the Assessment Report for copper carbonate by RMS France 2011.

The evidence regarding the safety of pyrithiones **with regards to endocrine disruptive effects** was reviewed with the following outcome:

Structural evidence for the active substances sodium pyrithione, zinc pyrithione and copper pyrithione and their environmental complexes and metabolites show no obvious similarities with those of known endocrine disrupting compounds for vertebrate sexual hormone systems – typical features of the latter such as alkyl/aryl backbones with terminal hydroxyl groups and secondary hydroxyl/keto groups are entirely absent in the pyrithiones.

Some effects that were seen in the 2-generation reproduction study in rats with copper pyrithione could however be endocrinal effects. These were 1) a substantial decrease (26% compared to control animals) in the relative uterus weight in the highest dosage group in F1-generation, and 2) a decreased relative thymus weight in F2-pups at the highest dosage level in both sexes (24% in males compared to control animals, 6% in females).

In developmental toxicity studies with zinc pyrithione some possible endocrine effects were seen like; increase of post-implantation loss and resorption as well as rare malformations (not depending on maternal toxicity) like cleft palate, microglossia, malformed testis and limb malformations.

Guidelines are under development from the EU Commission. Therefore we conclude that today, like for most chemicals, no firm conclusions can be drawn for the pyrithiones regarding risk to man or the environment through endocrine disruption.

The most widely agreed definition of endocrine disruptors (IPCS/WHO, 2002) requires that there is an at least plausible link between the endocrine mode of action and adverse effects in organisms and/or populations. No such plausible link has been established for copper pyrithione.

2.2.3.3 PBT assessment

Pyrithione does not meet the P-criteria. In ready tests, copper pyrithione and zinc pyrithione are not readily degradable, but sodium pyrithione is. The pyrithione moiety is therefore considered as readily degradable. And in simulation tests (more representative concentration of pyrithione salts in systems of water–soil, water–sediment) the pyrithione degrades to many metabolites which all transforms into the slightly more persistent metabolite PSA. Pyrithione salts fulfils the T-criteria since chronic NOECs are far under 10 µg/l. Pyrithione did not exceeded the B-criteria, and is not B.

The metabolite PSA is ready degradable and therefore does not meet the P-criteria. Its lowest not NOEC is 5.46 mg/l, which is above the criteria 10 µg/l, and therefore PSA is not T. Studies on bioaccumulation is missing, but based on K_{OW}, and its degradability indications are it is not B.

Since other metabolites degrade in a pathway which eventually leads to formation of PSA, it seems reasonable to assume the other metabolites are not P.

Some metabolites may be very toxic, for instance the pyrithione disulfide (OMDS), which has a 120-h NOEC of 80 µg/l (nominal) for algae, NOEC mortality for fish of 11 µg/l (nominal), and 4 µg/l (nominal) for an invertebrate, and therefore clearly meets the T-criteria (<10 µg/l) even when based on nominal concentration. However, all ecotoxicity tests (algae, aquatic plants, fish, invertebrates) typically and without exceptions demonstrate that toxicity decline (higher NOEC, EC) when test solutions are left to degrade. Thereby illustrating that the more long-lived metabolites are less toxic than pyrithione.

The metal ion of copper pyrithione (or of zinc pyrithione and sodium pyrithione) is obviously persistent. Please refer to the CAR for copper as biocide PT 8 and 21. In addition to the load of metal ion from the metal pyrithione salt, a typical PT 21 paint contains a higher percent copper ion (as a primary active substance) than pyrithione (which is only added in low percents as booster biocides). However, as being a metal, this metabolite is exempted from the PBT-assessment, which only concerns, organic- and organometallic compounds (REACH, i.e. EC 253/2011).

2.2.3.4 Exposure assessment and risk characterisation

The risks for the environment are characterized by comparing the toxicity of the substance (PNEC) with the exposure estimates (PEC).

Regarding the product-specific scenarios for the biocidal uses of copper pyrithione, four real products (“[redacted] from [redacted] “[redacted] from [redacted] “[redacted] from [redacted] “[redacted] from [redacted] were evaluated using methodologies

outlined in the emissions scenario document for PT 21 (OECD nr 13, ENV/JM/MONO(2005)8). These include calculations with the MAMPEC model (Marine Antifouling Model for PEC). Conclusions were drawn by comparing the exposure- and risk assessments to values which were derived for a dummy product:

Exposure was estimated due to use of a dummy product (antifouling paint with 4% copper pyrithione) with a theoretically estimated leach rate (the "CEPE mass balance method" which is the agreed method to use for active substance evaluation). Since the leaching rate is a crucial parameter for exposure assessment, and the agreed method for active substance evaluation is to use a theoretical leach rate (and hence no leaching rate studies were submitted), no attempt is made to assess the real products exposure and risks.

Acceptable risks due to its in-service life use were identified in OECD Commercial harbour (water, sediment 1 year, suspended matter), OECD Marina (water, sediment 1 year, suspended matter), and OECD Shipping lane (suspended matter). The active substance content is similar (4% or lower) in the products which are assessed (Appendix II). Thereby probably also the leaching rate is lower in the four real products. No unacceptable risks are therefore to be expected for the four real products, when differences in leaching rate were accounted for by the simplified assumption that leaching rate is only dependent on concentration in the paint.

Acceptable risks for surface water recipients (the OECD Commercial Harbour, the OECD Marina) and sediment therein, were also modelled for scenarios where emissions comes from construction/building, maintenance and repair, and removal of the PT21 paint. The scenario was for a dummy product paint with an assumed content of 4% copper pyrithione, and thereby the four real products, which have a maximum content of 4% or lower must also show acceptable risks (Table 2.2.3.4-2)4. The PEC-modelling approach used for this, builds on the assumption of instantaneous release of biocide from the particle into the water. This was thoroughly discussed at the TM-meetings, and many drawbacks were identified, for instance that accumulation of biocide-containing particles in bottom sediment is disregarded. However it was finally used as a harmonised approach for all antifoulants (MOTA version 6, PT 21 appendix point 1.4 and 5.3).

The handling of paint during maintenance and repair (Figure 2.2.3.4), as well as new building, however, lead to unacceptable risks for soil and groundwater on the sites where the boats are handled (Table 2.2.3.4-3 is for pyrithione[5]).

4 The PEC values in this table are for a fresh water recipient of an STP (dilution factor 10 in TGD). Emissions from a STP to seas would be even more diluted (dilution factor 100 in TGD) and so the conclusion of acceptable risk is valid also for marine scenario (OECD Commercial Harbour, OECD Marina, OECD Shipping Lane).

[5] similar risks are illustrated for PSA, but is only shown in Doc II BC in order to keep Doc I short

Figure 2.2.3.4. Emission of paint particles onto soil during maintenance and repair. (Photo by Britta Eklund, Stockholm University).

Regarding risk for groundwater contamination, the pyrithione PEC values from different use of dummy products with an assumed content of 4% copper pyrithione indicate unacceptable risk (>0.1 µg/l) in most scenarios. For the so called Worst-case scenarios, the PEC values were 1.9–52 µg/l, and for the so called Typical-case scenarios, the PEC values were 2.0–10 µg/l (fewer scenarios, hence more narrow range). Possible refinements were discussed at the biocide TM and CA-meetings for all antifoulants as a group, and specific conditions for uptake decisions using risk mitigation measures are what has been discussed so far (August 2013).

An e-consultation on the fish net scenario was initiated at TM III, 2011, and at present (2014) there is an ongoing discussion at the WG meetings of what a final harmonised scenario should be. There are also further questions under discussion such as fish health, residues in fish, emissions on land, leach data derivation. Our applicant's scenario is kept in this draft final CAR for documentation only and, due to that the ongoing discussions on harmonisation (in May 2014 the guidance document is on a 'to do list' in ECHA's WG ENV meeting), cannot be used for decisions on safe use for active substance approval.

For PEC air, see next chapter on cumulative PEC estimates.

Table 2.2.3.4-1. July 2013: Environmental risk assessment of in-service life for biocidal products with copper pyrithione.

		PEC	PNEC	RQ	PEC	PEC	PEC	PNEC	RQ	RQ	RQ	MAMPEC filenename
Leach rate 2.88 µg/cm2/day	Load to system	Marine water	Marine water	Marine water	Marine sed. 1 yr	Marine sed. 10 yr	Marine sed. susp	Marine sediment	Marine sed. 1 yr	Marine sed. 10 yr	Marine sed. susp	filename
Scenario	g/d	µg/l	µg/l	-	µg/g dw	µg/g dw	µg/g dw	µg/g dw	-	-	-	-
Copper pyrithione												
OECD Commercial Harbour	2870	2.6E-03	1.8E-02	1.5E-01	4.6E-05	3.5E-04	7.4E-04	8.5E-03	5.4E-03	4.1E-02	8.6E-02	CPT_2.88_CoHa_T1_W.txt
OECD Marina (246 boats)	220	2.4E-03	1.8E-02	1.3E-01	1.3E-04	5.9E-04	6.7E-04	8.5E-03	1.5E-02	7.0E-02	7.9E-02	CPT_2.88_Mari_T1_W.txt
OECD Shipping Lane	890	8.1E-05	1.8E-02	4.6E-03	2.9E-07	2.9E-06	4.8E-05	8.5E-03	3.4E-05	3.4E-04	5.7E-03	CPT_2.88_ShLa_T1_W_F3.txt
Metabolite PSA												
OECD Commercial Harbour	2870	2.6E-03	5.5E+00	4.7E-04	2.5E-05	7.2E-05	7.3E-05	5.7E-01	4.5E-05	1.3E-04	1.3E-04	PSA_2.88_CoHa_T1_W.txt
OECD Marina (246 boats)	220	2.4E-03	5.5E+00	4.3E-04	1.3E-05	6.0E-05	6.8E-05	5.7E-01	2.3E-05	1.0E-04	1.2E-04	PSA_2.88_Mari_T1_W.txt
OECD Shipping Lane	890	8.1E-05	5.5E+00	1.5E-05	3.0E-08	2.9E-07	4.9E-06	5.7E-01	5.2E-08	5.0E-07	8.5E-06	PSA_2.88_ShLa_T1_W_F3.txt

Table 2.2.3.4-2 Risk quotients (RQ = PEC/PNEC) for freshwater recipients (STP recipients) due to emissions vis STP originating from new buidling, maintence and repair of paints with 4% a.s. Worst- and typical case for each scenario.

Table# in ESD PT21	Pyrith. $Clocal_{water}$ (mg/l)	Pyrith. $Clocal_{sed}$ (µg/kg ww)	PSA $Clocal_{water}$ (mg/l)	PSA $Clocal_{sed}$ (µg/kg ww)	Pyrith. RQ water	Pyrith. RQ bottom sedim.	PSA RQ water	PSA RQ sedim.
Table number in this appendix	3.3.7-5	3.3.7-5	3.3.7-7	3.3.7-7	-	-	-	-
4.5 "new build pleasure craft, professional"	5.5E-6 0.00**	5.5E-3 0.00**	3.0E-8 0.00**	2.4E-1 0.00**	0.31 0.00**	2.9E-3 0.00**	5.4E-03 0.00**	1.9E-04 0.00**
4.47 "removal, pleasure craft, professional"	3.0E-9 7.5E-10	3.0E-3 7.5E-4	1.6E-8 4.0E-9	1.3E-2 3.2E-3	0.17 0.04	1.6E-3 3.9E-4	3.0E-03 7.4E-04	1.1E-04 2.6E-05
4.10 "application pleasure craft, professional"	4.5E-9 1.9E-9	4.5E-3 1.9E-3	2.4E-8 1.0E-8	1.9E-2 8.1E-3	0.26 0.11	2.4E-3 9.9E-4	4.4E-04 1.9E-03	1.6E-04 6.6E-05
4.49 "removal, pleasure craft, non-professional"	5.8E-9 4.6E-9	5.8E-3 4.6E-3	3.1E-8 2.5E-8	2.5E-2 2.0E-2	0.33 0.16	3.1E-3 2.4E-3	5.7E-03 4.5E-03	2.0E-04 1.6E-04
4.12 "application, pleasure craft, non-professional"	2.1E-10 2.1E-10	2.1E-4 2.1E-4	1.1E-09 1.1E-09	8.9E-4 8.9E-4	0.01 0.01	1.1E-4 1.1E-4	2.0E-04 2.0E-04	7.3E-06 7.3E-06

** background of 0 is assumed

Table 2.2.3.4-3. Pyrithione. Risk ratios (PEC/PNEC) for soil on ship- and boatyards due to contamination via leaching of biocide from paint particles of a dummy product with 4% a.i.

Emission scenario, Table #*	% a.i.	Worst case $Clocal_{soil}$ (mg/kg dw)***	Worst case PEC/PNEC	Typical case $Clocal_{soil}$ (mg/kg dw)	Typical case PEC/PNEC
New build ship, commercial, Table 4.2	4	§	§	§	§
New build pleasure craft, professional, Table 4.5/4.6	4	0.87	**5**	**§**	**§**
M & R** (application) ship, professional, Table 4.7	4	§	§	§	§
M & R (removal) ship, professional, Table 4.44	4	§	§	§	§
M & R (application) pleasure craft, professional, Table 4.10/4.11	4	0.44	**3**	0,18	1.1****
M & R (removal) pleasure craft, professional, Table 4.47/4.48	4	0.30	**2**	0.074	0.4
M & R** (application) pleasure craft, non-professional, Table 4.12	4	0.033^	0.2	^	^
M & R** (removal) pleasure craft, non-professional, Table 4.49/4.50	4	0.93	**5**	0.040	0.2

* Table numbers refer to numbers used in Appendix IIB3.3.1 "on ESD PT21 emissions etc".

** M & R is for maintenance and repair

§ no emission to soil according to default scenario in ESD for PT21.

^ESD does not distinguish worst- and typical case for this scenario.

**** 1.1 ~1 using rounding.

2.2.3.5 Cumulative use of pyrithione salts

The environmental assessment of cumulative use shall not be used as a basis for decision on Annex 1 inclusion of biocidal active substances into directive 98/8/EC (agreed at TM III, 2011). Nevertheless, it is left open for the initiative of individual MS to perform such an assessment.

The RMS considers that the information is needed for a proper interpretation of environmental data. For instance the lag phase of biodegradation in seawater is expected to be shorter if microorganisms are adapted to a background concentration of a biocide. In the CAR, an example of this is included. One seawater degradation study close to land had a short lag phase, while a study from open sea had a longer lag phase. Possibly this is consistent with a situation where cumulative emissions of pyrithione salts give higher background exposure close to land.

Furthermore, the outcome of a cumulative assessment can be used as a worst-case exposure, and serve as an argument for not requesting additional studies. In the CAR an example illustrates this. The exposure of soil due to sludge application on fields from cumulative assessment of all pyrithione sources gave acceptable risk to soil microorganims, based on a PNEC with a high assessment factor. It thereby didn't seem meaningful to request additional studies on soil microorganism for the dossier with only emissions from PT 21 use.

Due to the fact that the pyrithione salts (zinc pyrithione, sodium pyrithione and copper pyrithione) ionise and form similar species patterns in the environment, it was appropriate to also look at the cumulative exposure of pyrithione from all possible sources. These include non-biocidal use, which makes up a significant fraction, as exemplified with data from the Product register at the Swedish Chemicals Agency[6] (where in 2008 a total of 28 tonnes pyrithione salts were used in Sweden, most of which is likely to be various biocidal use). In addition to these 28 tonnes, there are estimates of an additional 10 tonnes per year for the cosmetic use (uncertain value from NGO reports; Swedish authorities do not keep record on cosmetic use).

We expect that for the cumulative emission of pyrithione salts the largest emission routes are via municipal waste water into local recipients. By inserting measured concentration of pyrithione (1.7 µg/l and 32 µg/l), which were monitored in influent water to Swedish STPs, into appropriate TGD equations the following PECs could be calculated (Table 2.2.3.5):

- PEC in outflowing water of a TGD-scenario STP ("$C\text{local}_{eff}$", based on the fraction going to water ($F\text{stp}_{,water} = 0.02$) measured in a OECD 304A STP-simulation study)
- PEC in the recipient surface water of the "TGD-STP" (based on the dilution factor 10 for the TGD standard recipient scenario)
- PEC for the TGD-STP recipient sediment (bottom sediment and suspended sediment has the same PEC in the TGD)
- PEC in sewage sludge of a TGD STP
- PEC in agricultural and grassland soils (TGD world).

[6] this data from the Swedish product register is open to the public via http://www.kemi.se/en/Start/Statistics/

Table 2.2.3.5-1: PEC and PEC/PNEC for pyrithione in surface water and STP based on monitoring data as described in the text

Monitored conc.	Input to STP* (mg/l)	Output from STP (mg/l)	PEC in receiving water (mg/l)	PNEC (mg/l)	PEC/PNEC surface water (STP)
	$Clocal_{inf}$	$Clocal_{eff}$	$Clocal_{water}$	PNEC aq (PNECstp)	
"1.7 µg/l"	1.7×10^{-3}	3.4×10^{-5}	3.4×10^{-6}	1.76×10^{-5} (3.2×10^{-3})	0.19 (0.011)
"32 µg/l"	3.2×10^{-2}	6.4×10^{-4}	6.4×10^{-5}	" "	**3.6** (0.20)

* Monitoring data, see text.

Table 2.2.3.5-2: PEC and PEC/PNEC for pyrithione in fresh water sediment based on monitoring data as described in the text

Monitored conc.	Local PEC in freshwater sediment (mg/kg ww)	PNEC (mg/kg ww)	PEC/PNEC
"1.7 µg/l"	3.4×10^{-6}	0.0019	0.0018
"32 µg/l"	6.4×10^{-5}	"	0.034

Table 2.2.3.5-3. PEC for pyrithione in sewage sludge and PEC/PNEC for soil based on monitoring data as described in the text

Measured environmental concentraion	$Elocal_{water}^{*}$ (kg/d)	Csludge (mg/kg dw)	$Csludge_{soil1}(0)$ agricultural, grassland (mg/kg dw)	PNEC for soil (mg/kg dw)	PEC/PNEC agricultural, grassland
"1.7 µg/l"	3.40×10^{-3}	13.4	2.2×10^{-2} 8.9×10^{-1}	0.17 "	1.3×10^{-1} 5.3×10^{-2}
"32 µg/l"	6.40×10^{-2}	252	4.2×10^{-1} 1.7×10^{-1}	" "	$\mathbf{2.5}\times10^{-0}$ 9.9×10^{-1}

Where it was relevant, PEC values were also compared to the measured data for recipient surface water and recipient bottom sediment. The PEC values are for fresh water STP-recipient scenarios (since the dilution factor 10 is assumed). The monitoring study did however cover fresh, brackish and marine recipients.

The cumulative PEC in fresh water STP recipient, indicates risk (PEC/PNEC ratio was up to 3.6 when inflow to STP was set to 32 µg/l; Table 2.2.3.5-1). But in the monitoring study, all samples of recipient surface water showed concentrations below the LOD (15 ng/l), which in turn is lower than the PNEC, and therefore does not indicate risk (PEC/PNEC at highest 0.05).

Levels of pyrithione in biota are not reported from the open literature as far as RMS know, but attempts to generate monitoring data are reported. However, these samples gave no direct results regarding concentrations due to analytical difficulties.

Regarding agricultural- and grassland soils, which potentially can be contaminated via application of sewage sludge, the risk ratios due to cumulative pyrithione usage were above 1 in one scenario (Table 2.2.3.5-3) and indicate unacceptable risk if such sludge were to be used on agricultural soils.

A worst case local PECair above point source recipients is 0.43–14 pg per litre air. This PEC reflects cumulative exposure of all pyrithiones (sodium-, zinc, copper), and many sources of pyrithione, since it is based on monitored concentration in influent water to an STP. The PEC can be compared to the human 90-days NOAEC of 500 000 pg/l air. Hence, PEC/PNEC is 2.8×10^{-5}, which is far below the agreed level of protection (PEC/PNEC = 1), and thereby does not indicate risk for air breathing organisms.

2.2.4 Compliance with the environmental criteria for approval of active substance according to Annex VI of Directive 98/8/EC

Our assessment is that pyrithione is not a PBT substance. It is T, but not B or P. The metabolite PSA is neither P, nor B, nor T. The metabolite copper ion (+II) is clearly P. Regarding the assessment of B and T for copper ion, we refer to the CAR for copper as biocide PT 8 and 21. However, as being a metal, this metabolite is exempted from the PBT-assessment, which only concerns, organic- and organometallic compounds (REACH, i.e. EC 253/2011).

Exposure as estimated in established scenarios for biocidal use of pyrithione in PT 21 products gives acceptable risk to air breathing organisms.

Biocidal use of pyrithione in PT 21 products is not likely to cause high concentrations in aquatic species, either directly or through the food webs (secondary poisoning).

Exposure as estimated in established scenarios for biocidal use of pyrithione in PT 21 products gives acceptable risk to aquatic organisms in the adjacent surroundings to the recipient water[7] and sediment to in-service life use of the paints (= leaching from boat hulls). (Table 2.2.3.4).

Using the ESD scenarios, risks due to leaching from paint flakes and dust at repair- and maintenance stations (land adjacent to marinas) gives acceptable risk to recipient water and sediment.

Risks due to leaching from paint flakes, paint scrapings and dust at repair- and maintenance stations (e.g. land at marinas) gives unacceptable risk to soil and groundwater. Regarding the unacceptable risk to soil-living organisms, these must be prevented by risk mitigation

7 “wider environment” as defined in MOTA version 6, appendix on PT21 ENV, point 1.7.

measures, in accordance with finalised discussions at the CA meeting March 2014[8]. Unacceptable risks for soils are seen for several antifouling products in the EU biocide evaluation programme. The CA-document handles both generic (for all antifoulants) and substance-specific measures. One example which is mentioned is that "labels and, where provided, safety data sheets of products authorised shall indicate that application, maintenance and repair activities shall be conducted within a contained area, on an impermeable hard standing with bunding or on soil covered with an impermeable material to prevent losses and minimize emissions to the environment, and that any losses or waste containing [the substance] shall be collected for reuse or disposal". We assume one such installation could be rinse boards (Figure 2.2.4).

Figure 2.2.4. The CA-meeting March 2014 requires harmonised risk mitigation measures for to minimise emissions to the environment. Biocide associated with paint particles are emitted at land-based boat washing areas. One possible way of achieving this is regulating that antifouling paint must only be handled on rinse boards (photo).

2.2.5 List of endpoints

In order to facilitate the work of granting or reviewing authorisations, the most important endpoints, as identified during the evaluation process, are listed in Appendix I.

8 CA-meeting document (CA-March14-Doc.4.2-Final .doc) Antifouling (PT21). Way forward for the management of active substances and the authorisation of biocidal products. Publicly available.

2.3 Overall conclusions

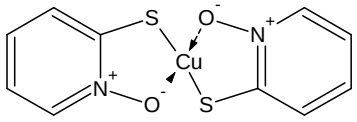
The outcome of the assessment for copper pyrithione in product-type 21 is specified in the BPC opinion following discussions at the 6th meeting of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA website.

APPENDIX I: LIST OF ENDPOINTS

Chapter 1: Identity, Physical and Chemical Properties, Classification and Labelling

Active substance (ISO Common Name)	copper pyrithione (synonym not a ISO common name)
Product-type	PT 21

Identity

Chemical name (IUPAC)	bis(1-hydroxy-1H-pyridine-2-thionato-O,S)copper
Chemical name (CA)	copper, bis[1-hydroxy-2-(1H)-pyridinethionato-O,S]-
CAS No	14915-37-8
EC No	238-984-0
Other substance No.	None
Minimum purity of the active substance as manufactured (g/kg or g/l)	950 g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	Technical copper pyrithione does not contain any impurities that are considered as relevant
Molecular formula	$C_{10}H_8N_2O_2S_2Cu$
Molecular mass	Copper pyrithione 315.86 g/mol Metabolite PSA: 159.1
Structural formula	

Physical and chemical properties

Melting point (state purity)	Decomposition upon melting at 273–280°C (>98%–98.8%)
Boiling point (state purity)	Not relevant as decomposition occurs upon melting
Temperature of decomposition	Decomposition upon melting at 273–280°C (>98%–98.8%)
Appearance (state purity)	Green odourless powder (solid) (>98%–98.8%)
Relative density (state purity)	1.80–1.86 (96.8%–98.8%)
Surface tension	Not applicable as the solubility in water is below 1 mg/l
Vapour pressure (in Pa, state temperature)	<5 x 10^{-7} Pa at 25°C by direct measurement (98.8%) 4.3 x 10^{-17} Pa at 25 ºC by extrapolation from measurements in the range 190-210°C (>98%)
Henry's law constant (Pa m^3 mol^{-1})	3.48 x 10^{-13} Pa * mol/m^3 (from extrapolated vapour pressure at 25°C and water solubilityof 39 µg/l at 6.3–6.8)
Solubility in water (g/l or mg/l, state temperature)	49 µg/l at 10°C, 60 µg/l at 20 °C and 150µg/l at 30°C in non-buffered water at pH 5.9–7.1 (99%) In buffered solutions at 25°C (99%): pH 5: 55 µg/l pH 7: 102 µg/l pH 9: 109 µg/l The differences in water solubility is not considered significant or to be attributed to any dissociation under the conditions of the test.
Solubility in organic solvents (in g/l or mg/l, state temperature)	Technical material (97.1%) in mg/l: 15ºC / 25ºC hexane <0.2 / <0.2 acetone 152 / 176 octanol 7 / 8 xylene 29 / 32 Purified material (99.5%) in mg/l: 10ºC / 20ºC / 30°C methanol 17 / 20 / 28 acetone 188 / 239 / 278
Stability in organic solvents used in biocidal products including relevant breakdown products	Showed to be stable at a concentration of 2% copper pyrithione in an antifouling paint containing >60 xylenes for two weeks at 54°C
Partition coefficient (log P_{OW}) (state temperature)	For purified material in distilled water at pH 7 and 21°C (99.0%): log P_{ow}=2.44 For technical material in distilled water at pH 5.8-6.1 and 22.5°C (>98%): log P_{ow}=2.84 No significant pH dependency expected but given the findings for the water solubility a log P_{ow} of ~2.7 at pH 5 is anticipated.
Hydrolytic stability (DT_{50}) (state pH and temperature)	Se chapter 4 below.
Dissociation constant	Copper pyrithione does not have acid or base properties.

	Moreover, a formation constant of >8.5 for the complex copper pyrithione is given in the open literature which indicates that copper pyrithione is stable in the environmentally relevant pH range. The pKa for free pyrithione is quoted as 4.67 in open literature.
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	In acetonitrile (99.0%): λ_{max} [nm] ε (l mol^{-1}.cm^{-1}) 250.1 39504 319.8 16105 570.1 89.8 In methanol (>99.9%): pH 2: λ_{max} [nm] ε (l mol^{-1}.cm^{-1}) 247 37700 321 17100 Neutral: λ_{max} [nm] ε (l mol^{-1}.cm^{-1}) 249 37400 319 17100 pH 9: λ_{max} [nm] ε (l mol^{-1}.cm^{-1}) 248 37200 320 16500
Photostability (DT_{50}) (aqueous, sunlight, state pH)	Se chapter 4 below.
Quantum yield of direct phototransformation in water at Σ > 290 nm	In solutions of 0.1–1 µg/l of these pyrithiones: Φ^c_E = 0.11 for copper pyrithione Φ^c_E = 0.14 for zinc pyrithione Φ^c_E = 0.15 for sodium pyrithione Φ^c_E = 0.11–0.24 for zinc pyrithione with 2.5 µg/l Cu^{2+} was added.
Flammability	Not highly flammable (≥98%)
Explosive properties	Not explosive (≥98%))

Classification and proposed labelling

with regard to physical/chemical data	None
with regard to toxicological data	T+; R21/22, R26, R37, R41, R48/23/25, R63 GHS: H311, H301, H330, H335, H318, H372, H361
with regard to fate and behaviour data	
with regard to ecotoxicological data	R50 GHS: H400 (M = 100), H410 (M = 100)

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	HPLC-UV
Impurities in technical active substance (principle of method)	Confidential-see the document III-A confidential Annex for the respective manufacturer.

Analytical methods for residues

Soil (principle of method and LOQ)	Pyrithione as a derivative (appropriate in relation to the residue definition Total pyrithione expressed as copper pyrithione): LC-MS/MS (LOQ 5 µg/kg)
Air (principle of method and LOQ)	Copper pyrithione (proposed residue definition): HPLC-UV (LOQ 0.58 µg/m^3).
Water (principle of method andLOQ)	Pyrithione as a derivative (appropriate in relation to the residue definition Total pyrithione expressed as copper pyrithione): LC-MS/MS (LOQ 0.1 µg/l for drinking and sea water)
Body fluids and tissues (principle of method and LOQ)	2-pyridinethiol-1-oxide glucoronide (major rat metabolite; proposed residue definition): LC-MS/MS (LOQ 50 µg/l) Due to rapid metabolism and excretion of copper pyrithione in the rat no residue definition is proposed for body tissues
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Not relevant as exposure is not expected
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	In general no method is required as exposure is not expected. For fish and shellfish a tentative residue definition as Total pyrithione expressed as copper pyrithione has been proposed by RMS in the absence of data showing no exposure at all. For fish: Pyrithione as a derivative (appropriate in relation to the proposed tentative residue definition): LC-MS/MS (LOQ 0.5 µg/kg) No more data has been requested for shell-fish as the status on the requirement for a method at all is unclear.

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	Following oral administration, copper pyrithione disassociates to liberate Cu and the pyrithione moiety, which are then absorbed independently. Absorption is slow but extensive through the GI tract. Oral absorption of pyrithione is 80–90 %.
Rate and extent of dermal absorption:	Copper pyrithione is slowly absorbed via the skin. Human skin *in vitro* (copper pyrithione dissolved in ethanol, 16mg/ml, 1.6% w/v): *ca* 3 %. For the different products evaluated the following dermal absorption has been used for calculations (discussed and agreed at TMIII 2011: [redacted] Dermal absorption 3% Dermal absorption 0.6 % Dermal absorption 5% Dermal absorption 3 %
Distribution:	The highest tissue levels were observed in liver and kidneys. A high $T_{1/2}$ value in whole blood and spleen indicates retention of blood cells. Radioactivity was also found in spleen, lungs, skin, heart, and adrenals.
Potential for accumulation:	No potential for accumulation.
Rate and extent of excretion:	Copper pyrithione is extensively and rapidly excreted (>80 % in 48 h, >95 % in 72 h), principally via the urine as metabolites (65–94 %), faecal excretion being a minor route of excretion (2.6–20 %).
Toxicologically significant metabolite(s)	Major metabolite: 2-pyridinethiol-1-oxide-S-glucuronide. (read across studies with zinc pyrithione and Na PT)

Acute toxicity

Rat LD_{50} oral	200–500 mg/kg bw
Rat LD_{50} dermal	400–2000 mg/kg bw
Rat LC_{50} inhalation	0.07 mg/L (4 h, nose only)
Skin irritation	Not irritating
Eye irritation	Corrosive
Skin sensitization (test method used and result)	Not sensitising (maximisation test and Buehler test)

Repeated dose toxicity

Species/ target / critical effect	Rat (oral): mortality, hind limb paralysis, muscle atrophy and degeneration, emaciation, body weight decrease and effect on kidneys. Rat (dermal): reduced bw gain and food consumption in females. Rat (inhalation): mortality, reduced bw, decreased thymus and spleen weight, bronchial interstitial pneumonitis, increased lactate dehydrogenase in the BALF.

Lowest relevant oral NOAEL / LOAEL	Acute NOAEL = 2 mg/kg bw/day based on effects seen after 2.5 hours in a 90 day rat study with sodium pyrithione. Medium term NOAEL = 0.5 mg/kg bw/day estimated by taken all available medium time pyrithione studies in account (7 with copper pyrithione, 3 with zinc pyrithione and 5 with sodium pyrithione, 13 on rats, one on rabbits and one on dogs). Long term NOAEL = 0.25 mg/kg bw/day based on LOAELs from two 2 year sodium pyrithione rat studies.
Lowest relevant dermal NOAEL / LOAEL	Medium term NOAEL = 100 mg/kg bw/day based on a 90 day rat study with zinc pyrithione. Long term NOAEL = 40 mg/kg bw/day based on 80 week cancer study on mouse.
Lowest relevant inhalation NOAEL / LOAEL	Systemic medium term NOAEC = 0.0015 mg/L based on a 28 day rat study. Local medium term NOAEC = 0.005 mg/L based on a 28 day rat study.

Genotoxicity

Genotoxicity	Clastogenic *in vitro* Not genotoxic *in vivo*

Carcinogenicity

Species/type of tumour	Rat / no evident test substance-induced tumour increase
lowest dose with tumours	Not applicable

Reproductive toxicity

Species/ Reproduction target / critical effect	Rat and Rabbit: It can not be excluded that copper pyrithione can cause reprotoxic effects.
Lowest relevant reproductive NOAEL / LOAEL	NOAEL = 0.7 mg/kg bw/day (based on sodium pyrithione rat study)
Species/Developmental target / critical effect	Rat and Rabbit: post inplantation loss, resorption, skeletal malformations
Developmental toxicity	
Lowest relevant developmental NOAEL / LOAEL	NOAEL = 0.5 mg/kg bw/day (based on zinc pyrithione rabbit study)

Neurotoxicity / Delayed neurotoxicity

Species/ target/critical effect	Rat (acute): mortality, reduced motor activity, reduced bw, food intake and body temperature Rat (subchronic): mortality in one male
Lowest relevant NOAEL / LOAEL	Rat (acute) NOAEL = 25 mg/kg bw (study with zinc pyrithione) Rat 90-day NOAEL = 1.25 mg/kg bw/day

Other toxicological studies

.....	None

Medical data

.....	During 30 years of manufacturing experience with pyrithiones, minor transient mucous membrane irritation has been noted but no neurological abnormalities have been identified. Medical surveillance on manufacturing plant personnel is performed periodically; no abnormalities have been reported. No data exist in public literature on clinical cases or poisoning incidents.

Summary

	Value	Study	Safety factor
ADI (acceptable daily intake, external long-term reference dose)	0.0025 mg/kg bw/day	Two chronic studies with sodium pyrithione	200 (as only LOAEL could be derived)
AEL-S (Operator Exposure) short term and intermediate inhalation AEL	0.002 mg/kg bw/day	28 day inhalation study	200 (as unexplained mortality was seen at LOAEL)
Short and intermediate dermal AEL is the same as intermediate oral AEL	0.005 mg/kg bw/day	Based on all available oral copper pyrithione, zinc pyrithione and sodium pyrithione subacute, subchronic, teratogenicity and 2-generation studies	100
Long-term inhalation AEL	0.001 mg/kg bw/day	28 day inhalation study	400 (extrapolation from short-term to long-term exposure)
Long-term dermal AEL is the same as ADI	0.0025 mg/kg bw/day	Two chronic studies with sodium pyrithione	200 (as only LOAEL could be derived)
ARfD (acute reference dose)	0.02 mg/kg bw/day	Effects seen after 2.5 hour in a 90 day study with sodium pyrithione	100

Acceptable exposure scenarios (including method of calculation)

Professional users	
Production of active substance:	Operator exposure at this level is considered to be adequately addressed under the framework of The Chemical Agents at Work Directive (98/24/EC, within 89/391/EEC), and controlled using PPE and RPE as appropriate according to The Personal Protective Equipment at Work Regulations 1992 (EU Directive 89/656/EEC).
Formulation of biocidal product	Operator exposure at this level is considered to be adequately addressed under the framework of The Chemical Agents at Work Directive (98/24/EC, within 89/391/EEC), and controlled using PPE and RPE as appropriate according to The Personal Protective Equipment at Work Regulations 1992 (EU Directive 89/656/EEC).
Intended uses	Professionals: Application by brush and roller ("HEEG Opinion on the paper by Links et al. 2007 on occupational exposure during application and removal of antifouling paints" that was endorsed at TM IV 2012) Net coating Net deployment
Secondary exposure	
Non-professional users	Removal of paint. ("HEEG Opinion on the paper by Links et al. 2007 on occupational exposure during application and removal of antifouling paints" that was endorsed at TM IV 2012
Indirect exposure as a result of use	No risk for consumers eating seafood

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water (for pyrithione unless otherwise stated)

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	Probably related to pH. These half-lives are determined at 20–25°C. 63–infinite half-life at pH 3 (n = 2) 8–230 days at pH 5 (n = 4) 108–infinite days at pH 7 (n = 5) 12.9–96 days in seawater at pH 8.2 (n = 3) 7.4–123 days at pH 9 (n = 3) 41–infinite half-life at pH 11 (n = 2).
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	Pyrithiones phototransform readily in sunlight, please see quantum yield in previous table (Chapter 1). Different metabolites form depending on starting concentration, pH and water type. In seawater at low concentrations, irradiance in 12-hour cycles produced PSiA at a maximum of 44% after one hour, and PSA at a maximum of 74% after 14 days. No other metabolites were relevant under these conditions.
Readily biodegradable (yes/no)	No, for suspension of zinc- and copper pyrithione Yes, for solution of sodium pyrithione Metabolite PSA: ready biodegradable
Biodegradation in seawater	Single first order biological degradation rate in seawater was 0.21–0.23 d^{-1} ($^{sfo}DT_{50}$ of 4.4.–4.7 days) at 22°C, after a lag phase of 2–3 days. Metabolite PSA: DT50 = 15 days coastal water, 50 days open marine water (TGD default values for a ready degradable substance).
Non-extractable residues	Often high, but never exceeded 70% of the added dose to the system.
Distribution in water / sediment systems (active substance)	In one experiment with the test system OECD 303 A (simulation test aerobic sewage treatment activated sludge units) 98.2% of the influent radioactivity dissipated from the water into the sediment. In an experiment with an aerobic test system made of test tubes with 5 g dw sediment and 10 ml seawater, 17% of the radioactivity remained in water at day 0, and it increased to 38% on day 30. In an experiment with a microcosm made of aquarias with 3.56 kg dw sediment and 127 l seawater, ~100% of the added dose remained in water day 0, and decreased to ~70% by day 30.
Distribution in water / sediment systems (metabolites)	Not explicitly studied for metabolites, but in a microcosm made of 4.88 kg ww sediment and 31.3 l freshwater, the metabolite PSA lay at 16–19 µg/kg ww sediment, and 23–26 µg/l in the water column during day 12–55. During the same period, the added mother substance, zinc pyrithione, had decreased from an initial concentration of 50 µg/l to below detection limit in both sediment and water.
Degradation in water sediment system	Depending on how a PEC model is parameterised different combinations of degradation data may be

	appropriate as inputs to the model. In the case with the MAMPEC model we decided to use the following: • aerobic water-sediment whole system degradation DT50 of 21 d (at 25°C)as input for sediment compartment (extrapolations to other temperatures: 76 days at 9°C; 59 days at 12°C). • anaerobic water-sediment whole system degradation DT50 of 0.12–0.41 d (as supporting information) (extrapolations to other temperatures: 0.43–1.5 days at 9°C; 0.34–1.2 days at 12°C). • aerobic water-only whole-system degradation DT50 of 5.2 d as input of for water column (extrapolations to other temperatures: 13 days at 9°C; 10 days at 12°C) Metabolite PSA: • DT50 of 1000 days as input for sediment compartment (a "zero value"). • aerobic water-only whole-system degradation DT50 of 15–50 days as input of for water column. (extrapolations to other temperatures: 36–121 days at 9°C; 28–95 days at 12°C)

Route and rate of degradation in soil

Mineralization (aerobic)	Not determined
Laboratory studies (range or median, with number of measurements, with regression coefficient)	DT_{50lab} (aerobic): 44 hours (extrapolated to 12°C) (SFO, regression coefficient is not applicable since it is a 2-point estimate based on 2 experiments, where DT_{50} was 13 h and 15.5 h at 25°C, pH 6.6 sandy loam).
	DT_{90lab} (20°C, aerobic): Not studied, but 73.7% and 67.2% were observed to degrade during an ageing period of 25 h in darkness (26.3% and 32.8% remaining as zinc pyrithione).
	DT_{50lab} (10°C, aerobic): not studied
	DT_{50lab} (20°C, anaerobic): not studied
	Degradation in the saturated zone: not explicitly studied, but the soil leaching column study indicate similar rate as during the ageing period, during which the soil was not water saturated.
Field studies (state location, range or median with number of measurements)	DT_{50f}: not investigated
	DT_{90f}: not investigated
Anaerobic degradation	Not investigated
Soil photolysis	Not investigated
Non-extractable residues	In the soil columns for the leaching study 6.7–39.1% of the 14C dose was non-extractable. Different soil types and leaching times were studied, and both factors may have influenced the percentage.
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	OMSiA (omadine sulfinic acid) and OMSA (omadine sulfoninc acid) were detected as the largest metabolites in the leachate water from the soil study. Concentration of each was around and above 10% in 4 of the 11 studied soil columns.

Soil accumulation and plateau concentration	No accumulation of pyrithione seen. in a single dose study. (Metal copper ion is not studied).

Adsorption/desorption

Ka , Kd	Not relevant; highly variable with pH, concentration tested.
Ka,oc , Kd,oc	Ka,oc for 14C-pyrithione ranged from 780 to 11,000 l/kg$_{OC}$ at 1 mg/l (log Ka,oc 2.9–4.0). Determined from Freundlichfitting of isotherm within 0.5–4.0 mg/l. Kd,oc was not signficantly different from Ka,oc Metabolite PSA: log Koc = 3 (log l//kg oc) at ~20 µg/l.
pH dependence (yes / no) (if yes type of dependence)	Yes, pH dependent. The adsorption and desorption log K_{OC} varied linearly with soil or sediment pH. It was positively related to pH in experiments where the total pyrithione concentrations was 0.5–4 mg/l, but negatively related to pH in experiments where the total pyrithione concentration was 10–100 mg/l. It is not meaningful to make an average of the Ka$_{,OC}$, since it varies strongly with pH, tested concentration, sorption time and water type. A rough estimate of for fate calculations is to use log Koc = 3.5 (pH 7, soil or sediment, 1 mg/l). A modeller which is about to use the Koc values must consider that Koc is expected to be roughly 1 log unit lower at pH 5 (in systems where the pyrithione concentration is lower than 4 mg/l), in essence log Koc = 2.5 (pH 5, soil or sediment, 1 mg/l). The modeller must also consider that judging from a review of varying studies and the non-linearity constant observed in the OECD tests, the Koc will be be roughly 1 log unit higher (i.e. log Koc = 5) in solutions with pyrithione concentrations ~1 µg/l, possibly even higher at yet lower solute concentrations. In-situ Koc values are possibly as high as log Koc = 6, but then the influence of aged sorption, and bound residue formation can not be separated. Until next round of evaluation of biocides (5–10 years from 2012), the TM agreed all PT 21 applicants should submit new sorption studies. Until then a compromise log Koc of 4 (l/kg$_{OC}$) can be entered for MAMPEC calculations for pyrithione.

Fate and behaviour in air

Direct photolysis in air	Not investigated.
Quantum yield of direct photolysis	Not investigated
Photo-oxidative degradation in air	AOPWIN model using OH radical concentration as in the TGD (0.5×10^6 radicals per ml) predicts a DT_{50} of 26–160 h
Volatilization	No volatilisation expected from water due to low Henrys laws constant. Air–water partitioning: log K_{AW} ~–6 Octanol–air partitioning: log K_{OA} ~9.

Monitoring data, if available

Soil (indicate location and type of study)	No known studies.
Surface water (indicate location and type of study)	Swedish monitoring (Woldegiorgis et al., 2007), pyrithione concentration were below the LOD of 15 ng/l in 14 out of 17 samples on incoming water to STP. In their three most contaminated samples on incoming water to STP concentrations ranged from 1.7 to 32 µg/l. In recipients all water samples were below LOD. All samples of bottom sediment in recipients were below LOD (20 µg/kg dw). Fish was also analysed, but at the time of the study the analytical problems were to large. Metabolite PSA: No data available. Harino et al (2007) reported copper pyrithione above detection limits (LOD was 8 µg/kg dw) in three out of 32 bottom sediment (Ekman-Birge grab) samples taken in July 2005 in Otsuchi Bay, Northwest coast of Japan.
Ground water (indicate location and type of study)	No known studies.
Air (indicate location and type of study)	No known studies.

Chapter 5: Effects on Non-target Species

Toxicity data for aquatic species (most sensitive species of each group) **Pyrithione**

Species	Time-scale	Endpoint	Toxicity
Fish			
Pimephales promelas “ “ “	96 hours “ 32 days “	LC50 NOEC LOEC* NOEC* *survival, length, weight, behaviour all gave same	2.6 µg/l (TWA) 1.1 µg/l (TWA) 1.9 µg/l (TWA) 0.98 µg/l (TWA)
Invertebrates			
Marine copepod *Mysidopsis bahia* “	48 hours “	LC50 NOEC	6.3 µg/l (TWA) 1.6 µg/l (TWA)
Marine sea urchin *Arbacia puntulata* “	3 hours “	LOEC fertilization NOEC fertilization	1.7 µg/l (initial conc.) 1.0 µg/l (initial conc.)
Paracentrotus lividus (geomean two studies)	48 hours “	EC50 larval growth EC50 embryonic develop.	4.2 µg/l (TWA) 3.7 µg/l (TWA)
Marine bivalve *Mytilus edulis*	48 hours	EC50 embryonic develop.	2.2 µg/l (TWA)
Marine tunicate *Ciona intestinalis*	48 hours	EC50 settlement of newly hatched larvae	30.2 µg/l (TWA)
Freshwater sediment dweller *Hyalella azteca*	10 days	EC50	1.9 mg/kg ww (TWA)

Algae			
Marine diatom *Skeletonema costatum* (geometric mean from four studies)	48 hours “	EC50 NOECtwa	0.80 µg/l (TWA.) 0.176 µg/l (TWA)
Microorganisms			
Activated sludge “ *Pseudomonas putida*	30 minutes 16 hours	EC50 respiration NOEC respiration EC50 growth inhibition NOEC growth inhibition	>0.32 mg/l (nominal) 0.032 mg/l (nominal) 0.22 mg/l (nominal) 0.063 mg/l (nominal)

Toxicity data for aquatic species (most sensitive species of each group) **Metabolite PSA**

Species	Time-scale	Endpoint	Toxicity
Fish			
Pimephales promelas “ *Cyprinodon variegates* “ *Oncorhyncus mykiss* “	96 hours “ 28 days 96 hours “ 96 hours “	LC50 NOEC NOEC LC50 NOEC LC50 NOEC	>55.2 mg/l (TWA) 55.2 mg/l (TWA) >10 µg/l (nominal) >127 mg/l (TWA) 127 mg/l (TWA) >46.9 mg/l (TWA) 28.5 mg/l (TWA)
Invertebrates			
Daphnia magna “ *Mysidposis bahia* “ *Crassostrea virginica*	48 hours “ 96 hours “ 96 hours	LC50 mortality (immob.) NOEC LC50 mortality NOEC LC50 shell growth NOEC	>122 mg/l (TWA) 122 mg/l (TWA) 71.6 mg/l (TWA) 51.9 mg/l (TWA) 85.6 mg/l (TWA) 51.1 mg/l (TWA)
Algae			
Marine diatom *Skeletonema costatum*	120 hours “	EC50 NOECini	> 32 mg/l (TWA.) 5.46 mg/l (TWA.)
Microorganisms			
Activated sludge		no tests available	–

Effects on earthworms or other soil non-target organisms

Reproductive toxicity to Collembola (*Folsomia candida*)	Static single dose, stock solutions mixed into soil, nominal concentrations LC50= 329 mg/kg dw soil (nominal) 7,14-d NOEC moratilty = 200 mg/kg dw soil (nominal) 28-d NOEC reproduction =100 mg/kg dw soil (nominal) 28-d NOEC reproduction = 8.7 mg/kg dw soil (16-d TWA)
Earthworm (*Eisenia fetida*)	Static single dose, stock solutions mixed into soil, nominal concentrations 7, 14-d NOEC mortality = 400 mg/kg dw soil 28-d NOEC body weight = 40 mg/kg dw soil

Effects on soil micro-organisms

Nitrogen mineralization	Not studied
Carbon mineralization	Not studied

Effects on terrestrial vertebrates

Acute toxicity to mammals	See human toxicity section regarding studies on rats
Acute toxicity to birds	For Northern Bobwhite (*Colinus virginanus*) the 14 days LD50 was 60 mg/kg body weight, NOEC was 31.2 mg/kg body weight
Dietary toxicity to birds	For Northern Bobwhite (*Colinus virginanus*) the 8 days LC50 was 1110 mg/kg food, LC0 was 492 mg/kg food
Reproductive toxicity to birds	Not studied

Effects on honeybees

Acute oral toxicity	Not studied
Acute contact toxicity	Not studied

Effects on other beneficial arthropods

Acute oral toxicity	Not studied
Acute contact toxicity	Not studied
Acute toxicity to ……..	Not studied

Bioconcentration

Bioconcentration factor (BCF)	A typevalue for BCF in fish is 7.7 l/kg ww or log BCF = 0.88 log (l/kg ww). For BCF in invertebrates the typevalue is 8.0 l/kg ww or log BCF = 0.91 log (l/kg ww).
Depuration time (DT_{50}) (DT_{90})	3.4–14 days (shortest–longest from two Oyster tests) 11–23 days (low and high dose, one Oyster test)
Level of metabolites (%) in organisms accounting for > 10 % of residues	Not determined in experiments where BCF was low (3 out of 4 tests). In a test where BCF was high, the 14C-activity was associated with either insoluble or polar degradation products. However, this test is considered not reliable due to guideline protocol deviations.

Chapter 6: Other End Points (examples)

Toxicity to aquatic plant (*Lemna gibba* G3)	(nominal concentrations, 7 water renewals per day) 7+7-d NOEC of 4.0 µg/l, 7+7-d EC50 of 9.6 µg/l (the applicant will reinterpret the EC50 since it is not based on growth rate from frond number).
Toxicity to aquatic plant (*Lemna gibba*)	(nominal concentrations, 1 water renewal per day) 7-d NOEC of 21 µg/l 7-d EC50 of >78 µg/l
Toxicity to aquatic plant (*Lemna gibba*)	(nominal concentrations, no water renewal)

	7-d NOEC (not reported) 7-d EC50 360–1400 µg/l
Toxicity to higher plants (seedling emergence, *Oryzea orysa* sative)	single dose to soil, 5 doses studied, 16-days post emergence NOEC = 100 mg/kg dw soil (nominal)
Toxicity to higher plants (seedling emergence, various species)	single dose + watered by solution every day NOEC >0.50 µg/l (nominal, copper pyrithione) NOEC >0.49 µg/l (nominal, zinc pyrithione)
Toxicity to higher plants (seedling emergence, *Oryzea orysa* sative)	5 test conc. of ZPT sprayed onto the plants for 14 day NOEC = 49 g/l spray solution (nominal) LOEC = 88 g/l spray solution (nominal) EB50 = 116 g/l spray solution (nominal)
Other	The open research literature contains studies on marine or aquatic enclosures/mesocosms and effects are evaluated using the concept of pollution-induced community tolerance (PICT). Other researchers report endpoints such as phosphate flux from sediment to water are studied, and avoidance tests with sediment dwellers.

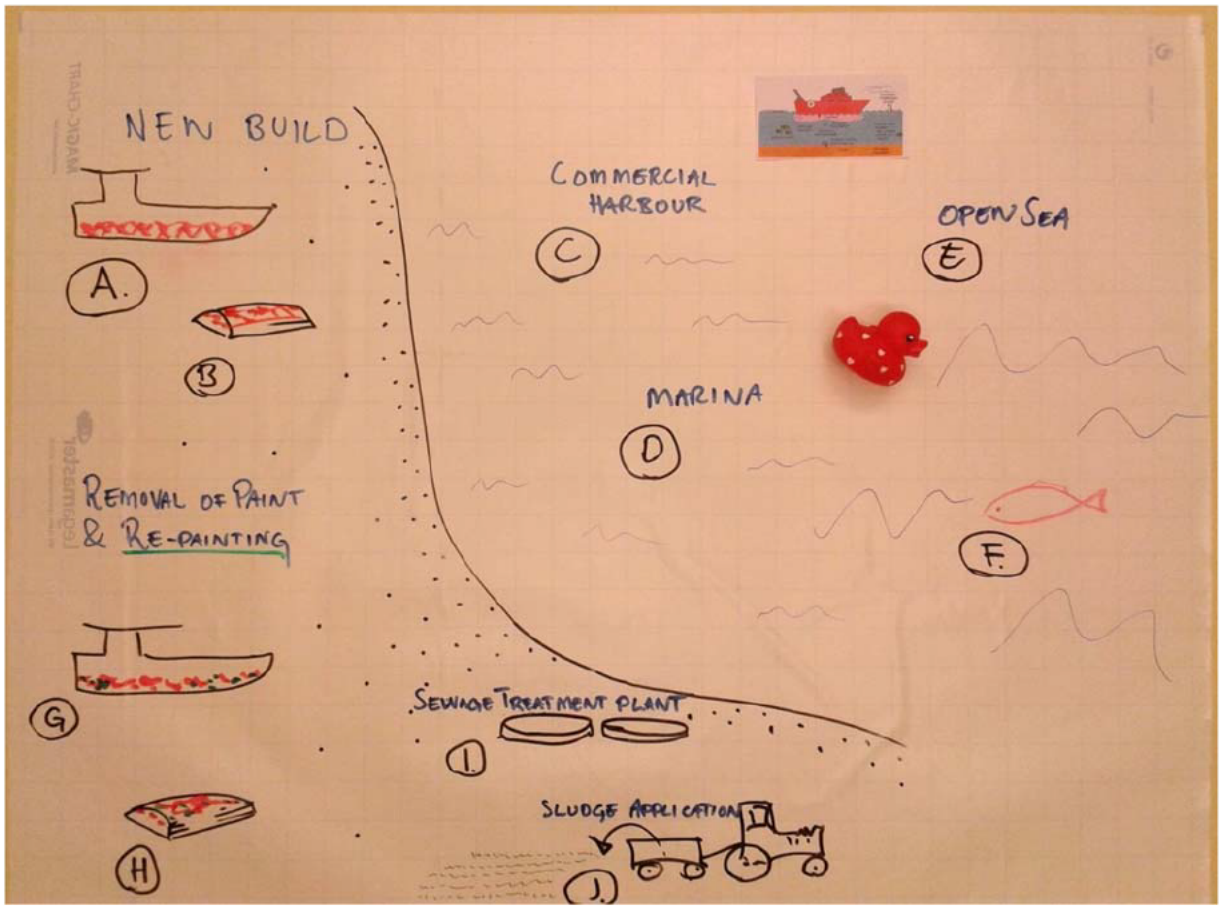


Figure 2 All scenarios which are assessed with respect to risk for the human health and the environment.

Figure 2 is intended to give an overview of all scenarios which are assessed for risk to human health and also with respect to the environment when antifouling paint is used on different types of boats and ships. An antifouling paint is assumed to give rise to exposure in all these scenarios, and the risk to human health and to the environment needs to be acceptable in the whole life of the paint (**A–J**).

A represent painting during new building of commercial ships, an activity which is assumed to be performed by professional workers. For the human health and professional use the exposure from all evaluated products are acceptable when brush and roller are used. However, the scenario "airless spraying" causes unacceptable exposure for the same products. For the environment, all application procedures leads to emission to soil and groundwater, for which risks are unacceptable. (But are unacceptable for all antifouling products which are discussed at ongoing CA-meetings during 2013).

B represent new painting of non-commercial boats, a job which assumed to be done by non-professionals. For the human health, the antifouling products can not be acceptable for amateur use due to a unacceptable risk.. For the environment risks are unacceptable for soil and groundwater.

C, D and E represent in-service life of the paints, where leaching from the boat hulls gives exposure of organisms in the water column, and organisms living in the bottom sediments. For these scenarios risks are acceptable for the environment, and there are no health risk scenarios to assess.

F represent contamination of seafood (fish, oysters etc.) as a result of emissions from any activity (A, B, G, H, I) or leaching from the in-service life (C, D, E). Contamination of seafood is acceptable with respect to secondary poisoning (transfer in ecosystem food webs) and the contamination is also acceptable with respect to exposure of humans which are eating the sea food.

G represent removal of paint (scraping, sand-blasting etc) and re-painting of commercial ships, a job which is assumed to be performed by professional workers. The product [redacted] gives acceptable exposure in these scenarios and it might be possible to produce a product that also gives acceptable exposure; if the copper pyrithione concentration is not too high and the dermal absorption can be shown to be really low. For the environment, risk to soil and groundwater is unacceptable.

H represent dito activity but for smaller boats, in essence work assumed to be done by non-professionals (see photo in Figure 2.2.3.4). Please see the arguments regarding amateur use of copper pyrithione products under A. It can be added that it seems possible to produce a product that would give acceptable exposure for the removal of paint scenario. For the environment risk to soil and groundwater is unacceptable.

I represent contamination of sewage treatment plants (STP) due to transport from waste-collection facilities at marinas and boat yards which are connected to STP. Risk is acceptable for the microorganisms in the sludge, and also to the recipient water (fresh water and marine recipient).

J represent application of contaminated sewage sludge onto agricultural- and grassland soils. Risk due to emissions from antifoulant paints are acceptable to the soil organisms. (Contamination of crops or groundwater is not assessed).

APPENDIX II: LIST OF INTENDED USES

Product type	Target organisms	Claim*	User category	Concentration used	Remarks
PT 21	Fouling species: slime, aquatic plants (including weeds, grasses, etc.), animals (barnacles, mussels, other shell fouling etc.)	Not provided.	An industrial use is not intended. Professional use only, by spraying. Not intended to be used by general public.	1.5% by weight in the wet paint.	[redacted] b.v., [redacted]
PT 21		Not provided.	Application will only be carried out by professionals, who may use spraying techniques and/or brush and roller.	3.5% by weight in the wet paint.	[redacted]
PT 21		Antifouling paint Prevents settlement and inhibits growth of fouling organisms on surfaces intended to be submersed into the aquatic environment.	The product is only intended to be used by professionals.	2.9% by weight in the wet paint.	[redacted]
PT 21		Antifouling paint: effective against slime, algae, and invertebrate fouling species. [redacted] is a High performance TBT free, self polishing copolymer (SPC) antifouling system with patented copper acrylate technology.	Professional application of antifouling product to ships and other objects intended to be submersed into water. Non-professional application of antifouling product to leasure craft	4.01% by weight in the wet paint.	[redacted]
PT 21		Not provided.	Professional application of antifouling product to ships and other objects intended to be submersed into water. Non-professional application of antifouling product to leisure craft	4.0% by weight in the wet paint.	Arch Chemicals "Dummy product 4%"
PT 21		Not provided.	Professional workers in facilities for fish net impregnation.	2.0% by weight in the wet paint.	Arch Chemicals "Dummy product 2%"

* All applicants claim that copper pyrithione is a booster antifouling substance, in essence it is not the main biocide in the product, but acts to remove the most problematic fouling organisms. ** Please note that the environmental risk assessment is based on a fictive product containing 4% copper pyrithione by weight, with a theoretically estimated leaching rate (using the "CEPE mass balance method"). The PEC values for the specific product is however extrapolated from the dummy product, using the simplified assumption that leach rate is

directly proportional to the active substance concentration.

APPENDIX III: LIST OF STUDIES

Section No / Reference No[9]	Author(s)[10]	Year	Title[11] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
Doc II and Doc I	Links, I; Van der Jagt, K. E.; Christopher, Y.; Lurvink, M.; Schinkel, J.; Tielemans, E.; van Hemmen, J. J.:	2007	Occupational Exposure During Application and Removal of Antifouling Paints. Annals of Occupational Hygiene 51(2):207-218	No	Open literature

APPENDIX IV: LIST OF STANDARD TERMS AND ABBREVIATIONS

List 1 : List of standard terms and abbreviations

Stand. term / Abbreviation	**Explanation**
A	ampere
ACh	acetylcholine
AChE	acetylcholinesterase
ADI	acceptable daily intake
ADME	administration distribution metabolism and excretion
ADP	adenosine diphosphate
AE	acid equivalent
AF	assessment factor
AFID	alkali flame-ionisation detector or detection
A/G	albumin/globulin ratio
ai or as	active ingredient or active substance
ALD_{50}	approximate median lethal dose, 50%
ALT	alanine aminotransferase (SGPT)
Ann.	Annex
AOEL	acceptable operator exposure level
AMD	automatic multiple development
ANOVA	analysis of variance
AP	alkaline phosphatase
approx	approximate
ARC	anticipated residue contribution
ARfD	acute reference dose
as	active substance
AST	aspartate aminotransferase (SGOT)
ASV	air saturation value
ATP	adenosine triphosphate
BAF	bioaccumulation factor
BCF	bioconcentration factor
bfa	body fluid assay
BOD	biological oxygen demand
bp	boiling point
BPD	Biocidal Products Directive
BSAF	biota-sediment accumulation factor
BSE	bovine spongiform encephalopathy
BSP	bromosulfophthalein
Bt	*Bacillus thuringiensis*
Bti	*Bacillus thuringiensis israelensis*
Btk	*Bacillus thuringiensis kurstaki*
Btt	*Bacillus thuringiensis tenebrionis*
BUN	blood urea nitrogen
bw	body weight
c	centi- (x 10^{-2})
°C	degrees Celsius (centigrade)
CA	controlled atmosphere
CAD	computer aided design
CADDY	computer aided dossier and data supply (an electronic dossier interchange and archiving format)
cd	candela
CDA	controlled drop(let) application
cDNA	complementary DANN
CEC	cation exchange capacity
cf	confer, compare to
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CL	confidence limits
cm	centimetre
CNS	central nervous system
COD	chemical oxygen demand
CPK	creatinine phosphatase
CPU	4-chlorophenylurea
cv	coefficient of variation
Cv	ceiling value
d	day(s)
DES	diethylstilboestrol
DFBA	2,6-difluorobenzoic acid
DIS	draft international standard *(ISO)*

Stand. term / Abbreviation	**Explanation**
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dna	designated national authority
DO	dissolved oxygen
DOC	dissolved organic carbon
dpi	days post inoculation
DRP	detailed review paper *(OECD)*
$DT_{50(lab)}$	period required for 50 percent dissipation (under laboratory conditions) (define method of estimation)
$DT_{90(field)}$	period required for 90 percent dissipation (under field conditions) (define method of estimation)
dw	dry weight
DWQG	drinking water quality guidelines
ε	decadic molar extinction coefficient
EC_{50}	median effective concentration
ECD	electron capture detector
ED_{50}	median effective dose
EDI	estimated daily intake
EINECS	European inventory of existing commercial substances
ELINCS	European list of notified chemical substances
ELISA	enzyme linked immunosorbent assay
e-mail	electronic mail
EMDI	estimated maximum daily intake
EN	European norm
EPMA	electron probe micro-analysis
ERL	extraneous residue limit
ESPE46/51	evaluation system for pesticides
EUSES	European Union system for the evaluation of substances
F	field
F_0	parental generation
F_1	filial generation, first
F_2	filial generation, second

Stand. term / Abbreviation	**Explanation**
FBS	full base set
FELS	fish early-life stage
FIA	fluorescence immuno-assay
FID	flame ionisation detector
F_{mol}	fractional equivalent of the metabolite´s molecular weight compared to the active substance
FOB	functional observation battery
f_{oc}	organic carbon factor (compartment dependent)
fp	freezing point
FPD	flame photometric detector
FPLC	fast protein liquid chromatography
g	gram(s)
GAP	good agricultural practice
GC	gas chromatography
GC-EC	gas chromatography with electron capture detector
GC-FID	gas chromatography with flame ionisation detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GEP	good experimental practice
GFP	good field practice
GGT	gamma glutamyl transferase
GI	gastro-intestinal
GIT	gastro-intestinal tract
GL	guideline level
GLC	gas liquid chromatography
GLP	good laboratory practice
GM	geometric mean
GMO	genetically modified organism
GMM	genetically modified micro-organism
GPC	gel-permeation chromatography
GPS	global positioning system
GSH	glutathione
GV	granulosevirus

Stand. term / Abbreviation	**Explanation**
h	hour(s)
H	Henry's Law constant (calculated as a unitless value)
ha	hectare(s)
Hb	haemoglobin
HC5	concentration which will be harmless to at least 95 % of the species present with a given level of confidence (usually 95 %)
HCG	human chorionic gonadotropin
Hct	haematocrit
HDT	highest dose tested
hL	hectolitre
HEED	high energy electron diffraction
HID	helium ionisation detector
HPAEC	high performance anion exchange chromatography
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography - mass spectrometry
HPPLC	high pressure planar liquid chromatography
HPTLC	high performance thin layer chromatography
HRGC	high resolution gas chromatography
H_S	Shannon-Weaver index
Ht	haematocrit
HUSS	human and use safety standard
I	indoor
I_{50}	inhibitory dose, 50%
IC_{50}	median immobilisation concentration or median inhibitory concentration 1
ICM	integrated crop management
ID	ionisation detector
IEDI	international estimated daily intake
IGR	insect growth regulator
im	intramuscular

Stand. term / Abbreviation	**Explanation**
inh	inhalation
INT	2-p-iodophenyl-3-p-nitrophenyl-5-phenyltetrazoliumchloride testing method
ip	intraperitoneal
IPM	integrated pest management
IR	infrared
ISBN	international standard book number
ISSN	international standard serial number
IUCLID	International Uniform Chemical Information Database
iv	intravenous
IVF	*in vitro* fertilisation
k *(in combination)*	kilo
k	rate constant for biodegradation
K	Kelvin
Ka	acid dissociation constant
Kb	base dissociation constant
K_{ads}	adsorption constant
K_{des}	apparent desorption coefficient
kg	kilogram
K_H	Henry´s Law constant (in atmosphere per cubic metre per mole)
K_{oc}	organic carbon adsorption coefficient
K_{om}	organic matter adsorption coefficient
K_{ow}	octanol-water partition coefficient
Kp	solid-water partition coefficient
kPa	kilopascal(s)
l, L	litre
LAN	local area network
LASER	light amplification by stimulated emission of radiation
LBC	loosely bound capacity
LC	liquid chromatography
LC-MS	liquid chromatography- mass spectrometry

Stand. term / Abbreviation	**Explanation**
LC_{50}	lethal concentration, median
LCA	life cycle analysis
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LDH	lactate dehydrogenase
ln	natural logarithm
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
log	logarithm to the base 10
LOQ	limit of quantification (determination)
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counting or counter
LSD	least squared denominator multiple range test
LSS	liquid scintillation spectrometry
LT	lethal threshold
m	metre
M	molar
µm	micrometre (micron)
MAC	maximum allowable concentration
MAK	maximum allowable concentration
MC	moisture content
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MDL	method detection limit
MFO	mixed function oxidase
µg	microgram
mg	milligram

Stand. term / Abbreviation	**Explanation**
MHC	moisture holding capacity
MIC	minimum inhibitory concentration
min	minute(s)
MKC	minimum killing concentration
mL	millilitre
MLT	median lethal time
MLD	minimum lethal dose
mm	millimetre
MMAD	mass median aerodynamic diameter
mo	month(s)
MOE	margin of exposure
mol	mole(s)
MOS	margin of safety
mp	melting point
MRE	maximum residue expected
MRL	maximum residue level or limit
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
MT	material test
MW	molecular weight
n.a.	not applicable
n-	normal (defining isomeric configuration)
n	number of observations
NAEL	no adverse effect level
nd	not detected
NEDI	national estimated daily intake
NEL	no effect level
NERL	no effect residue level
ng	nanogram
nm	nanometre
NMR	nuclear magnetic resonance
no, n°	number
NOAEC	no observed adverse effect concentration

Stand. term / Abbreviation	**Explanation**
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NOIS	notice of intent to suspend
NPD	nitrogen-phosphorus detector or detection
NPV	nuclear polyhedrosis virus
NR	not reported
NTE	neurotoxic target esterase
OC	organic carbon content
OCR	optical character recognition
ODP	ozone-depleting potential
ODS	ozone-depleting substances
OEL	occupational exposure limit
OH	hydroxide
OJ	Official Journal
OM	organic matter content
Pa	pascal
PAD	pulsed amperometric detection
2-PAM	2-pralidoxime
pc	paper chromatography
PC	personal computer
PCV	haematocrit (packed corpuscular volume)
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
PED	plasma-emissions-detector
pH	pH-value
PHED	pesticide handler's exposure data
PIC	prior informed consent

Stand. term / Abbreviation	**Explanation**
pic	phage inhibitory capacity
PIXE	proton induced X-ray emission
pKa	negative logarithm (to the base 10) of the acid dissociation constant
pKb	negative logarithm (to the base 10) of the base dissociation constant
PNEC	predicted no effect concentration (compartment to be added as subscript)
po	by mouth
POP	persistent organic pollutants
ppb	parts per billion (10^{-9})
PPE	personal protective equipment
ppm	parts per million (10^{-6})
PPP	plant protection product
ppq	parts per quadrillion (10^{-24})
ppt	parts per trillion (10^{-12})
PSP	phenolsulfophthalein
PrT	prothrombin time
PRL	practical residue limit
PT	product type
PT(CEN)	project team CEN
PTDI	provisional tolerable daily intake
PTT	partial thromboplastin time
QA	quality assurance
QAU	quality assurance unit
(Q)SAR	quantitative structure-activity relationship
r	correlation coefficient
r^2	coefficient of determination
RA	risk assessment
RBC	red blood cell
REI	restricted entry interval
RENI	Registry Nomenclature Information System
Rf	retardation factor
RfD	reference dose
RH	relative humidity
RL_{50}	median residual lifetime

Stand. term / Abbreviation	**Explanation**
RNA	ribonucleic acid
RP	reversed phase
rpm	revolutions per minute
rRNA	ribosomal ribonucleic acid
RRT	relative retention time
RSD	relative standard deviation
s	second
S	solubility
SAC	strong adsorption capacity
SAP	serum alkaline phosphatase
SAR	structure/activity relationship
SBLC	shallow bed liquid chromatography
sc	subcutaneous
sce	sister chromatid exchange
SCAS	semi-continous activated sludge
SCTER	smallest chronic toxicity exposure ratio (TER)
SD	standard deviation
se	standard error
SEM	standard error of the mean
SEP	standard evaluation procedure
SF	safety factor
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SIMS	secondary ion mass spectroscopy
S/L	short term to long term ratio
SMEs	small and medium sized enterprises
SOP	standard operating procedures
sp	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogen free
spp	subspecies
SSD	sulphur specific detector
SSMS	spark source mass spectrometry
STEL	short term exposure limit
STER	smallest toxicity exposure ratio (TER)

Stand. term / Abbreviation	**Explanation**
STMR	supervised trials median residue
STP	sewage treatment plant
t	tonne(s) (metric ton)
$t_{½}$	half-life (define method of estimation)
T_3	tri-iodothyroxine
T_4	thyroxine
T_{25}	tumorigenic dose that causes tumours in 25 % of the test animals
TADI	temporary acceptable daily intake
TBC	tightly bound capacity
TCD	thermal conductivity detector
TG	technical guideline, technical group
TGD	Technical guidance document
TID	thermionic detector, alkali flame detector
TDR	time domain reflectrometry
TER	toxicity exposure ratio
TER_I	toxicity exposure ratio for initial exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
tert	tertiary (in a chemical name)
TEP	typical end-use product
TGGE	temperature gradient gel electrophoresis
TIFF	tag image file format
TLC	thin layer chromatography
Tlm	median tolerance limit
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TMRC	theoretical maximum residue contribution
TMRL	temporary maximum residue limit
TNsG	technical notes for guidance
TOC	total organic carbon
Tremcard	transport emergency card
tRNA	transfer ribonucleic acid

Stand. term / Abbreviation	**Explanation**
TSH	thyroid stimulating hormone (thyrotropin)
TTC	2,3,5-triphenylterazoliumchloride testing method
TWA	time weighted average
UDS	unscheduled DNA synthesis
UF	uncertainty factor (safety factor)
ULV	ultra low volume
UR	unit risk
UV	ultraviolet
UVC	unknown or variable composition, complex reaction products
UVCB	undefined or variable composition, complex reaction products in biological material
v/v	volume ratio (volume per volume)
vis	visible
WBC	white blood cell
wk	week
wt	weight
w/v	weight per volume
ww	wet weight
w/w	weight per weight
XRFA	X-ray fluorescence analysis
yr	year
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

List 2 : **Abbreviations of Organisations and Publications**

Abbreviation	**Explanation**
ASTM	American Society for Testing and Materials
BA	Biological Abstracts (Philadelphia)
BART	Beneficial Arthropod Registration Testing Group
BBA	German Federal Agency of Agriculture and Forestry
CA(S)	Chemical Abstracts (System)
CAB	Centre for Agriculture and Biosciences International
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCFAC	Codex Committee on Food Additives and Contaminants
CCGP	Codex Committee on General Principles
CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Food
CE	Council of Europe
CEC	Commission of the European Communities
CEFIC	European Chemical Industry Council
CEN	European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CIPAC	Collaborative International Pesticides Analytical Council Ltd
CMA	Chemicals Manufacturers Association
COREPER	Comite des Representants Permanents
COST	European Co-operation in the field of Scientific and Technical Research
DG	Directorate General
DIN	German Institute for Standardisation
EC	European Commission

Abbreviation	**Explanation**
ECB	European Chemicals Bureau
ECCO	European Commission Co-ordination
ECDIN	Environmental Chemicals Data and Information Network of the European Communities
ECDIS	European Environmental Chemicals Data and Information System
ECE	Economic Commission for Europe
ECETOC	European Chemical Industry Ecology and Toxicology Centre
EDEXIM	European Database on Export and Import of Dangerous Chemicals
EEC	European Economic Community
EHC	Environmental Health Criteria
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMIC	Environmental Mutagens Information Centre
EPA	Environmental Protection Agency
EPAS	European Producers of Antimicrobial Substances
EPFP	European Producers of Formulated Preservatives
EPO	European Patent Office
EPPO	European and Mediterranean Plant Protection Organization
ESCORT	European Standard Characteristics of Beneficials Regulatory Testing
EU	European Union
EUPHIDS	European Pesticide Hazard Information and Decision Support System
EUROPOEM	European Predictive Operator Exposure Model
EWMP	European Wood Preservation Manufacturers
FAO	Food and Agriculture Organization of the UN
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FRAC	Fungicide Resistance Action Committee

Abbreviation	**Explanation**
GATT	General Agreement on Tariffs and Trade
GAW	Global Atmosphere Watch
GIFAP	Groupement International des Associations Nationales de Fabricants de Produits Agrochimiques (now known as GCPF)
GCOS	Global Climate Observing System
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GEDD	Global Environmental Data Directory
GEMS	Global Environmental Monitoring System
GRIN	Germplasm Resources Information Network
IARC	International Agency for Research on Cancer
IATS	International Academy of Toxicological Science
ICBP	International Council for Bird Preservation
ICCA	International Council of Chemical Associations
ICES	International Council for the Exploration of the Seas
ILO	International Labour Organization
IMO	International Maritime Organisation
IOBC	International Organization for Biological Control of Noxious Animals and Plants
IPCS	International Programme on Chemical Safety
IRAC	Insecticide Resistance Action Committee
ISCO	International Soil Conservation Organization
ISO	International Organization for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
JECFA FAO/WHO	Joint Expert Committee on Food Additives

Abbreviation	**Explanation**
JFCMP	Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme
JMP	Joint Meeting on Pesticides (WHO/FAO)
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
MITI	Ministry of International Trade and Industry, Japan
NATO	North Atlantic Treaty Organization
NAFTA	North American Free Trade Agreement
NCI	National Cancer Institute (USA)
NCTR	National Center for Toxicological Research (USA)
NGO	non-governmental organisation
NTP	National Toxicology Program (USA)
OECD	Organization for Economic Co-operation and Development
OLIS	On-line Information Service of OECD
OPPTS	Office of Prevention, Pesticides and Toxic Substances (US EPA)
OSPAR	Oslo Paris Convention (Convention for the Protection of the Marine Environment of the North-East Atlantic)
PAN	Pesticide Action Network
RIVM	Netherlands National Institute of Public Health and Environmental Protection
RNN	Re-registration Notification Network
RTECS	Registry of Toxic Effects of Chemical Substances (USA)
SETAC	Society of Environmental Toxicology and Chemistry
SI	Système International d'Unitès
SITC	Standard International Trade Classification
TOXLINE	Toxicology Information On-line

Abbreviation	**Explanation**
UBA	German Environmental Protection Agency
UN	United Nations
UNEP	United Nations Environment Programme
WFP	World Food Programme
WHO	World Health Organization
WPRS	West Palearctic Regional Section
WTO	World Trade Organization
WWF	World Wildlife Fund