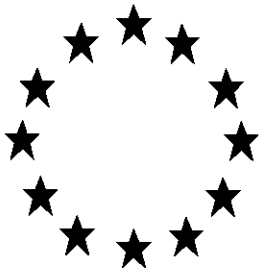
Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report



Tralopyril

Product-type 21
(Antifouling Products)

14 April 2014

- CONTENTS

1. STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1. Procedure followed

This assessment report has been established as a result of the evaluation of the new active substance tralopyril as product-type PT21 (Antifouling products), carried out in the context of Regulation (EU) No 528/2012, with a view to the possible approval of this substance.

On 17/07/2007, the UK competent authority received a dossier from the applicant. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation on 03/09/2008.

On 28/08/2009, the Rapporteur Member State submitted to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report.

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 Agency. Revisions agreed upon were presented at the Biocidal Products Committee and its Working Groups meetings and the competent authority report was amended accordingly.

1.2. Purpose of the assessment report

The aim of the assessment report is to support the opinion of the Biocidal Products Committee and a decision on the approval of tralopyril for product-type 21, and, should it be approved, to facilitate the authorisation of individual biocidal products. 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.

For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report, which is available from the Agency web site, 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 for that purpose has been granted to that applicant.

2. OVERALL SUMMARY AND CONCLUSIONS

2.1. Presentation of the Active Substance

2.1.1. Identity, Physico-Chemical Properties & Methods of Analysis

The main identification characteristics and the physico-chemical properties of tralopyril are given in Appendix I to this document. The methods of analysis for the active substance as manufactured and for the determination of impurities have been validated. The applicant must address a data requirement for the reference source, details of which are outlined in the Confidential Annex, Section 3.

LC-MS/MS methods have been validated for the determination of tralopyril in sediment and natural seawater. As seawater will be a worse case matrix the validation data can be extrapolated to cover fresh water and drinking water. These methods have not been sufficiently validated. The further validation data required are outlined in the BPC opinion, which is available from the ECHA website.

The use pattern is on parts of ships, boat hulls and static structures that will be submerged in the marine environment. There will be no application to boats under 25 m in overall length, so only large marine-going vessels including super yachts will be treated. In view of this, there is no assessment of freshwater or soil exposure. On this basis there is no technical need for a freshwater method or a soil method to support the Approval assessment. However, this will need to be reassessed if pleasure craft uses are requested in the future and freshwater exposure is possible.

It was agreed that a method for the analysis of the active in air would be necessary for monitoring purposes. The Applicant has commenced work developing a method but it is still outstanding. This can be provided at Member State level.

The Applicant has submitted analytical methods for animal and human body fluids and tissues, and method(s) for residues in fish and shellfish. Some additional validation data, as outlined in the BPC opinion, which is available from the ECHA website, are required for the method for residues in fish and shellfish.

It should be noted that a new source of tralopyril has been assessed for technical equivalence, agreed as acceptable, and adopted as the reference source. The specifications of this reference source are covered by the batches used in toxicology and ecotoxicology studies. This has been confirmed by consideration of the original and new source specifications, existing toxicology and ecotoxicology data, and a new Ames study required to confirm that two impurities found in the new source were not mutagenic. Full details of the technical equivalence assessment for the new source are provided in the Confidential Annex. The Applicant must address data requirements for this new source, at or prior to the product authorisation stage, the details of which are outlined in the technical equivalence assessment.

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) and the evaluation of the summary data provided in support of the efficacy of the accompanying product, establishes that the 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.

2.1.2.1. Field of use envisaged / function and organisms to be controlled

Main group 4 (MG04) – Other biocidal products
Product-type 21 (PT21) – Antifouling products

Anti-fouling products containing tralopyril are to be used on hulls and other immersed parts of large marine-going vessels such as commercial boats and ships, navy and other government vessels and super-yachts (25 meter or more in overall length) and can also be used on immersed objects/structures to protect submerged surfaces from fouling by marine barnacles, hydroids, slime, adherent slime, weed and brown felt. All surfaces are treated while they are in dry-dock (i.e. out of the water). Application will be by professional users via airless spray, brush or roller in a paint.

Treated submerged surfaces will be exposed to a variety of fouling species. As the trading pattern of a commercial vessel (or potential destination of a pleasure craft) can cross multiple marine biotopes, the number of organisms to which it will be exposed is vast.

2.1.2.2. Humaneness

Not applicable.

2.1.2.3. Resistance

The Applicant has provided evidence to demonstrate that development of resistance is not an issue. This is considered to be due to the mode of action of the biocide, which is by uncoupling mitochondrial oxidative phosphorylation. Development of resistance against compounds with this mode of action can be considered unlikely and rare for a variety of reasons; a lack of target site for mutation, the need for combined mechanisms in order to enable detoxification or uptake decrease, and a steep concentration-dependence in uncoupling phosphorylation.

It is considered that the submitted data and information on resistance are sufficient to support approval.

2.1.3. Classification and Labelling

The classification and labelling of the active substance tralopyril according to Annex I of Council Directive 67/548/EEC as indicated by the Applicant is shown in Table 2.1.

Table 2.1 Classification / labelling of tralopyril as indicated by the Applicant

Hazard symbol:	T, N
Indication of danger:	Toxic Dangerous for the environment
R-phrases:	*R23/25: Toxic by inhalation and if swallowed* *R50/53: Very toxic to aquatic organisms; may cause long-term adverse effects in the aquatic environment* *R55: Toxic to fauna* *R57: Toxic to bees*

2.1.4. Proposed classification

Proposed classification based on Directive 67/548/EEC:

Hazard symbol:	T+, N
Indication of danger:	Very toxic Dangerous for the environment
R-phrases:	*R26: Very toxic by inhalation* *R25: Toxic if swallowed* *R21: Harmful in contact with skin* *R48/25: Danger of serious damage to health by prolonged exposure if swallowed* *R48/20: Danger of serious damage to health by prolonged exposure if inhaled* *R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment* *R55: Toxic to fauna* *R57: Toxic to bees*

Proposed classification based on CLP Regulation:

SIGNAL WORD	DANGER
PICTOGRAMS	GHS06, GHS08, GHS09
Hazard Class and Category Codes	Acute Tox. 2 H300 Acute Tox. 3 H311 Acute Tox. 2 H330 STOT RE 1 H372 (oral) STOT RE 2 H373 (inhalation) Acute Aquatic 1 Chronic Aquatic 1
Hazard Statement Codes	H300: Fatal if swallowed H311: Toxic in contact with skin H330: Fatal if inhaled H372: Causes damage to organs through prolonged or repeated oral exposure H373: May cause damage to organs through prolonged or repeated inhalation exposure H400: Very toxic to aquatic life H410: Very toxic to aquatic life with long lasting effects
Specific Concentration limits, M-Factors	M = 1000 (acute) and 100 (chronic)

2.2. Summary of the Risk Assessment

2.2.1. Human Health Risk Assessment

The product, International Copper Free, is a liquid metal-free antifouling paint containing 4.17 % w/w tralopyril for application by professional operators. International Copper Free is to be applied by professionals to the part of the cleaned ship that will be immersed and boat hulls in dockyards and slipways and static structures (such as oil rig and drilling platform legs, oil/gas pipeline valves and dry dock doors) using high pressure airless spraying (>100 bar) and from time to time by brush/roller. Vessels <25 m in overall length will not be treated. Exposure to International Copper Free may also occur when paint is removed from the hull of vessels using methods such as abrasive blasting, hydro-blasting and abrasion.

In line with the TNsG on Human Exposure to Biocidal Products, the UK CA has carried out for this product (International Copper Free) and its specified uses an exposure assessment for human health based on a tiered approach. The UK has started each exposure assessment using worst-case assumptions (e.g. duration of spraying, assuming no personal protective equipment other than gloves is worn etc.). If the risks to human health following exposure to tralopyril were considered to be acceptable following comparison of the predicted systemic dose with the appropriate NOAEL/NOAEC from animal studies, then no further refinement of the exposure scenario was carried out. The UK CA accepts that in many cases (e.g. Tier 1 assessments) the exposure scenarios presented are highly conservative but consider further refinement of the

exposure scenarios is unnecessary, if no unacceptable risk is identified. If an unacceptable risk is identified for a particular exposure scenario, then a further refinement of the exposure/risk assessment was carried out using additional parameters (e.g. additional PPE etc.).

The risk characterisation follows the principles agreed by the Biocides Technical Meeting, described in Technical Guidance Documents for Risk Characterisation of Systemic Effects[1] and Local Effects[2]. The risk characterisation for systemic effects is conducted by comparison of the exposure and the toxicity by both the margin of exposure (MOE) approach and the Acceptable Exposure Limit (AEL) approach for systemic toxicity and the Acceptable Exposure Concentration (AEC) approach for local toxicity. The MOE is calculated as: MOE = N(L)OAEL (mg/kg bw/day) /Exposure (mg/kg bw/day) and this is then compared to the acceptable minimal MOE that has been derived. In the AEL concept the exposure estimates are compared with the determined systemic AEL = N(L)OAEL (mg/kg bw/day)/overall Assessment Factor (AF). Risk are considered acceptable if the calculated MOE is > minimal MOE or if the Exposure/AEL ratio is < 1. Where appropriate, the risk characterisation for local effects is conducted by comparing external exposure concentrations with the derived AEC = N(L)OAEC/overall assessment factor. Risks are considered acceptable if the external exposure concentration is < AEC.

2.2.1.1. Hazard identification

The toxicity of tralopyril has not been investigated in humans, although this is not considered a data gap. All studies were conducted to GLP and virtually all were guideline compliant. Where deviations existed, the studies were still considered to be of an acceptable standard. Overall, there is no concern over the quality of the data submitted.

The potential for tralopyril and International Copper Free to cause adverse effects has been investigated in studies in laboratory animals. Some of the data requirements for tralopyril have been met in part with existing studies on CL 303,630, a metabolic precursor of tralopyril. At TMII2010 it was agreed that the data requirements for tralopyril could be satisfied qualitatively using data on CL 303,630 but the AELs derived for use in the risk characterisation should be based on data on tralopyril (90-day studies via the oral, dermal and inhalation routes are available). The UK considers that certain properties of tralopyril can be reliably predicted by read across from the CL 303,630 studies for the following reasons:

1. Based on similar physicochemical properties and similar structures it can be assumed that the extent and speed of absorption via the oral route will be similar for CL 303,630 and tralopyril.

2. It has been demonstrated that a major and immediate metabolite of CL 303,630 is tralopyril. Thus, it can be predicted that the toxic properties of CL 303,630 and tralopyril are likely to have similarities. The speed and extent of the conversion of CL 303,603 to tralopyril is not completely understood, but full knowledge of the

[1] http://ec.europa.eu/environment/biocides/pdf/tnsg_4_1.pdf

[2] http://ecb.jrc.ec.europa.eu/documents/Biocides/TECHNICAL_NOTES_FOR_GUIDANCE/Guidance %20Risk %20Characterization %20Local %20Effects_2009.pdf

comparative toxicokinetics is not crucial to the acceptance of the read across approach because there is good information on the comparative sub-chronic toxicity of the two substances.

3. Rat oral (dietary administration) sub-chronic studies are available for both CL 303,630 and tralopyril, which show that the repeat dose toxicity of the two substances is qualitatively similar. However, there appear to be quantitative differences in the dose levels causing a key effect of neurohistopathological changes in male rats. This is apparent when the results of the 90-day studies conducted with tralopyril and CL 303,630 were compared (the only directly comparable studies available). These results indicate that equivalent N(L)OAELs for tralopyril are likely to be up to 10-fold lower than for CL 303,630.

The endpoints addressed by studies conducted with CL 303,630 (at least in part) are toxicokinetics, sub-chronic toxicity, chronic toxicity, carcinogenicity, reproductive toxicity and neurotoxicity.

With regard to the potential toxicity of International Copper Free, information on tralopyril and the other co-formulants has been used to predict the likely health hazards of this formulation.

Following single and repeat oral doses, CL 303,630 is absorbed (64-87 %) over approximately 8-hours and the extent of absorption appears to be dose dependent. The extent of tralopyril absorption has not been investigated, but on the basis of mainly calculated physicochemical properties it appears that absorption of the neutral forms of both CL 303,630 and tralopyril will be similar. Following absorption, CL 303,630 is widely distributed with radiolabel detected in every tissue investigated. Elimination after oral administration occurs mainly in the faeces (comprising unabsorbed and biliary excreted metabolites), but metabolites were also detected in the urine. The majority of excretion occurred within the first 48 hours and was practically complete within 168 hours. Tralopyril is the first predominant metabolite of CL 303,630 and it is likely that there are no intermediates formed during the metabolism of tralopyril that are not present following administration of CL 303,630. However, it is unclear from the data provided what proportion of CL 303,630 is metabolised to tralopyril. The rate at which CL 303,630 is converted to tralopyril is also unknown, but based on the presence of un-metabolised CL 303,630 in tissues after 168 hours it can be concluded that metabolism is slow. Therefore, it is likely that the systemic dose of tralopyril following CL 303,630 administration will be less than would be the case following the administration of the same dose of tralopyril. No data on the metabolism of tralopyril has been provided. Due to these considerations, it has been decided only to use information from studies conducted with tralopyril in the risk characterisation.

For the purposes of risk assessment an absorption value of 100 % by the oral route is proposed for humans. This value is based on the observation that the degree of absorption appears to decrease with increasing dose and that human exposure to tralopyril in the product is likely to be less than 2 mg/kg, a dose at which 78-83 % absorption was observed. For the purposes of extrapolating between routes in animals studies it is proposed that a value of 70 % is used for doses in the region of 20 mg/kg and 80 % is used for doses in the region of 2 mg/kg bw.

The physiochemical and acute inhalation data support an estimate of 100 % for the extent of

inhalation absorption.

No data are available on the absorption of tralopyril itself through human or animal skin. An *in vitro* study is available in which the potential for tralopyril (4.17 %) to pass through human skin when formulated as International Copper Free was investigated. A dermal absorption value of 2 % for tralopyril was derived.

Tralopyril is an arylpyrrole that acts by uncoupling mitochondrial oxidative phosphorylation. Like most compounds with this mode of action, tralopyril is a weak lipophilic acid that transports protons back into the mitochondrial inner matrix and as such dissipates the proton gradient necessary for ATP formation.

An oral LD_{50} value of 28.7 mg/kg bw and a discriminating dose of 5 mg/kg bw in rats indicate that tralopyril meets the EU classification as Toxic (T; R25) under Directive 67/548/EEC and Acute Tox 2 – Oral (H300) under the CLP Regulation. By the dermal route, data are available for rats and guinea pigs. The dermal LD_{50} values were estimated to be > 2000 mg/kg in rats and 520-700 mg/kg bw in guinea pigs. Therefore, based on these data, classification as Harmful; R21 under Directive 67/548/EEC and Acute Tox 3 – Dermal (H311) under the CLP Regulation is considered appropriate. For the inhalation route, an estimation of the 4 h LC_{50} was not possible due to limitations in the available data. However, given that 100 % mortality was observed in one study at a concentration of 0.5 mg/L, it is likely that the classification criteria for Very Toxic T+; R26 under Directive 67/548/EEC and Acute Tox 2 – Inhalation (H330) will be met. Acute toxicity studies conducted with International Copper Free indicate that classification is not warranted by any route.

Tralopyril does not meet the criteria for classification as a skin or eye irritant in standard studies in the rabbit. However, in a skin irritation study with International Copper Free scores of > 2 for erythema were observed in 2/3 animals indicating that classification of the product as a skin irritant (R38 under Directive 67/548/EEC and Skin Irrit. 2 (H315) under the CLP Regulation) is appropriate. With regard to eye irritancy, the UK CA has agreed to waive conduct of this test and classify International Copper Free as irritating to eyes (R36 under Directive 67/548/EEC and Eye Irrit. 2 (H318) under the CLP Regulation) due to the presence of a co-formulant that is classified as a severe eye irritant. There is no evidence that tralopyril is a respiratory irritant following a single exposure by inhalation. Thus, no classification is considered appropriate. Similarly, none of the co-formulants of International Copper Free are classified as respiratory irritants and therefore, no classification is proposed. A negative result was reported with tralopyril in a guinea pig skin sensitisation study and therefore, classification is not considered appropriate. A similar study with International Copper Free also produced negative results. However, the positive control response in this study was weak and so there are concerns regarding the robustness of the negative result. Since one of the co-formulants is classified as a skin sensitiser and is present at around 9 %, the UK CA feels that it is prudent to regard International Copper Free as a skin sensitiser and classify it accordingly (R43 under Directive 67/548/EEC and Skin sens. 1 (H317) under the CLP Regulation).

There is insufficient information to determine whether or not tralopyril or International Copper Free can cause respiratory sensitisation. However, at the same time, there is no evidence that tralopyril or International Copper Free has caused respiratory sensitisation. Overall, no classification is proposed for this endpoint.

Repeated exposure to tralopyril has been investigated by the oral (28-day and 90-day studies), dermal (28-day and one 90-day studies) and inhalation (one 90-day study) routes in rat. Repeated exposure to CL 303,630 has been investigated by the oral route (90-day studies in rat and dog, 1-year dog study, 18 month mouse study and 2 year rat study) across a number of species. In the absence of any information to the contrary, the effects observed in these studies are considered relevant to humans.

Following oral exposure of rats to tralopyril for 28 days, increased liver and spleen weights are reported. At the lowest dose tested, increase in spleen weight is reported, therefore a NOAEL could not be established and a LOAEL of 11 mg/kg bw/day is derived from this study. Since only a limited number of parameters were investigated, this study is not considered appropriate for risk characterisation. Following oral exposure of rats to tralopyril for 90 days, decreased bodyweight and a dose-related increased incidence and severity of neurotoxicity characterised by histopathological changes in the central nervous system (CNS)(vacuolation of the white matter) is observed. At the lowest dose tested an increased incidence of vacuolation of the lumbar spinal cord is reported, therefore a NOAEL could not be established and a LOAEL of 5 mg/kg bw/day is derived from this study.

Following oral exposure of CL 303,630 to rats (90 days) and dogs (90 days and 1 year), reduced bodyweight was observed in both species, while neurotoxicity, as evidenced by an increased incidence of histopathological changes to the CNS, was only observed in rats. NOAELs of 3 and 4 mg/kg bw/day were reported in the dog following 90 days and 1-year exposure, respectively, based on reductions in bodyweight. In the rat, a NOAEL of 24 mg/kg bw/day was derived based on a significant reduction in bodyweight and presence of spongiform myelopathy observed in males and increased in liver weight in females.

Following chronic exposure of CL 303,630 to rats, no evidence of neurotoxicity was noted (possibly due to the dose levels employed) and a NOAEL of 4 mg/kg bw/day was derived based on decreased bodyweight at higher dose levels. Following chronic exposure of CL 303,630 to mice, neurotoxicity was observed as evidenced by histopathological changes in the CNS. A NOAEL of 3 mg/kg bw/day was derived.

Overall, following oral exposure, based on the neurotoxicity observed in the rat following 90 days exposure to tralopyril at 5 mg/kg bw/day and above and also in the 1 year neurotoxicity study (see later), the UK CA considers classification of tralopyril with T; R48/25 under Directive 67/548/EEC and as STOT RE 1 – Oral (H372) under the CLP Regulation is appropriate. With regard to International Copper Free, none of the other co-formulants are currently classified for repeated dose toxicity via the oral route, therefore, based on the criteria in the Dangerous Preparations Directive, the concentration of tralopyril (4.17 %) in International Copper Free indicates that classification with Xn; R48/22 under Directive 67/548/EEC and STOT RE 2 (via the oral route) under the CLP Regulation is appropriate.

Following dermal administration of tralopyril to rats, no adverse effects were noted following administration 6 h/day, 5 days/week for 28 days at dose levels up to 1000 mg/kg bw/day. However, as investigations were limited, this study is not considered appropriate for risk characterisation. Following administration for 6 h/day, 5 days/week for 90 days, a significant increase in absolute liver weight at the top dose (1000 mg/kg bw/day) was reported. Although

it could be argued that since no histopathological changes were observed that the increase may constitute an adaptive rather than adverse effect, the UK CA considers that it is prudent to adopt a conservative approach and set the NOAEL at the dose level below that at which these effects were observed. Therefore, a NOAEL of 300 mg/kg bw/day is derived from this study. Overall, no classification for repeat dose toxicity following dermal exposure is considered appropriate. Similarly, as none of the other co-formulants in International Copper Free are classified, no classification of International Copper Free for repeated exposure via the dermal route is proposed.

Following inhalation exposure to rats 6 h/day for 90 days, histopathology revealed a dose-related increase in incidence of epithelial inflammation of the respiratory tract at all exposure concentrations (20, 40 and 80 mg/m^3). Three treatment-related deaths and increased liver weight were reported at the top exposure concentration (80 mg/m^3), with decreased bodyweight reported at the top two exposure concentrations (40 and 80 mg/m^3). Based on the epithelial inflammation observed at the lowest exposure concentration, a NOAEC could not be established for local toxicity, therefore, a local LOAEC of 20 mg/m^3 is derived. A systemic NOAEC of 20 mg/m^3 is also derived. Overall, based on the mortality observed at 80 mg/m^3, the UK CA considers that classification with classification with Xn; R48/20 under Directive 67/548/EEC and as STOT RE 2 (H373) under the CLP Regulation is appropriate. With regard to International Copper Free, none of the other co-formulants are currently classified for repeated dose toxicity via the inhalation route; therefore, based on the criteria in the Dangerous Preparations Directive, the concentration of tralopyril (4.17 %) in International Copper Free indicates that classification of the product for toxicity following repeated inhalation exposure is not appropriate.

The potential for CL 303,630 to cause neurotoxicity has been investigated in an acute and a one-year oral neurotoxicity study in rats. No neurobehavioral or motor activity effects of treatment were evident in an acute neurotoxicity study conducted and NOAELs of 43 and 180 mg/kg were derived for general toxicity and neurotoxicity, respectively. No effects on the functional observation battery or motor activity assessments were observed in a 52-week neurotoxicity study. However, neurohistopathological alterations were observed in male rats and a NOAEL of 3 mg/kg bw/day was derived for this effect. These findings are consistent with the neurohistopathological findings observed in repeat dose studies conducted with both CL 303,630 and tralopyril. The UK CA considers vacuolation of the white matter to be a severe effect and classification with T; R48/25 under Directive 67/548/EEC and as STOT RE 1 – Oral (H372) under the CLP Regulation has been proposed.

The result of an Ames test with tralopyril was equivocal as a dose-related increase in revertant colonies was observed in one strain but the criterion for a positive result was not met due to cytotoxicity at the top dose level. The results of a repeat Ames test with tralopyril were unequivocally negative. The results of the *in vitro* mammalian cell gene mutation study and *in vivo* micronucleus study were negative. In view of these data, the UK CA considers that classification for mutagenicity is not appropriate. Likewise, as none of the other co-formulants are classified for mutagenicity, no classification for International Copper Free is proposed.

The carcinogenic potential of CL 303,630 has been investigated in two life-time studies in rats and mice. No carcinogenicity or neoplastic changes were observed in either study at concentrations that significantly reduced survival in mice and led to a significant reduction in

body weight in rats. Overall, it is concluded that tralopyril is not carcinogenic and therefore, no classification is considered appropriate. Similarly, as none of the other co-formulants are classified for carcinogenicity, no classification for International Copper Free is proposed.

Three oral developmental studies have been conducted, two of which were conducted with the precursor: CL 303,630. In the study conducted with tralopyril, a NOAEL of 10 mg/kg bw/day was derived for maternal toxicity and for developmental toxicity. The developmental toxicity manifested itself as an increase in the number of resorptions and a slight delay in development. These effects were observed in association with maternal toxicity and are likely to be a secondary non-specific consequence of the maternal toxicity.

No developmental effects were noted in the rat or rabbit study conducted with CL 303,630 at 225 mg/kg bw/day and 30 mg/kg bw/day , respectively, which were the highest doses tested. Overall, the available data do not support classification of tralopyril for developmental toxicity. Similarly, as none of the other co-formulants are classified for developmental toxicity, no classification for International Copper Free is proposed.

The potential effect of CL 303,630 on fertility was investigated in a two-generation oral (dietary) reproduction study in rats. No adverse effects on fertility parameters including mating, gestation indices and length, number of pups born, or development were observed at any dose in either generation. From this study, a NOAEL of 29 mg/kg bw/day was derived for maternal effects based on effects on bodyweight and bodyweight gain. A NOAEL of 6 mg/kg bw/day was derived for offspring effects based on lower pup weights. Overall, these data indicate that exposure to tralopyril does not produce effects on fertility and no classification is considered appropriate. Similarly, as none of the other co-formulants are classified as having effects on fertility, no classification for International Copper Free is proposed.

2.2.1.2. Effects assessment

Critical endpoints

Although a negative result was reported in a guinea pig sensitisation study with International Copper Free, the positive control response was weak and so there are concerns regarding the robustness of the negative result. Since one of the co-formulants in International Copper Free is classified as a skin sensitiser and is present at a concentration of around 9 %, the UK CA feels that it is prudent to regard International Copper Free as a skin sensitiser and classify it accordingly (R43).

Following repeated dermal administration of tralopyril to rats 6h/day for 90 days, a NOAEL of 300 mg/kg bw/day is identified based on increased liver weight observed at the top dose (1000 mg/kg bw/day). Although, in the absence of any histopathological changes, it could be argued that this finding represented an adaptive rather than adverse effect, the UK CA consider that it is prudent to adopt a conservative approach and, as such, has selected the 300 mg/kg bw /day dose level as the NOAEL for this study. Given the assumption that the dermal absorption of tralopyril through rat skin is 2 %, a systemic NOAEL of 6 mg/kg bw/day will be used in the risk characterisation for medium-term dermal exposure scenarios.

Following repeated inhalation exposure of rats to tralopyril 6 h/day for 90 days, a systemic NOAEC of 20 mg/m^3 (equivalent to 5.8 mg/kg bw/d; based on decreased bodyweight and mortality at higher exposure concentrations) and a local LOAEC of 20 mg/m^3 was derived (based on epithelial irritation).

Uncertainties

Dermal Absorption Values Used in the Risk Assessment

The ability of International Copper Free to penetrate human skin was examined *in vitro*. Radiolabelled tralopyril was formulated into an anti-fouling paint preparation at 4 % w/w and the absorption of Tralopyril investigated over a total of 24 hours. Although the length of exposure to the formulation was given as 8 hours, due to the nature of the substance (i.e. it is a paint), very little was washed off after this time (0.36 % of the applied dose). Therefore, the study effectively measured absorption following a 24-hour exposure period. Receptor fluid and rinse accounted for 0.78 % (range 0.35-1.50 %) of the applied dose, 0.15 % (range 0.01-0.27 %) was located in the skin below the stratum corneum and 95.34 % (range 82.59-104.34 %) was retained in the stratum corneum. The majority of label retained within the stratum corneum was located in the first five strips (94.69 % range 82.36-104.12 %), suggesting that the majority of the test substance was on the surface of the skin within the paint. The amount of label contained within the other layers of the stratum corneum totalled 0.68 % (range 0.11- 4.07 %). The rate of absorption increased linearly over the first 10 hours and peaked at this time point (3.0 µg equiv./cm^2/h). After this time, the rate of absorption levelled off and remained constant throughout the remainder of the study (0.24-2.5 µg equiv./cm^2/h). Therefore, the absorbed dose estimation consists of the sum of the amount in the receptor fluid and rinse, all but the first five layers of the stratum corneum, the skin below the stratum corneum and the unexposed skin around the test site, producing a mean total of 1.58 %. Consequently, UK CA feels that a dermal absorption value of 2 % through human skin is appropriate to use in the risk characterisation of tralopyril as formulated in International Copper Free.

In the rat, the extent of the dermal absorption of tralopyril is not known. However, the effects observed in the dermal toxicity studies suggest that dermal absorption is low. In the absence of any data on the extent of dermal absorption through rat skin, it would be appropriate to use a default value, the most suitable in this case being 10 %. However, the UK has taken a more conservative approach and will calculate systemic NOAELs in the rat following dermal exposure using a value of 2 %.

Inter- and Intra-species Variability

There is no definitive information to identify the relative sensitivities of humans compared with experimental animals in relation to the ability of tralopyril to cause toxicity. Similarly, there are no data to reliably inform on the potential for inter-individual variability in the susceptibility to the effects. Given these uncertainties, standard defaults of 10 to account for potential inter-species and of 10 to account for intra-species variability will be included in the risk characterisation for systemic toxicity following dermal and inhalation exposure.

Following inhalation exposure, epithelial inflammation is also observed. Thus, to account for

this a risk characterisation for local effects is also included. Based on the Technical Notes For Guidance document agreed at the technical meeting[3] for this scenario an interspecies factor of 2.5 is proposed. Given that no irritation is reported in standard skin and eye irritation tests, the local effects observed could be the result of metabolism of tralopyril at the site of contact and so an intraspecies factor of 10 is also proposed.

Route to Route Extrapolation

Toxicokinetic studies indicate that there does not appear to be significant first-pass metabolism, so following absorption similar toxicokinetic and toxicodynamic profiles of tralopyril would be expected after oral, dermal and inhalation exposures. However, although route to route extrapolation is possible, given the uncertainties in the toxicology package arising from the conversion of the CL 303,630 to tralopyril equivalents, it has been agreed that only data on tralopyril will be used in the risk characterisation to derive route-specific AEL values. In addition, an AEC will also be derived for the local risk characterisation of inhalation exposure scenarios. It should be noted that although the dermal and inhalation databases are not as extensive as the oral database, similar toxicity profiles were observed by the oral, dermal and inhalation routes. In addition, no concerns were identified for carcinogenicity and reproductive toxicity, two endpoints identified exclusively by the oral route.

Dose-response/severity of key health effect

Although a negative result was reported in a guinea pig sensitisation study with International Copper Free, the positive control response was weak and so there are concerns regarding the robustness of the negative result. Since one of the co-formulants in International Copper Free is classified as a skin sensitiser and is present at a concentration of around 9 %, the UK CA feels that it is prudent to regard International Copper Free as a skin sensitiser and classify it accordingly (R43). No dose-response information on the skin sensitisation potential of the product is available.

There are 4 key repeat-dose studies, all conducted with tralopyril, that will be used in the risk characterisation. The NOAELs/LOAELs derived from these studies are for effects observed in the most sensitive species over a particular time period via the relevant route of exposure. The studies comprise a rat developmental toxicity study for acute oral exposure scenarios; a 90-day rat study for medium term and chronic oral exposure scenarios; a 90-day dermal study for all dermal exposure scenarios and a 90-day inhalation study for all inhalation exposure scenarios.

Oral exposure scenarios

In a rat developmental study conducted with tralopyril, an overall NOAEL of 10 mg/kg bw/day was identified. No additional assessment factors are considered necessary.

Thus, for acute oral exposure scenarios, an Acceptable Exposure Level (AEL) value of 0.08 mg/kg bw/day is derived, based upon an overall assessment factor of 100 (10 x 10) and an 80 % oral absorption value. Risks are considered acceptable if the MOE is > 100 or if the

[3] http://ecb.jrc.ec.europa.eu/documents/Biocides/TECHNICAL_NOTES_FOR_GUIDANCE/Guidance %20Risk %20Characterization %20Local %20Effects_2009.pdf

systemic exposure/AEL ratio is < 1.

Vacuolation of the white matter of the CNS was the most severe effect observed in a 90-day (rat) study, conducted with tralopyril, and a LOAEL of 5 mg/kg bw/day was derived for this effect. As the value is a LOAEL, an additional factor of 3 is required to extrapolate between a LOAEL and a NOAEL.

Thus, for medium-term oral exposure scenarios, an overall assessment factor of 300 (10 x 10 x 3) and an oral absorption factor of 80 % is proposed for medium term oral exposure scenarios, giving an AEL of 0.013 mg/kg bw/day. Risks are considered acceptable if the MOE is > 300 or if the systemic exposure/AEL ratio is < 1.

No chronic data on tralopyril are available, the data requirements being satisfied with data on CL 303,630. To derive chronic AEL values it is proposal to apply an additional assessment factor of 2 to the NOAEL/LOAEL values derived from the corresponding 90-day studies.

Thus, for chronic oral exposure scenarios, an AEL of 0.007 mg/kg bw/day is derived based on an overall assessment factor of 600 (10 x 10 x 2 x 3) and an oral absorption value of 80 %. Risks are considered acceptable if the MOE is > 600 or if the systemic exposure/AEL ratio is < 1.

Dermal exposure scenarios

In a 90-day dermal (rat) study, a NOAEL of 300 mg/kg bw/day was derived following exposure to tralopyril for 6h/day, 5 days/week, due to a significant 14 % increase in female absolute liver weight and relative liver weight in both sexes at 1000 mg/kg bw/day. Although in the absence of any histopathological effects this finding could be considered adaptive rather than adverse, given the extent of the effects the UK CA consider that it is prudent to adopt a conservative approach and set the NOAEL at a dose level below that at which the effects were observed. Given that a 2 % dermal absorption value of tralopyril across rat skin is assumed, the systemic NOAEL is 6 mg/kg bw/day (i.e. NOAEL x dermal absorption value = 300 x 2/100). Based on these data, no additional assessment factors are necessary for acute and medium-term exposure scenarios. However, as no chronic dermal study is available, an additional factor of 2 will be used for establishing the acceptable MOE/AEL for chronic exposure scenarios to account for using data from a sub chronic study.

Thus, for acute and medium-term exposure scenarios an overall assessment factor of 100 (10 x 10) is proposed, giving an AEL of 0.06 mg/kg bw/day. Risks are considered acceptable if the MOE is > 100 or if the systemic exposure/AEL ratio is < 1.

For chronic dermal exposure scenarios an overall assessment factor of 200 (10 x 10 x 2) is proposed, giving an AEL of 0.03 mg/kg bw/day. Risks are considered acceptable if the MOE is > 200 or if the systemic exposure/AEL ratio is < 1.

Inhalation exposure scenarios

Rats were exposed to tralopyril by inhalation (nose only) to 0, 20, 40 and 80 mg/m^3 6 h/day for 90 days. At 80 mg/m^3, 3 treatment related deaths were observed in males. At this dose, there

was a general reduction in food consumption (up to 18 %) and terminal bodyweight was significantly decreased (16/10 % in M/F). FOB (Functional Observational Battery) observations included, stained fur (both sexes), increased open-field grooming counts in males (1.4 compared to 0.2 in the controls) during week 3 and an overall decrease in both total locomotor and ambulatory activity in males in week 3 (33/35 %, respectively) and week 12 (32 %: total locomotor activity only). Absolute lung weights in females (11 %) and relative lung weights in both sexes (25/26 % in M/F) were statistically significant increased, but no histopathological effects were observed. Histopathological changes were noted in several regions of the nasal passages. These changes consisted of inflammation (9/7 for M/F), ulceration/ erosion (9/8 for M/F), squamous/ respiratory metaplasia (7/8 for M/F) and olfactory/ respiratory degeneration (5/10 in M/F). The severity of these effects was considered minimal to mild, but in a few animals moderate epithelial erosion was observed. In the 40 mg/m^3 group, terminal body weights were statistically significantly lower in both sexes (11/8 % in M/F). FOB observations were limited to stained fur and a decrease in total locomotor activity in males (19 % compared to the controls) on week 3. Histopathology effects in nasal passages were evident, with inflammation (8/5 for M/F), ulceration/erosion (6/8 for M/F) squamous/ respiratory metaplasia (1/2 for M/F) and olfactory/ respiratory degeneration (6/9 for M/F) being observed. In the 20 mg/m^3 group, terminal male body weight was statistically significantly reduced (8 %) and stained fur was again evident but in fewer animals. At this dose, the incidence of nasal lesions was limited to minimal degeneration of the olfactory epithelium of two females.

A NOAEC of 20 mg/m^3 is derived for systemic toxicity based on decreased bodyweight in males of the 40 mg/m^3 group. This is equivalent to a systemic NOAEL of 5.8 mg/kg bw/day (assuming a rat breathing rate of 0.8 l/min/kg bw). Based on these data no additional assessment factor is proposed for acute and medium-term scenarios. However, as no chronic inhalation study is available, an additional factor of 2 will be used for establishing the acceptable MOE/AEL for chronic exposure scenarios to account for using data from a sub-chronic study.

Thus, for systemic toxicity arising from acute and medium-term inhalation exposure scenarios an overall assessment factor of 100 (10 x 10) is proposed, giving an AEL of 0.058 mg/kg bw/day. Risks are considered acceptable if the MOE is > 100 or if the systemic exposure/AEL ratio is < 1. For systemic toxicity arising from chronic inhalation exposure scenarios an overall assessment factor of 200 (10 x 10 x 2) is proposed, giving an AEL of 0.029 mg/kg bw/day. Risks are considered acceptable if the MOE is > 200 or if the systemic exposure/AEL ratio is < 1.

A LOAEC of 20 mg/m^3 is derived for local toxicity based on histopathological changes in the nasal passages. Based on these data an additional assessment factor of 3 will be included in the risk characterisation for local effects. No other assessment factors are proposed for acute and medium-term scenarios. However, as no chronic inhalation study is available, an additional factor of 2 will be used for establishing the acceptable MOE/AEL for chronic exposure scenarios to account for using data from a sub-chronic study.

Thus, for local toxicity arising from acute and medium-term inhalation exposure scenarios an overall assessment factor of 75 (2.5 x 10 x 3) is proposed, giving an AEC of 0.27 mg/m^3. For local toxicity arising from chronic inhalation exposure scenarios an overall assessment factor of

150 (2.5 x 10 x 3 x 2) is proposed, giving an AEC of 0.13 mg/m^3. For all exposure scenarios, risks are considered acceptable if the exposure concentration is below the appropriate AEC.

The potential for residues of tralopyril in food and feed of marine origin was not assessed as part of this evaluation. Member States should be aware to fully evaluate, as part of a dietary risk assessment, the potential for food/feed residues of tralopyril if application at product authorisation is being sought where there is a risk of food/feed contamination, such as its potential use on aquaculture structures. Such an evaluation should include the establishment of maximum residue levels (MRLs).

2.2.1.3. Exposure assessment

Primary exposure

Professional (Industrial) Users

The potential routes of exposure for the professional operator are via the dermal and the inhalation routes through spraying International Copper Free to vessels in dockyards and slipways at high pressure using airless spraying; mixing/loading International Copper Free into reservoirs for airless spraying for professional operations; from application by brush/roller; and removing old paint from the surface of vessels using abrasive blasting. The route of exposure for cleaning of brushes/rollers used to apply the product is dermal only. Potential exposure via the oral route is considered to be unlikely from these professional uses of products containing tralopyril.

The UK CA considers that tasks carried out by professional operators working with products containing tralopyril will be intermittent and episodic. Therefore, it is considered the most appropriate NOAEL/Acceptable Exposure Limit (AEL) for use in the risk characterisation is that for exposures of medium-term duration.

The potential exposure of operators (body weight = 60 kg) was determined using the calculation models and assumptions given in the TNsG - Human Exposure to Biocidal Products, as revised by User Guidance version 1 (EC, 2002), which represent a reasonable scenario for risk assessment purposes. The systemic dose from the total of dermal and inhalation exposures and, where appropriate, combined exposures for tralopyril have been calculated. The exposure assessments summarised below include airless spraying; mixing and loading from a reservoir; application by brush/roller, and cleaning of brushes/rollers; and removal by abrasive blasting. The exposure assessments are described in detail in Document II-B, and the predicted primary exposures to tralopyril through professional use of International Copper Free are summarised below for dermal and inhalation exposure routes and are given in Table 2.2.

Primary exposure from airless spraying, mixing and loading, application by brush/roller (including cleaning of brushes/rollers) and abrasive blasting

(a) Tier 1 assessment

In this assessment it is assumed that there is 2 % penetration of tralopyril through the skin and

100 % absorption of tralopyril via inhalation. For mixing/loading, spraying and application by brush/roller, it is also assumed that no PPE is worn other than gloves (the model data assumes gloves are present and they have therefore been considered in this assessment, as outlined in Document II-B, Section 3.2.3). The worst-case duration of airless spraying, mixing and loading and abrasive blasting tasks is 6 hours. For washing out of brushes/rollers, it is assumed no gloves are worn.

(b) Tier 2 assessment

Tier 2a - The Tier 1 assessment is refined because airless spraying, mixing and loading and abrasive blasting tasks using International Copper Free are unlikely to occur for more than 3 hours in a day. The exposure assessment is further refined to take account of the protection afforded by PPE (in addition to gloves, boots, eye/face protection, single impermeable coveralls (default penetration = 4 %) and eye/face protection). For application by brush/roller, the task duration is reduced to a more realistic level of 180 minutes.

Tier 2b – For mixing/loading and spraying, the Tier 2a assessment is further refined to take account of the protection afforded by double coveralls (default penetration = 1 %). For application by brush/roller, the single impermeable coverall value (default penetration = 4 %) is retained but the task duration is reduced to a more realistic level of 90 minutes.

Tier 2c – The Tier 2a assessment (single impermeable coveralls of penetration 4 %) is further refined to take account of the protection afforded by respiratory protective equipment (air-fed respiratory protective equipment; 40-fold protection factor). No assessment has been undertaken for application by brush/roller.

Tier 2d – The Tier 2b assessment (double coveralls of penetration 1 %) is further refined to take account of the protection afforded by respiratory protective equipment (air-fed respiratory protective equipment; 40-fold protection factor). No assessment has been undertaken for application by brush/roller.

Table 2.2 Summary of primary exposure assessments for professional uses of International Copper Free: airless spraying (Task 1); mixing and loading from reservoir (Task 2); applying by brush/roller (Task 3); cleaning brushes/rollers (Task 4) and removal by abrasive blasting (Task 5)

Exposure Scenario (PPE worn)		Estimated Internal Exposure			
		estimated oral uptake [mg/kg bw/day]	**estimated inhalation uptake** [mg/kg bw/day]	**estimated dermal uptake** [mg/kg bw/ day]	**estimated total uptake** [mg/kg bw/day]
Sprayman (Task 1)					
Tier 1 (gloves)	**Professional applying International Copper Free to vessels in dockyards and on slipways at high pressure (>100 bar) using airless sprayer** (Medium term)	NA	0.0902	1.2612	1.3514
Tier 2a (gloves, boots, eye/face protection, single coveralls - 4 % penetration; no RPE)		NA	0.0451	0.0301	0.0752
Tier 2b (gloves, boots, eye/face protection, double coveralls - 1 % penetration; no RPE)		NA	0.0451	0.0114	0.0565
Tier 2c (gloves, boots, eye/face protection, single coveralls – 4 % penetration; RPE protection factor - 40)		NA	0.0011	0.0301	0.0313
Tier 2d (gloves, boots, eye/face protection, double coveralls- 1 % penetration; RPE protection factor – 40)		NA	0.0011	0.0114	0.0125
Potman (Task 2)					
Tier 1 (gloves)		NA	0.0099	0.5014	0.5113
Tier 2a (gloves, boots, eye/face protection, single coveralls - 4 % penetration; no RPE)	**Professional mixing and loading International Copper Free into reservoirs for airless spraying in dockyards and on slipways** (Medium term)	NA	0.0049	0.0297	0.0347
Tier 2b (gloves, boots, eye/face protection, double coveralls - 1 % penetration; no RPE)		NA	0.0049	0.0228	0.0278
Tier 2c (gloves, boots, eye/face protection, single coveralls – 4 % penetration; RPE protection factor - 40)		NA	0.0001	0.0297	0.0299
Tier 2d (gloves, boots, eye/face protection, double coveralls - 1 % penetration; RPE protection factor– 40)		NA	0.0001	0.0228	0.0229

Exposure Scenario (PPE worn)		Estimated Internal Exposure			
		estimated oral uptake [mg/kg bw/day]	**estimated inhalation uptake** [mg/kg bw/day]	**estimated dermal uptake** [mg/kg bw/ day]	**estimated total uptake** [mg/kg bw/day]
Application by brush/roller (Task 3)					
Tier 1 (gloves)	**Professional applying International Copper Free by brush/roller** (Medium term)	NA	2.6×10^{-4}	0.2462	0.2465
Tier 2a (gloves, boots, eye/face protection, single coveralls - 4 % penetration; no RPE; task duration = 180 min)		NA	1.3×10^{-4}	0.0494	0.0495
Tier 2b (gloves, boots, eye/face protection, single coveralls - 4 % penetration; no RPE; task duration = 90 min)		NA	6.5×10^{-5}	0.0247	0.0247
Cleaning of brushes/rollers (Task 4)					
Tier 1 (no gloves)	**Professional cleaning a paint brush used to apply the antifouling.** (Medium term)	NA	NA	0.0143	0.0143
Tier 2 (with gloves)		NA	NA	0.0014	0.0014
Paint removal (Task 5)					
Tier 1 (gloves)	**Professional removing coatings of International Copper Free by abrasive blasting.** (Medium term)	NA	0.0036	0.0505	0.0541
Tier 2a (gloves, boots, eye/face protection, single coveralls - 4 % penetration; no RPE)		NA	0.0018	0.0012	0.0030
Tier 2b (gloves, boots, eye/face protection, double coveralls -1 % penetration; no RPE)		NA	0.0018	0.0005	0.0023
Tier 2c (gloves, boots, eye/face protection, single coveralls – 4 % penetration; RPE protection factor - 40)		NA	0.00005	0.0012	0.0013
Tier 2d (gloves, boots, eye/face protection, double coveralls -1 % penetration; RPE protection factor – 40)		NA	0.00005	0.0005	0.0005

Secondary exposure

Application and removal of International Copper Free will only take place in dry docks or at other facilities such as slipways that can handle vessels >25 m in overall length. Such sites will be inaccessible to the general public. Also, the product label will carry the phrase 'Unprotected persons should be kept out of treatment areas'. Consequently, secondary exposures to International Copper Free should not take place.

Combined exposure

It is considered that the only situation where a combined exposure (exposure that could arise from a number of tasks that could arise in a single day) could occur is for the professional applying the antifouling product, International Copper Free, by brush/roller and then on the same day washing out the paint brush/roller. In this assessment it is assumed the professional worker wears gloves, boots, eye/face protection, single coverall (4 % penetration) and no RPE when painting with brush/roller [Tier 2a (180 minutes exposure); Tier 2b (90 minutes exposure)] and gloves (Tier 2) when washing out the brush. It is anticipated that professionals will usually wear gloves when cleaning brushes/rollers. The combined exposures for these tasks are given in Table 2.3 below.

Table 2.3 Summary of combined primary exposure assessments for professional uses of International Copper Free: application by brush/roller (Task 3) and cleaning of brush/roller (Task 4)

Exposure Scenario (PPE worn)		**Estimated Internal Exposure**			
		estimated oral uptake [mg/kg bw/day]	**estimated inhalation uptake** [mg/kg bw/day]	**estimated dermal uptake** [mg/kg bw/ day]	**estimated total uptake** [mg/kg bw/day]
Professional Worker (Tasks 3 and 4)					
Tier 2a for painting (gloves, boots, eye/face protection, single coveralls - 4 % penetration; no RPE; task duration = 180 min) + **Tier 2 for brush/roller cleaning** (with gloves)	**Professional applying International Copper Free to vessels in dockyards and slipways by brush/roller and cleaning brush/roller.** (Medium term)	NA	1.3×10^{-4}	0.0495 0.0014	0.0509
Tier 2b for painting (gloves, boots, eye/face protection, single coveralls - 4 % penetration; no RPE; task duration = 90 min) + **Tier 2 for brush/roller cleaning** (with gloves)		NA	6.5×10^{-5}	0.0247 0.0014	0.0261

2.2.1.4. Risk characterisation

2.2.1.2.1. Primary Exposure

The risk characterisation will follow the tiered approach for relevant exposure scenarios. Risks of systemic toxicity associated with dermal and inhalation exposures were characterised using the values determined for medium–term exposure scenarios. For the risk characterisation of total systemic exposure (dermal and inhalation combined), the relevant primary exposures are compared with a systemic NOAEL of 6 mg/kg bw/d and an AEL value of 0.06 mg/kg bw/d. Risks are considered acceptable if the MOE is > 100 or if the systemic exposure/AEL ratio is < 1.

Risks of local effects following inhalation exposure were characterised using the AEC of 0.27 mg/m^3 for medium-term exposure scenarios. Risks are considered acceptable if the external concentration is < 0.27 mg/m^3.

Professional (Industrial) Users

Systemic exposure of professional users to tralopyril in International Copper Free will potentially occur by both dermal and inhalation routes. Thus, the overall conclusions of the risk characterisation are based on the predicted total systemic body burden. The scenarios identified all represent medium-term exposure. Given that it is proposed to classify International Copper Free as a skin sensitiser, it is recommended that professional workers will carry tasks using appropriate PPE.

The Tier 2c and2d assessments of airless spraying of International Copper Free gave acceptable MOE values of 192 and 480, respectively, indicating the risks to human health under these conditions are acceptable.

The Tier 2a and 2b assessments of mixing and loading of International Copper Free gave MOE values of 173 and 216, respectively, indicating risks to human health were acceptable under these conditions. However, it is anticipated that personnel performing this task would be wearing RPE, the Tier 2c and 2d assessments under these conditions giving MOE values of 201 and 262, respectively.

The Tier 1 assessments for application by brush/roller of International Copper Free gave an MOE of 24.3. Refined dermal exposure estimates were therefore derived (as discussed in Section 3) in which protection afforded by single coveralls (Tier 2a refinement) and by taking into account a more realistic task durations. The Tier 2a (task duration = 180 minutes) and 2b (task duration = 90 minutes) assessments for brush/roller application of International Copper Free gave MOEs of 121and 242 respectively. This indicates that the risks to human health under these conditions are acceptable when gloves and single coveralls are worn whether the duration of the task is 180 or 90 minutes. Also, given that it is proposed to classify International Copper Free as a skin sensitiser, it is recommended that professional workers will carry out this tasks wearing appropriate PPE. For washing out of brushes/rollers it was assumed no gloves would be worn for Tier 1 but for Tier 2 that gloves would be worn; MOEs were respectively 419 and 4285. Also, given that it is proposed to classify International Copper Free as a skin sensitiser, it is recognised that professional workers will carry out this task

wearing gloves. This indicates that the risks to human health under these conditions are acceptable when gloves are worn.

It is considered that the only situation where a combined exposure (exposure arising from a number of tasks undertaken in a single day) could occur is for the professional applying the antifouling product, International Copper Free, by brush/roller and then on the same day washing out the paint brush/roller. In this assessment it is assumed the professional worker wears gloves, boots, eye/face protection, single coverall (4 % penetration) and no RPE when painting with brush/roller [Tier 2a (180 minutes exposure); Tier 2b (90 minutes exposure)] and gloves (Tier 2) when washing out the cleaning brush. It is anticipated that professionals will usually wear gloves when cleaning brushes/rollers. For 90 minutes application by brush/roller, with gloves being worn to clean brushes/rollers, an acceptable MOE value of 229 was achieved. The MOE of 117 was also acceptable for professionals applying International Copper Free, by brush/roller for 180 minutes; gloves being worn when cleaning brushes/rollers. Given that it is proposed to classify International Copper Free as a skin sensitiser, it is recommended that professional workers will carry out these tasks using appropriate PPE.

An MOE of 111 was derived in the "worst case", Tier 1 assessment of removal of International Copper Free by abrasive blasting. However, given that it is proposed to classify International Copper Free as a skin sensitiser, it is recommended that professional workers will carry out these tasks using appropriate PPE. Tier 2a and 2b refinements gave MOE values of 2000 and 2609, respectively, indicating the risk to human health under these conditions is acceptable.

The predicted external exposure concentration of tralopyril for mixing and loading, application by brush/roller and removal by abrasive blasting of International Copper Free are 0.079, 0.002 and 0.011/0.065 mg tralopyril/m^3 respectively, below the AEC for medium-term exposure scenarios of 0.27 mg/m^3. This indicates that the risks to human health as a result of local toxicity under these conditions are acceptable. No inhalation exposure is anticipated during cleaning of brushes/rollers.

For application of International Copper Free by airless spraying, the predicted external exposure concentration of tralopyril is 0.721 mg/m^3, above the AEC. However, in this scenario the operators will be wearing RPE (as indicated above in the Tier 2c refinement); therefore the risks to human health as a result of local toxicity under these conditions are acceptable.

Overall, the UK proposes the following risk mitigation measures for professional use of International Copper Free:

a) Professional operators (sprayers) exposed to antifouling products containing tralopyril must wear RPE. Appropriate RPE includes air-fed respiratory equipment with combined protective helmet and visor to protect the skin of the head and neck. Impairment of vision should be avoided. For non-sprayers, the need for RPE should be informed by a suitable risk assessment [in the UK this is an assessment under The Control of Substances Hazardous to Health regulations 2002 (as amended)].

b) Professional operators (sprayers) exposed to antifouling products containing tralopyril should wear a disposable coverall with hood (providing head protection) and a second overall beneath this coverall of a contrasting colour to the antifouling product being applied. All bare

skin should be covered. The outer disposable coverall should normally be used for no more than one spraying session. The second overall should be changed regularly and whenever product break-through has been detected.

c) Professional operators (non-sprayers) exposed to antifouling products containing tralopyril should wear overalls of a contrasting colour to the antifouling product being applied. The overalls should be changed regularly and whenever product break-through has been detected.

d) All professional operators working with antifouling products containing tralopyril should wear eye/face protection and impermeable gloves of a type recommended by the antifouling manufacturer as suitable for use with the formulation. These gloves should be changed regularly, e.g. after one or two days use. Operators should wear impermeable (and non-slip) footwear that protects the lower leg.

e) The following authorisation conditions apply and they should be reflected on product labels using the following precautionary phrases:

> WEAR SUITABLE PROTECTIVE CLOTHING (COVERALLS OF A CONTRASTING COLOUR TO THE PRODUCT BEING APPLIED), SUITABLE GLOVES, EYE/FACE PROTECTION AND IMPERVIOUS FOOTWEAR THAT PROTECTS THE LOWER LEG.
>
> UNPROTECTED PERSONS SHOULD BE KEPT OUT OF TREATMENT AREAS
>
> DO NOT BREATHE SPRAY MIST
>
> DISPOSE OF PROTECTIVE GLOVES AFTER USE

If the product is to be applied by spray:

> WEAR SUITABLE RESPIRATORY EQUIPMENT SUCH AS AIR-FED RESPIRATORY EQUIPMENT WITH COMBINED PROTECTIVE HELMET AND VISOR WHEN SPRAYING
>
> WEAR SUITABLE PROTECTIVE CLOTHING (COVERALLS OF A CONTRASTING COLOUR TO THE PRODUCT BEING APPLIED, BENEATH A DISPOSABLE COVERALL WITH HOOD), SUITABLE GLOVES, EYE/FACE PROTECTION AND IMPERVIOUS FOOTWEAR THAT PROTECTS THE LOWER LEG.

2.2.2. Environmental Risk Assessment

2.2.2.1. Fate and distribution in the environment

Fate in the aquatic compartment (including sediment)

[^{14}C]-tralopyril was shown to be hydrolytically unstable, with the rate of hydrolysis increasing as the pH value increased, as the most rapid was found at pH 9. In all tests the main metabolite CL322,250 was identified along with traces of a second metabolite CL325,195. Using equation 25 of the TGD a DT_{50} of 16 h was calculated for artificial seawater at 9 °C in order to reflect the EU acceptable temperatures for marine risk assessment (Technical Guidance Document, Section 4.2; EC, 2003).

The acceptable photolysis study suggested that tralopyril is unlikely to persist in waters where sunlight is able to penetrate. In solutions buffered to pH 7 (and 10 °C) the direct photolysis degradation rate equated to an SFO DT50 of 8.9 h. In solutions of synthetic humic water (also buffered to pH 7 and maintained at 10 °C) the total photolysis degradation rate including direct and indirect photolysis equated to an SFO DT50 of 5.1 h. In total a mixture of up to 9 photolysis products were identified, of which 6 occurred in major (>10 %) amounts over the 96 h study in either pH7 or synthetic humic water. As a conservative approach the impact of photolysis on the breakdown of parent tralopyril has not been taken into account in the environmental exposure assessment. However the potential risks posed by the photolysis products have been addressed. This approach was also agreed during the technical discussion on tralopyril during TMIV2011. However it was further noted that at product authorisation stage the photolysis route may be considered relevant for inclusion in refined environmental exposure assessments, pending further evaluation of the existing information.

Tralopyril cannot be regarded as readily biodegradable but degradation under both aerobic and anaerobic sediment-water conditions was demonstrated, with degradation being shown to be more rapid in the marine than the freshwater systems. In the marine systems, tralopyril [which remained largely associated with the sediment] was shown to hydrolyse to CL322,250 and another component (compound B = CL322,248) [both of which remained largely in the aquatic phase]; with only minor other components (< 10 %) evident. For the freshwater test system, degradation was slower, although the partitioning and pattern of degradation was virtually identical.

For the purpose of risk assessment refinement, a marine aquatic total system DT50 of 0.68 d (16.3 h) (at 21 °C) derived from the anaerobic marine system is proposed for the water phase (corrected to 0.74 d at 20 °C). This value has been selected in preference to the slightly shorter value derived from the total aerobic test system due to the degree of uncertainty associated with the results in the aerobic study. For the sediment compartment a default DT50 of 1000 d is proposed.

Table 2.4 Maximum levels of identified major and minor metabolites formed in sediment-water systems following the exposure to tralopyril

Environmental conditions		Maximum metabolite levels (% of Applied Radioactivity)		
		CL322,250	CL322,248	CL325,195
Hydrolysis	**Sterile**	72.7	-	-
Photolysis	**Synthetic humic water (indirect)[a]**	8.09	21.85	19.90
Freshwater	**Aerobic**	52	-	0.38
	Anaerobic	54	36	1.23
Marine	**Aerobic**	76	30	1.87
	Anaerobic	70	73	7.05

- Not detected

[a] Maximum values for these metabolites were observed in the indirect photolysis test in the presence of synthetic humic water and are therefore recorded here

In addition to degradation, data have been provided that indicates that both tralopyril and its metabolite; CL322,250 have a strong potential to adsorb to soil/sediments and that this process is largely irreversible with K_{aOC} of 4585 l/kg and 2074 for marine sediments respectively. However, the data for the metabolite is contradictory with the sediment-water systems, which demonstrated that the metabolite remained largely in the aquatic phase but that the parent compound did associate mainly with the sediment phase. This aspect has been further addressed in the exposure assessment for this metabolite.

Fate in air

No degradation in air data have been submitted or are considered necessary due to;

- physicochemical properties of tralopyril (vapour pressure 1.9 x 10^{-8} Pa at 20 °C)
- limited exposure of this environmental compartment and
- the intended use pattern.

All of which suggest that this substance would be unlikely to enter the air compartment to any significant levels. Therefore, it has been accepted that there is justification for the non-submission of data for this endpoint. However in order to consider tralopyril against the POP criteria with regard to long range transport potential, the UK CA has estimated the atmospheric half-life due to reaction with OH radicals (using the AOPWINNT v 1.92a tool). The estimation resulted in a half-life of 77.5 h (equivalent to 6.5 d assuming a 12 h day and an OH radical concentration of 1.5E6 OH/cm^3). This is clearly above the 2 d trigger for raising concern of potential for long-range transport. However, when taking into account the very low vapour pressure, likely limited environmental exposure and rapid degradation in the main exposed environmental compartment (e.g. water), the UK CA concluded that the risk of long range transport will in reality be very low.

Fate in the terrestrial compartment

No soil degradation data have been submitted or are considered necessary due to limited exposure of this environmental compartment. The mobility of tralopyril and its metabolites has already been discussed within the aquatic fate section above.

2.2.2.2. Effects assessment

Predicted No Effects Concentration in STP

Only non-standard NOEC data against tralopyril are available for fresh and marine sediment-water microbial biomass, which are not considered acceptable. However, the ready biodegradation study does provide an endpoint for use in determining a PNEC value for tralopyril, as under the conditions tested; 39.4 mg a.s. l^{-1} did not inhibit the respiration of the STP microorganisms as shown by the toxic control.

Therefore, in the absence of any other data the UK CA has taken 39.4 mg a.s. l^{-1} as the NOEC and applied an AF of 10 to derive a $PNEC_{STP}$ of **3.94** mg a.s. l^{-1}.

Predicted No Effects Concentration in surface waters

The toxicity of tralopyril and its major (CL322,250 and CL322,248) and minor (CL325,195) metabolites to aquatic organisms have been documented by acute and long-term studies. The most sensitive endpoints for each trophic level tested are;

Tralopyril

Data against a range of marine and freshwater species have been evaluated. The most sensitive endpoints for each trophic level tested are;

Acute

- Rainbow trout (*O. mykiss*): LC_{50} (96 h) = 1.3 µg l^{-1}
- Eastern oyster (*C. virginica*): EC_{50} (96 h) = 0.66 µg l^{-1}
- Freshwater algae (*P. subcapitata*): EC_{50} (48 h) = 12 µg l^{-1}
- Freshwater aquatic plant (*L. gibba*): EC_{50} (7 d) = 88 µg l^{-1}

Chronic

- Zebra fish (*D. rerio*): $NOEC_{larval\ weight}$ (33 d) = 0.17 µg l^{-1}
- Water flea (*D. magna*): NOEC (21 d) = 0.20 µg l^{-1}
- Freshwater algae (*N. pelliculosa*): NOE_rC (48 h) = 0.73 µg l^{-1}

The available data show that the Eastern oyster is the most acutely sensitive and the Zebra fish the most sensitive following chronic exposure. The tralopyril risk assessment has to address concerns to the marine and freshwater environment and so the additional guidance within the TGD on the marine effects assessment has been considered.

The AF needed to calculate a PNEC in the marine environment requires endpoints from 2 additional invertebrate taxonomic groups, in order to establish the most sensitive invertebrate species. Without this the TGD recommends an additional factor of 10 compared to the freshwater AF derivation. For tralopyril the available acute invertebrate endpoints includes a freshwater crustacean, a marine crustacean and a marine mollusc (growth not mortality measured), which provides only one additional marine taxonomic group compared the available freshwater species. Unfortunately, the available chronic endpoints include only the marine and freshwater crustaceans, when the marine mollusc was the most sensitive species tested following acute exposure. However, the reproducibility and reliability of chronic studies against molluscs and other marine invertebrates is relatively unknown for regulatory purposes. Overall, the fish data has been shown to be the most sensitive, and whilst the lack of chronic data against molluscs may be of concern for some Member States it is important to note that such organisms are also the target organism, and so the sensitivity observed is to be expected.

An assessment factor of 100 has been applied to the lowest available chronic endpoint in order to derive a marine $PNEC_{surface\ water}$ and an assessment factor of 10 for a freshwater $PNEC_{surface\ water}$;

- Marine $PNEC_{surface\ water}$ = 0.17 µg l^{-1}/100 = **0.0017 µg l^{-1}**
- Freshwater $PNEC_{surface\ water}$ = 0.17 µg l^{-1}/10 = **0.017 µg l^{-1}**

CL322,250

Data against a range of marine and freshwater species have been evaluated. The most sensitive endpoints for each trophic level tested are;

Acute

- Rainbow trout (*O. mykiss*): LC_{50} (96 h) = 520 µg l^{-1}
- Eastern oyster (*C. virginica*): EC_{50} (96 h) = 290 µg l^{-1}
- Marine algae (*S. costatum*): EC_{50} (96 h) = 660 µg l^{-1}
- Freshwater aquatic plant (*L. gibba*): EC_{50} (7 d) = > 990 µg l^{-1}

Chronic

- Zebra fish (*D. rerio*): $NOEC_{larval\ survival}$ (35 d) = 69 µg l^{-1}
- Mysid shrimp (*A. bahia*): NOEC (28 d) = 82 µg l^{-1}
- Marine algae (*S. costatum*): NOE_rC (96 h) = 500 µg l^{-1}

As for the parent compound, the available data show that probably with the exception of aquatic plants, toxicity of CL322,250 is within the same order of magnitude across the trophic levels, with the Eastern oyster proving to be the most acutely sensitive and the Zebra fish the most sensitive following chronic exposure.

The same approach has been applied to the data for this metabolite as that for the parent compound and an assessment factor of 100 has been applied to the lowest available chronic endpoint in order to derive a marine $PNEC_{surface\ water}$ and an assessment factor of 10 for a freshwater $PNEC_{surface\ water}$;

- Marine $PNEC_{surface\ water}$ = 69 µg l^{-1}/100 = **0.69 µg l^{-1}**
- Freshwater $PNEC_{surface\ water}$ = 69 µg l^{-1}/10 = **6.9 µg l^{-1}**

CL322,248

Data against a range of marine and freshwater species have been evaluated. The most sensitive endpoints for each trophic level tested are;

Acute

- Sheepshead minnow (*C. variegatus*): LC_{50} (96 h) = 89,000 µg l^{-1}
- Mysid shrimp (*A. bahia*): LC_{50} (96 h) = 4600 µg l^{-1}
- Freshwater algae (*N. pelliculosa*): EC_{50} (72 h) = > 980 µg l^{-1}
- Freshwater aquatic plant (*L. gibba*): EC_{50} (7 d) = > 930 µg l^{-1}

Chronic

- Marine algae (*S. costatum*): NOE_rC (96 h) = 630 µg l^{-1}

The chronic endpoint for algae cannot be considered the most sensitive, since the acute effect level against algae was not established (> 980 µg l^{-1}) and so may have not been the most acutely sensitive. Therefore, the 96 h acute LC_{50} endpoint available for the marine shrimp *A. bahia* of 4600 µg l^{-1}, and applied an AF of 10000 for the marine PNEC and 1000 for the freshwater PNEC. This is because the Mysid shrimp endpoint has been established but does not provide data from the wider marine invertebrate species as required by the TGD.

- Marine $PNEC_{surface\ water}$ = 4600 µg l^{-1}/10000 = **0.46 µg l^{-1}**
- Freshwater $PNEC_{surface\ water}$ = 4600 µg l^{-1}/1000 = **4.6 µg l^{-1}**

CL325,195

Data against a range of marine and freshwater species have been evaluated. The most sensitive endpoints for each trophic level tested are;

Acute

- Sheepshead minnow (*C. variegatus*): LC_{50} (96 h) = 16000 µg l^{-1}
- Mysid shrimp (*A. bahia*): LC_{50} (96 h) = 12000 µg l^{-1}
- Freshwater algae (*N. pelliculosa*): EC_{50} (72 h) = 1500 µg l^{-1}
- Freshwater aquatic plant (*L. gibba*): EC_{50} (7 d) = 13000 µg l^{-1}

Chronic

- Zebra fish (*D. rerio*): $NOEC_{larval\ survival}$ (35 d) = 91.1 µg l^{-1}
- Freshwater algae (*N. pelliculosa*): NOE_rC (96 h) = 850 µg l^{-1}

According to the acute toxicity data, it is the algal species that are the most sensitive species to this minor metabolite. The fish and invertebrates are of the same order of magnitude, but unfortunately no chronic endpoint has been submitted for the invertebrates. However, the UK CA has taken the most sensitive chronic endpoint available for the Zebra fish of 91.1 µg l^{-1} (35 d $NOEC_{larval\ survival}$) and applied an AF of 1000 instead of taking the 96 h acute LC_{50} endpoint available for the marine shrimp *A. bahia* and using an AF of 10000, as the resulting PNEC is lower. For the freshwater PNEC an assessment factor of 100 is used. This is because without chronic data against the Mysid shrimp, the UK CA cannot be confident that a PNEC based on fresh water endpoints would be sufficiently protective of the marine environment.

- Marine $PNEC_{surface\ water}$ = 91.1 µg l^{-1}/1000 = **0.0911 µg l^{-1}**
- Freshwater $PNEC_{surface\ water}$ = 91.1 µg l^{-1}/100 = **0.911 µg l^{-1}**

Predicted No Effects Concentration in sediments

For all substances tested only acute toxicity endpoints are available. According to the TGD, where only acute toxicity results are available (at least one) the risk assessment is performed both on the basis of the test result of the most sensitive species using an assessment factor of 1000 and on the basis of the Equilibrium Partition Method (EPM):

$$PNEC_{sediment} = \frac{K_{susp-water}}{RHO_{susp}} \times PNEC_{aquatic} \times 1000$$

Therefore, the UK CA has presented 2 PNEC values for tralopyril and its primary metabolite; CL322,250.

Tralopyril

$PNEC_{data}$

Acute (survival and growth) data against one marine and one freshwater sediment species have been evaluated. The endpoints for each are;

Acute

- Marine amphipod (*L. plumulosus*): LC_{50} (10 d) = 1.1 mg kg^{-1} (dry weight)
- Freshwater amphipod (*H. azteca*): LC_{50} (10 d) = 2.2 mg kg^{-1} (dry weight)

The most sensitive endpoint is 1.1 mg kg^{-1}. Therefore; the freshwater or marine sediment;

- $PNEC_{data\text{-}sediment}$ = 1.1/1000 = **0.001 mg kg^{-1}** (dry weight)

$PNEC_{EPM}$

The UK CA has used the following inputs for the EPM equation to derive the PNEC;

RHO_{susp} = 1150 kg m^{-3} (bulk density of wet suspended matter)

$K_{susp-water}$ = 115.5 m^3 m^{-3} (marine) or 465.6 m^3 m^{-3} (freshwater) (calculated using equation 23 and 24, p 47 of the TGD based on Koc values of 4585 l/kg (marine) or 18586.5 l/kg (freshwater))

$PNEC_{aquatic}$ = 0.0000017 mg l^{-1} (marine) or 0.000017 mg l^{-1} (freshwater)

Equation 70 of the TGD based on equilibrium partitioning theory gives the formula for deriving the PNECsed:

$$PNEC_{sed} = \frac{K_{susp-water}}{RHO_{susp}} \cdot PNEC_{water} \cdot 1000$$

This gives $PNEC_{sediments}$ of;

- Marine $PNEC_{EPM\text{-}sediment}$ = **0.00017 mg kg^{-1}** (wet weight)
- Freshwater $PNEC_{EPM\text{-}sediment}$ = **0.0069 mg kg^{-1}** (wet weight)

Conclusion

Following the guidance within the TGD, the UK has concluded that the most appropriate $PNEC_{sediment}$ endpoint for use in marine risk assessment is **0.00017 mg kg^{-1}** (wet weight).

Note that this value has been derived assuming equilibrium partitioning and uses the bulk density of wet suspended matter. This value is appropriate for use in risk assessments with the simple Tier 1 PECsediment values, which have also been derived assuming equilibrium partitioning and using a bulk density of wet suspended matter and are therefore expressed as a wet weight value. Since both the PEC and PNEC for sediment at Tier 1 are derived using the same assumptions, the overall PEC:PNEC ratios are identical to those derived for surface water at Tier 1 (see Tables 2.3 and 2.12 of Doc IIC).

However some of the environmental exposure assessments reported in Doc IIB use the MAMPEC model to derive PECsediment values (e.g. in-service exposure assessments and Tier 2 application, maintenance and repair exposure assessments). These are also expressed as a suspended matter concentration based on the assumptions of equilibrium sorption, but concentrations from MAMPEC are expressed on a dry weight basis. The UK CA considers it inappropriate to compare a dry weight PEC with a wet weight PNEC and has therefore revised the sediment $PNEC_{epm}$ using the bulk density of dry suspended matter (i.e. 250 kg m^{-3} rather than 1150 kg m^{-3} based on the default assumptions of the TGD). Based on equation 70 of the TGD the revised dry weight marine PNECsediment is calculated to be **0.00079 mg kg^{-1}** (dry weight). This value, which is lower than the measured dry weight PNECsediment, will be used against the dry weight PECsediment values from MAMPEC. Further discussion on this point

is included in Doc IIC.

CL322,250

PNEC$_{data}$

Acute (survival and growth) data against one marine and one freshwater sediment species have been evaluated. The endpoints for each are;

Acute

- Marine amphipod (*L. plumulosus*): LC_{50} (10 d) = > 70 mg kg^{-1} (dry weight)
- Freshwater amphipod (*H. azteca*): LC_{50} (10 d) = > 35 mg kg^{-1} (dry weight)

The LC_{50} was not established in either test with < 50 % effect reported at the highest concentration tested. However, for the purpose of risk assessment a precautionary LC_{50} of 35 mg kg^{-1}has been assumed. Therefore; the freshwater or marine sediment;

- $PNEC_{data\text{-}sediment}$ = 35/1000 = **0.035 mg kg^{-1}** (dry weight)

PNEC$_{EPM}$

The UK CA has used the following inputs for the EPM equation to derive the PNEC;

RHO_{susp} = 1150 kg m^{-3} (bulk density of wet suspended matter)

$K_{susp\text{-}water}$ = 52.9 m^3 m^{-3} (marine) or 287.4 m^3 m^{-3} (freshwater) (calculated using equation 23 and 24, p 47 of the TGD based on Koc values of 2079 l/kg (marine) or 11459 l/kg (freshwater)))

$PNEC_{aquatic}$ = 0.00069 mg l^{-1} (marine) or 0.0069 mg l^{-1} (freshwater)

This gives $PNEC_{sediments}$ of;

- Marine $PNEC_{EPM\text{-}sediment}$ = **0.032 mg kg^{-1}** (wet weight)
- Freshwater $PNEC_{EPM\text{-}sediment}$ = **1.72 mg kg^{-1}** (wet weight)

Conclusion

Following the guidance within the TGD, the UK has concluded that the most appropriate $PNEC_{sediment}$ endpoint for use in marine risk assessment is **0.032 mg kg^{-1}** (wet weight). It would be technically possible to correct this PNECsediment value based on the dry bulk density of suspended matter as was done for tralopyril above. However in this case the UK CA does not consider this additional refinement necessary because if the $PNEC_{EPM}$ were to be corrected in the same manner, the lowest dry weight PNECsediment for risk assessment would then revert to being the measured value of 0.035 mg kg^{-1}. Since the difference between the two

values is small, and no risks for the metabolite were identified based on the lower, more conservative PNEC value of 0.032 mg kg^{-1} no further refinement is considered necessary.

CL322,248

Although there are 2 data endpoints available, against the marine amphipod (*L. plumulosus*) with an LC_{50} (10 d) of > 75 mg kg^{-1} and the freshwater amphipod (*H. azteca.*) with an LC_{50} (10 d) of > 37 mg kg^{-1}, unfortunately, as no K_{oc} endpoint is available the use of the EPM method is not possible. It is the UK CA's opinion that as the endpoint is no more toxic than the major metabolite CL322,250, which will be formed in greater quantities than that of this metabolite, the sediment assessment for CL322,250 will be sufficient to assess the risk for this metabolite also.

CL325,195

Although there are 2 data endpoints available against the marine amphipod (*L. plumulosus*) with an LC_{50} (10 d) of > 27 mg kg^{-1} and the freshwater amphipod (*H. azteca.*) with an LC_{50} (10 d) of > 49 mg kg^{-1}. Unfortunately, as no K_{oc} endpoint is available the use of the EPM method is not possible. It is the UK CA's opinion that as the endpoint is no more toxic than the major metabolite CL322,250, which will be formed in greater quantities than that of this metabolite, the sediment assessment for CL322,250 will be sufficient to assess the risk for this metabolite also.

Predicted No Effects Concentration in soil

The only available endpoint is against seedling emergence in rice (*O. sativa*) against tralopyril, which is an EC_{25} of > 170 µg l^{-1}. Therefore, the UK CA has again used the EPM method available in the TGD (eq. 72) for the soil PNEC of tralopyril and primary major metabolite CL322,250;

$$PNEC_{soil} = \frac{K_{soil-water}}{RHO_{soil}} xPNEC_{aquatic} x1000$$

This gives soil PNECs of;

- Tralopyril is 0.003 mg kg^{-1}
- CL322,250 is 0.82 mg kg^{-1}

Predicted No Effects Concentration in biota

The log Kow of the parent compound tralopyril (R107894) is pH dependant with values of 4.4, 3.5 and 2.4 reported for pH 4, 7 and 9 respectively.

A bioconcentration study has been conducted in carp (*Cyprinus carpio*). Two concentrations were used and these were equivalent to average measured concentrations of 0.0048 and 0.048 µg l^{-1}. Data on the uptake of tralopyril indicated that mean measured tissue

concentrations were below the level of detection of 0.15 ng g^{-1}. As the steady state BCF for tralopyril was less than 3.2 ml g^{-1} neither the uptake nor depuration rate constants were determined.

It is proposed, as a very worst case estimate, to assume, in the first instance that the BCF is equal to 3.2 ml g^{-1}. It should be noted that not only is this figure an over-estimate based on the above study, it is also an over estimate based on the fact that tralopyril will be rapidly degraded to the primary and secondary metabolites CL322,250 and CL322248. CL322,250 has a log K_{ow} of 0.54. No log $_{Kow}$ is available for CL322,248, however on the basis of structural similarity to CL322,250 it is considered to have a log $_{Kow}$ that is similar to CL322,250, i.e. less than 3.

Birds

Tralopyril

One short-term dietary test is available with tralopyril. The study was 11 days in duration; however exposure to the test compound was for 5 days only. The LC_{50} for the Mallard Duck is 10.8 mg a.s. kg^{-1}. The Assessment Factor with endpoints from a 5-day dietary study is 3000 (see Equation 79 and Table 23 of the TGD).

Therefore the PNECoral is 0.0036 mg a.s. kg^{-1}.

Metabolites

Data has also been submitted on the toxicity of the metabolites CL322,250 and CL322,248. CL322,250 is of lower toxicity than the active substance with a 5-day LC_{50} of 962 mg kg^{-1}. It has a Log Kow of 0.54; therefore no secondary poisoning assessment is required. CL322,248 is of low toxicity with a 5-day LC50 of >5600 mg kg^{-1}. No Log Kow is available for this metabolite, however it is considered to of a similar order to CL322,250, hence no secondary poisoning assessment is required for this metabolite.

Mammals

According to Table 3.5 in Doc IIA and Section 1.1.3.4 in Doc IIC the key endpoint is from a 90 day oral toxicity study in the rat. The LOAEL is 80 mg kg^{-1} whilst the NOAEL is less than 80 mg kg^{-1}. As this NOAEL is a less-than figure it is proposed to use the same approach as outlined in Section 1.1.3.4 and hence adjust the LOAEL by a factor of 3, hence the predicted NOAEL is 26.7 mg kg^{-1}. According to Table 23 of the TGD if a 90 day study is used then an assessment factor of 90 should be used.

Therefore, the PNECoral is 0.3 mg kg^{-1}.

Earthworm

No data or estimations are considered necessary due to use pattern and properties of substance, which suggest that the scale of soil exposure should be minimal.

2.2.2.3. PBT and POP assessment

PBT assessment

Active substance

According to the TGD, 'The Persistent, Bioaccumulative and Toxic (PBT) assessment is considered to be different from the local and regional assessments approaches, as it seeks to protect ecosystems where risks are more difficult to estimate'. Under the Biocidal Products Directive (BPD), a PBT assessment is needed to demonstrate that a substance does not fulfil selection under the United Nations Environment Programme – Persistent Organic Pollutants convention (UNEP-POPs) to limit emissions to the environment of those chemicals with high potential for persistence, bioaccumulation, long-range transport and adverse effects on human health and the environment. Any substance that is found to be either a PBT or very Persistent very Bioaccumulative (vPvB) substance shall not be Approved unless releases to the environment can be effectively prevented.

Persistence

Data have been presented, which shows that tralopyril degrades rapidly in the aquatic environment (at 9 ºC) with predicted hydrolysis DT50 values of 16 h (pH 8.2). Tralopyril was also shown to degrade under both aerobic and anaerobic sediment-water conditions, with degradation being shown to be more rapid in the marine than the freshwater systems. An aerobic total system DT50 of 12.75 d (at 21 °C or 26.19 d at 12 °C) and 0.34 d (at 21 °C or 0.89 d at 9 °C) or an anaerobic DT50 of 35.46 d (at 21 °C or 72.6 at 12 °C) and 0.68 d (at 21 °C or 1.78 d at 9 °C) can be calculated for fresh and marine sediment-water whole systems respectively. Therefore, the a.s. does not fulfil the criteria for a persistent compound according to the TGD (> 40 d in freshwater or > 60 d in marine water and/or > 120 d in freshwater sediment or > 180 d in marine sediment). No data have been provided to assess the persistence in soil against the relevant criteria. However, taking into account the rapid degradation in the aquatic environment and the susceptibility of the substance to degradation via hydrolysis and aqueous photolysis, the UK CA concludes that tralopyril would be very unlikely to breach the persistence triggers in soil either. Therefore, no further data are required.

Bioaccumulation

A substance is considered to have the potential to fulfil the criterion of bioaccumulation when the log K_{ow} exceeds 4.5 and for tralopyril the log K_{ow} is pH dependant with values of 4.4, 3.5 and 2.4 reported for pH 4, 7 and 9 respectively. Therefore, under fresh and marine water conditions tralopyril does not meet the criteria set by the TGD.

In addition, a bioconcentration study has been conducted in carp (*Cyprinus carpio*) that indicated that the steady state BCF was < 3.2 ml g^{-1}. This value is < 2000 (trigger according to TGD) and suggests that there is no concern of bioaccumulation and biomagnification of tralopyril in the environment and the bioaccumulation criterion is not fulfilled.

Toxic

According to the most sensitive endpoint available for tralopyril (*C. virginica*: EC_{50} (96 h) = 0.66 µg l^{-1}) the acute endpoint is below the trigger of < 0.01 mg l^{-1}. Therefore, the toxic criterion is fulfilled according to the TGD.

Conclusion

With regard to the active substance, as tralopyril has only fulfilled one criterion (T) out of the three considered, it can be accepted that it is not a PBT substance and also should not be considered a candidate for substitution based on the PBT criteria.

Metabolites

With regard to metabolites, the issue of the PBT criteria for them was briefly discussed during the commenting round. One Member State was concerned that the potential persistence of some of the metabolites could mean that tralopyril itself should be considered to breach this trigger. However, the UK CA is of the view that the active substance and each metabolite should be considered individually against the various PBT criteria. This is in line with our understanding of the REACH guidance[4]. In the case of the main metabolites of tralopyril, it is clear that none of them would be considered a PBT substance. Neither metabolite CL322,250, 322,248 or 325,195 breaches the T trigger based on the submitted data sets of aquatic ecotox studies. With regard to the B criteria, the log Kow of CL322,250 is 0.54, and therefore clearly below the trigger of 3. This conclusion can also be read across to the structurally similar metabolite CL322,248 (in both substances the trifluromethyl group is replaced by the polar carboxylic acid group, greatly reducing bioaccumulation potential). Although there is less information available for CL325,195, from a structural point of view, the addition of the OH group would likely increase polarity and mean this structure is a lower bioaccumulation risk compared to parent tralopyril, which does not itself breach the B criteria. With regard to persistence, for CL322,250 the whole system half lives in water sediment studies were less than 30 d. For CL322,248, this may possibly breach the P criteria based on limited data from the water sediment studies. In some cases the duration of the water sediment studies was not long enough to determine a reliable indication of persistence of this metabolite. However even if this metabolite were conservatively considered to breach the P criteria, the absence of the B and T properties means that we can confidently conclude that none of the metabolites breach all three PBT criteria.

Conclusion

With regard to the metabolites (CL322,250, CL322,248 and CL325,195) none are considered to breach either the B and T criteria. Therefore, it is concluded that none of the metabolites would be considered to be a PBT substance. This was agreed at Technical Meeting, Competent Authority Meeting and Biocidal Products Committee Meeting.

[4] According to page 43 of ECHA PBT guidance (Chapter R.11) it is stated that "For all relevant metabolites it must be checked that **they do not fulfil the criteria for PBT or vPvB substances"**. Therefore the persistence of a metabolite should not influence the persistence criteria for active substances and should just be assessed as a PBT or vPvB substance in its own right.

Overall PBT conclusion

Tralopyril only fulfilled one criterion (T) out of the three considered and is therefore not a PBT substance; in addition, its metabolites were not considered PBT substances. Therefore, tralopyril should not be considered a candidate for substitution based on the PBT criteria.

POP assessment

The criteria for a substance being a persistent organic pollutant (POP) are 'P', 'B' and having the potential for long range transport. In addition, high toxicity can breach the 'B' criterion, in which case a substance will be a persistent organic pollutant if it is 'P', demonstrates the potential for long range transport, and is either 'B' or 'T'.

Tralopyril has been identified as 'T', but is not considered to be 'P nor 'B'. Theoretically, tralopyril does pose a possible risk of long-range transport, on the basis of an estimated atmospheric half-life of 77.5 h, equivalent to 6.5 d assuming a 12 h day and an OH radical concentration of 1.5E6 OH/cm^3 (estimated using the AOPWINNT v 1.92a tool). However, when taking into account the very low vapour pressure and low Henry's Law constant, likely limited environmental exposure and rapid degradation in the main exposed environmental compartment (e.g. water) the UK CA concluded that the risk of long-range transport will in reality be very low.

Given the above, tralopyril does not meet the criteria for being a persistent organic pollutant.

2.2.2.4. Exposure assessment

The environmental exposure assessment presented has been produced using all of the relevant information available in the Organisation for Economic Co-operation and Development (OECD) series on Harmonisation of Emission Scenario Documents (ESDs); '*An Emission Scenario Document for Antifouling Products in OECD countries*' (OECD, 2004) and where necessary the Technical guidance document for risk assessment (TGD; EC, 2003) and the conclusions of the Technical Meeting (TMIII 2011) where several generic issues on PT21 exposure assessments were discussed and agreed.

The antifouling product; 'International Copper Free', used to support the Approval of tralopyril may be applied by professional users via airless spray, brush or roller in a paint that can be applied to:

i) Hulls and other immersed parts of large marine-going vessels such as commercial boats and ships, navy and other government vessels and super-yachts (>25 m in overall length).

ii) Immersed marine structures.

Treatment of vessels <25 m in overall length is not being sought at this time.

Whilst, this product contains 2 a.s.; tralopyril (1 – 10 %) and zinc pyrithione (3 – 10 %), the

exposure and subsequent risk assessment, has concentrated on tralopyril alone, as the new a.s.. However, for product authorisation a consideration of the need for a combined risk assessment to both active substances will be necessary.

There are two main scenarios where the biocides from antifouling paints could enter the environment, the primary route being direct release to the aquatic environment during use, where the biocides will leach directly into the aquatic environment when the boat is in-service. The second situation revolves around vessel maintenance and construction. During these processes (application and removal) there is the potential for antifouling dry paint fragments, containing biocide, to reach surface soil and water. Therefore, the UK CA considers the main potential exposure routes for the environment from the use of antifouling products in general could include;

1) Application phase (new build and maintenance) through spray, brush or rollers may result in;

    a) Direct exposure of the immediate and local air compartment due to release of volatile/particulate residues, resulting during spraying.

    b) Professional application may result in losses to the local floor surface resulting in;
        i. Direct exposure of the sewage treatment plant (STP)/surface waters via collection sumps
        ii. Indirect exposure of soil (STP sludge disposal)
        iii. Indirect exposure of surface waters
        iv. Indirect exposure of biota (aquatic: fish →terrestrial: birds/mammals)

2) Removal phase (maintenance only) through high pressure water washing that will result in waste water containing antifouling paint particulates, which should be collected via sumps. Or physical scraping of painted surfaces to remove solid waste. Both of these methods of removal may result in;

    a) Direct exposure of the STP/surface waters via collection sumps
    b) Direct exposure of landfill/special waste facilities (solid waste)
    c) Indirect exposure of soil (STP sludge disposal)
    d) Indirect exposure of surface waters
    e) Indirect exposure of biota (aquatic: fish →terrestrial: birds/mammals)

3) In-service phase; leaching from the treated surfaces on contact with water will lead to;

    a) Direct exposure of surface waters (marine and freshwaters)
    b) Indirect exposure of fish →birds/mammals

Note that based on the current proposed uses on large marine-going vessels the standard OECD ESD assumptions are that no exposure to an STP or soil occurs and these environmental compartments have not been addressed as part of this assessment. Where a particular Member State concern exists, that is not covered by the scenarios available; the UK CA recommends that a detailed consideration of this should be made at the product authorisation stage.

The application and removal phases of use have been developed as part of the OECD ESD project and are considered together as there are similarities in terms of location of activity, emission controls and best practices. A tiered approach has been adopted. Tier 1 assumes that the emission loads based on the OECD ESD enter a static water body with the dimensions of the OECD-EU commercial harbour (appropriate for professional application and removal activities on large marine-going vessels). A refined Tier 2 assessment has also been performed using the same emission loads entering the OECD-EU commercial harbour environment simulated with the MAMPEC model. At Tier 2 the results are separated into the MAMPEC predictions for concentrations within the OECD-EU Commercial harbour (Tier 2a) and also the predictions for concentrations in the adjacent areas, taken as being representative of the wider environment (Tier 2b). All concentrations are reported as the average total concentrations predicted by MAMPEC at 9 °C for simplicity. A Tier 3 assessment includes consideration of risk mitigation measures and a reduced application factor of 30 % based on market share data.

The in-service use of the product is a principle route of entry into the environment for the a.s. after it is applied to the surface of a vessel. The leaching of an a.s. from a painted surface largely depends on the paint formulation and matrix type. A leaching rate can be estimated from real data (laboratory or field investigations), or predicted by modelling the total a.s. (or substance of concern) content against the in-service life of the paint. Typically, the leaching of compounds from antifouling paints exhibits an exponential decay rate (i.e. high initial loss of the compound followed by an asymptotic levelling off). Antifouling paints are designed to achieve this pattern of loss in order to give a continuous steady release of biocide over the lifetime of the paint. In doing so it can be guaranteed that there will be sufficient biocide release to ensure acceptable efficacy throughout the life of the paint.

For the simple first tier exposure assessment of tralopyril, the leach rate has been calculated using the CEPE mass balance method giving an estimated value of 2.46 µg tralopyril $cm^{-2} d^{-1}$. Levels of known metabolites have been estimated by applying the % reported from aerobic aquatic degradation studies (see Table 2.4) with adjustment for molecular mass. Additional data were available from laboratory leaching studies with comparable paint formulations using the ASTM leaching test method that investigated the effect on temperature on leaching. However these temperature corrected leaching rates were not used in the exposure assessments due to the lack of guidance available at the time of evaluation regarding how such data should be used in the exposure assessment. However if an adequately justified method of applying temperature correction is developed in the future, this refinement could be used in subsequent assessments e.g. at product authorisation. The CEPE mass balance method has been used to derive the leaching rate of 2.46 µg tralopyril $cm^{-2} d^{-1}$ with no further correction applied, despite the availability of substance specific leaching data. This approach is considered conservative. However the UK RMS considers that the use of the Finnie correction factor of 2.9 could potentially be supported in the future for additional assessments of tralopyril (e.g. at product authorisation level for example) once clear guidance on the use and justification of this correction factor is developed and agreed at EU level.

2.2.2.5. Risk characterisation

The ecotoxicological profiles clearly show that tralopyril is at least an order of magnitude more toxic in all compartments than its metabolites. However, the PNEC data suggests that the

toxicity of the metabolites increases with CL322,250 < CL322,248 < CL325,195 whilst, if we consider the actual acute and available chronic toxicity endpoints alone, the reverse is true; CL322,250 being > CL322,248, which is > CL325,195. This decreasing trend of magnitude is consistent with the levels of corresponding metabolites formed as a result of aerobic degradation of the a.s. with CL322,250 [~76 % a.s] > CL322,248 [~ 30 % a.s.] > CL325,195 [~ 2 % a.s.]. Therefore, the PNEC values can be shown to be an artefact of the size of the assessment factors used as a greater level of testing is available for the primary major metabolite than the secondary and tertiary metabolites. In fact these data would support the use of lower assessment factors for tertiary metabolites, where acute toxicity is shown to be significantly less than that of the parent compound. However, in the absence of an agreed approach to such issues, the assessment factors as proposed by following the TGD guidance have been used. In accepting this, no risk assessment against the minor metabolite; CL325,195, has been performed, which is also in line with approaches agreed (> 10 % metabolites are of concern) at Technical Meeting and within guidance given within the TGD on risk assessment.

The exposure and subsequent risk assessment based on the application and removal stages of use have also focussed on the a.s. and primary major metabolite CL322,250 only. This is because the risk quotients for CL322,250 are significantly < 1 and since the levels of CL322,248 would be ~30 % of the parent compound, compared to 70 % being CL322,250 then the UK CA considered that assessing the risk to CL322,250 alone would be sufficient for this part of the assessment.

An assessment of 8 photodegradates was also submitted. This assessment was largely based on an ECOSAR assessment and indicated that all photodegradates, except degradate 7, could be addressed by a comparison of toxicity data and data from ECOSAR. On the basis of this assessment, it can be seen that all photodegradates are of lower toxicity than the parent. Since both exposure and effect endpoints are likely to be lower for these photodegradates, it is proposed that no further assessment, i.e. derivation of PEC or PNEC is required. The UK CA had some concerns regarding the proposed read across from degradate 1 to degradate 7 in this assessment. However overall it was considered that the toxicity of this compound was unlikely to be greater than the active substance. In addition photodegradate 7 was only found at greater than 10 % (i.e. 15.75 %) at one time point and appeared to be transient in the sterile buffer samples, i.e. at 12 hours it was present at 4.88 %, at 24 hours at 15.75 % and at 48 hours at 6.93 %. It never exceeded 5 % in the synthetic humic water. The UK CA considers that due to its transient nature and likely low occurrence in natural waters that the risk is covered by the active substance and no further information is required.

During in service leaching the risks posed from the a.s. and both major metabolites (CL322,250 and CL322,248) has been modelled by MAMPEC v2.5 using the basic physico chemical and fate properties to predict the long-term exposure of the marine environment. The resulting patterns of risk also provided further support for the earlier decision not to consider CL322,248 during the application and removal stages, as in all cases the risk was lower for this metabolite than for CL322,250.

Overall, the quantities and effects seen for the major metabolite(s) should result in a risk assessment that is sufficiently protective of the environment to any additional minor metabolites that may form over time. This assumption is further supported by the fact that the PEC and PNEC values assume that the environment being considered has reached steady-state

and so is an ongoing long-term scenario.

2.2.2.6.1 Risk to the aquatic compartment (including sediment)

Aquatic compartment

Application and removal stages

The risks from direct emissions to the marine environment as a result of on-shore commercial activities have been characterised for both the a.s. and its primary major metabolite CL322,250. The assessment has shown that in all cases there are no risks to the aquatic compartment resulting from the exposure to CL322,250. However, depending on the level of the assessment (Tier 1 or 2) and assumptions (worst-case or typical case) there are some predictions of unacceptable risk from exposure to tralopyril. The following Table summarises the risk characterisations for direct emissions into the marine environment as a result of on-shore new build or M & R activities for tralopyril.

Table 2.5 PEC:PNEC values resulting from direct emissions of tralopyril to marine surface water associated with 'NEW BUILD' application and M & R removal scenarios (note that M & R application scenarios are not shown below as these are identical to the 'NEW BUILD' application scenarios already provided)

a) Commercial (shipping)

Scenario	Tier		Assumptions	Concentration µg l^{-1}		PEC:PNEC
				PEC_{marine}	$PNEC_{marine}$	
New build	1[a]		Worst-case	0.18	0.0017	105.88
			Typical case	0.04		23.5
	2a[b]		Worst-case	0.153		90.0
			Typical case	0.033		19.41
	2b		Worst-case	0.008		4.71
			Typical case	0.00172		1.01
M & R	REMOVAL[c]	1	Worst-case	0.12		70.6
			Typical case	0.017		10.0
		2a	Worst-case	0.11		64.7
			Typical case	0.015		8.8
		2b	Worst-case	0.0055		3.2
			Typical case	0.0008		0.47

[a]Tier 1 is simply the total daily emission load diluted into the water volume of the OECD-EU commercial harbour
[b]Tier 2 is estimated using the daily emission load as direct input to the MAMPEC model and simulating concentrations within the OECD-EU Commercial harbour scenario (Tier 2a) and in the adjacent areas as being representative of the wider environment (Tier 2b). Average total concentrations simulated by MAMPEC at 9 °C only are reported for simplicity.
[c]removal losses are based on the revised Fa.i. old paint value of 0.9

The data above (Table 2.5) suggest that in all 3 scenarios tested (New build application, removal and application during M & R), exposure levels of tralopyril would result in an unacceptable risk to the environment when calculations are performed according to the OECD ESD assumptions and Tier 1. In Tier 1, it is assumed that all of the a.s would dissolve

instantaneously and be bioavailable in the environment. However, this is not what is likely to occur in reality with antifouling paints designed to act as a controlled delivery system when dry. The Applicant considers that this approach is an oversimplification of the actual situation, and as such regards the OECD ESD scenarios as a Tier 1 assessment. The UK CA agrees with this. However options to quantitatively refine the new build, maintenance and repair exposure assessments has recently been considered by a PT21 e-consultation group made up of MS and Industry experts. When the results of this group were discussed at the TMIII 2011 meeting it was agreed that the uncertainties associated with quantifying the fate and behaviour of active substance released from intact paint particles in the natural environment would be highly uncertain and no formal method for refining this specific aspect of the assessment was agreed. However MS did consider that the MAMPEC model could be used to refine the simple Tier 1 exposure assessments by taking into account degradation and advective processes in the dynamic environments simulated by the MAMPEC model. Therefore in line with these discussions the UK CA has presented a simple Tier 1 assessment assuming emission loads based on the OECD ESD entering a static water body with the dimensions of the OECD-EU commercial harbour. A refined Tier 2 assessment has also been performed using the same emission loads entering the OECD-EU commercial harbour environment simulated with MAMPEC. At Tier 2 the results are separated into the MAMPEC predictions for concentrations within the OECD-EU Commercial harbour (Tier 2a) and also the predictions for concentrations in the adjacent areas, taken as being representative of the wider environment (Tier 2b). All concentrations are reported as the average total concentrations predicted by MAMPEC at 9 °C for simplicity. The data in Table 2.5 suggests that using the MAMPEC model to predict exposure within the OECD-EU Commercial harbour still results in unacceptable Risk Quotients for all activities and either worst case or typical case defaults (Tier 2a). Using MAMPEC to predict exposure in the adjacent areas leads to unacceptable Risk Quotients for all activities using the worst case defaults (Tier 2b worst-case) but an acceptable Risk Quotient for removal activities using typical case defaults (Tier 2b typical case; Risk Quotient = 0.47) and a minor exceedence of the Risk Quotient for application activities using the typical case defaults ((Tier 2b typical case; Risk Quotient = **1.01**). It should be further noted that running these Tier 2 simulations within MAMPEC v2.5 assumes repeated daily emission events until a steady state concentration is reached. In reality, emission events at the levels suggested by the OECD ESD are unlikely to occur day on day and actual exposure levels under more realistic conditions are likely to be somewhat lower. This would be expected to result in acceptable Risk Quotients in the areas adjacent to the OECD-EU commercial harbour provided risk mitigation measures were implemented to ensure professional activities were equivalent to the typical case defaults of the ESD. The UK CA therefore considers that the risks identified in Table 2.5 above should be managed at Member State level during product authorisation by implementing appropriate risk mitigation measures to minimise environmental releases during application and removal activities. The mechanism for adoption of such risk mitigation measures is still to be agreed at EU level and further discussion on this aspect has been included in the cumulative exposure assessment reported in Section 2.2.2.6.2 as well as in Section 3.4.3.3.4 of Doc IIB. However overall best available practice techniques adopted by professionals would be expected to reduce the worst-case emission assumptions made within the OECD ESD scenarios.

In service leaching

The following Table 2.6 characterises the risk to the marine aquatic environment from the use

of the antifouling paint product 'International Copper Free', which contains tralopyril. This results in exposure to the a.s. plus 2 major metabolites; CL322,250 and 322,248. For all 3 substances the mean exposure concentrations have been predicted using the MAMPEC model (v 2.5) for 2 OECD-EU defined environments; commercial harbour and shipping lane at default MAMPEC and TGD defined temperatures. In addition a revised marina scenario containing a small number of super yachts (>25 m) at berth has been simulated. For the harbour and adapted marina (super yacht) environments, the mean concentrations both within and adjacent these locations have been predicted. This is considered important as it can be expected that enclosed areas of high boating/shipping activity would be subject to a build up of substances associated with this i.e. fuel deposits, waste waters and antifouling substances. Therefore, in the UK it is accepted that whilst risk may be predicted to occur within these [often man-made] enclosed marine environments provided this risk is no longer present immediately outside [adjacent] the enclosed areas, the actual risk to the wider environment is acceptable. This approach was also agreed for the purposes of Annex I decision making at the TMIII 2011 meeting.

No risks have been predicted for the metabolites of tralopyril; therefore, only data on the a.s. are presented here for discussion.

The data in Table 2.6 suggests that the risks from tralopyril are acceptable within the OECD ESD defined shipping lane environment, irrespective of temperature or whether total or dissolved concentrations of the a.s. are considered. However, the data suggests that if 90 % of vessels within a harbour or adapted marina (super yacht) environment were treated with tralopyril containing antifouling paint that the risk to the aquatic marine species would be unacceptable. Concentrations of tralopyril for the areas adjacent to harbours and the adapted marina (super yacht) scenario are however considered acceptable. It should be noted that the percentage application used in the above calculation is the default 90 % and is considered to be worst case and hence the real concentration is expected to be less than that predicted. Note that the Applicant has now provided market share data from outside the EU to support a reduced but still conservative application factor. This was agreed for use for the new active substance tralopyril in the absence of EU market share data at TMIV2011 and is included in the Confidential Annex. This refined application factor has been taken into account as part of the cumulative exposure assessment in Table 2.6.

Table 2.6 PEC:PNEC values for tralopyril in water both (a) within and (b) in adjacent areas to OECD default MAMPEC environmental exposure scenarios

(a) Within;	% Application	PEC aquatic concentration (µg l^{-1})			$PNEC_{aquatic}$ (µg l^{-1})	PEC:PNEC
Commercial Harbour	90	15 °C [OECD]	Total	2.22E-02	0.0017	**13.1**
			Dissolved	2.21E-02		**13.0**
		9 °C [TGD]	Total	2.83E-02		**16.6**
			Dissolved	2.81E-02		**16.5**
Adapted marina (super yacht)	90	15 °C [OECD]	Total	6.96E-02		**40.9**
			Dissolved	6.92E-02		**40.7**
		9 °C [TGD]	Total	7.25E-02		**42.6**
			Dissolved	7.20E-02		**42.4**
Shipping Lane	90	15 °C [OECD]	Total	6.55E-05		0.04
			Dissolved	6.54E-05		0.04
		9 °C [TGD]	Total	6.67E-05		0.04
			Dissolved	6.66E-05		0.04

(b) Adjacent to;	% Application	PEC aquatic concentration (µg l^{-1})			$PNEC_{aquatic}$ (µg l^{-1})	PEC:PNEC
Commercial Harbour	90	15 °C [OECD]	Total	1.34E-03	0.0017	0.79
			Dissolved	1.33E-03		0.78
		9 °C [TGD]	Total	1.50E-03		0.88
			Dissolved	1.50E-03		0.88
Adapted marina (super yacht)	90	15 °C [OECD]	Total	5.75E-04		0.34
			Dissolved	5.71E-04		0.34
		9 °C [TGD]	Total	6.04E-04		0.36
			Dissolved	6.00E-04		0.35

Sediment compartment

Application and removal stages

Where emissions to water have been predicted, the dissipation to sediment has been considered and exposure of the sediment compartment predicted. The following tables consider the risks to marine sediment compartments resulting from the direct emissions of tralopyril. No risks have been suggested for the major metabolite CL322,250 with all PEC:PNEC values < 1, which can be considered very worst-case as the predicted values are derived using the Koc of 2079 l kg^{-1} when the results of the sediment-water degradation studies suggesting that the metabolite would remain largely associated with the aquatic phase. This is why it has been important to consider the initial aquatic concentrations without removal to sediment to ensure that risks from aquatic exposure alone can be dismissed.

Table 2.7 suggests that if the a.s. within the paint fragments is lost directly to the marine environment from on-shore commercial activities and was wholly available the instant it reached the aquatic environment there would be an unacceptable risk to the marine sediment

community as a result of losses during application at tiers 1 and 2a of the assessment, but would be acceptable at Tier 2b (adjacent areas) based on the typical case defaults (PEC:PNEC = 0.25). Similarly, losses during removal activities would result in an unacceptable risk to the marine sediment community at Tiers 1 and 2a, but would be acceptable at Tier 2b based on either the worst case or typical case defaults. It should be further noted that running these Tier 2 simulations within MAMPEC v2.5 assumes repeated daily emission events until a steady state concentration is reached. In reality, emission events at the levels suggested by the OECD ESD are unlikely to occur day on day and actual exposure levels under more realistic conditions are likely to be somewhat lower. This would be expected to result in lower PEC:PNECs in the areas adjacent to the OECD-EU commercial harbour from both application and removal activities.

Table 2.7 Sediment PEC:PNEC values resulting from direct emissions of tralopyril to marine surface water associated with commercial (shipping) scenarios (note that M & R application scenarios are not shown below as these are identical to the 'NEW BUILD' application scenarios already provided)

Scenario	Tier		Assumptions	mg kg^{-1}		PEC:PNEC
				PEC_{marine}	PNEC	
New build	1		Worst-case	0.018	0.00017 (Tier 1)[a]	**105.88**
			Typical case	0.004		**23.5**
	2a		Worst-case	0.02		**25.3**
			Typical case	0.004		**5.1**
	2b		Worst-case	0.001		**1.3**
			Typical case	0.0002		0.25
M&R	REMOVAL[b]	1	Worst-case	0.012	0.00079 (Tier 2a and 2b)[a]	**70.6**
			Typical case	0.0017		**10.0**
		2a	Worst-case	0.014		**17.7**
			Typical case	0.002		**2.5**
		2b	Worst-case	0.0007		0.9
			Typical case	0.00010		0.1

[a] As discussed in Section 4.3.1.3.1 of Doc IIA a different PNECsediment has been deriving assuming equilibrium partitioning using either the bulk density of wet sediment (for comparison against the wet weight PECsediment values at Tier 1) or using the bulk density of dry sediment (for comparison against the dry weight PECsediment values from MAMPEC at Tier 2a and 2b)

[b] removal losses are based on the revised Fa.i. old paint value of 0.9

In service leaching

MAMPEC has calculated the exposure of the sediment compartments contained within the OECD default environments (harbour and shipping lane) and the amended adapted marina (super yacht) scenario by using the leaching rate in conjunction with the physico chemical and fate input parameters for tralopyril and CL322,250. The sediment phase has been presented in terms of the suspended sediment PEC only. No risk assessment has been carried out for CL322,248 as the levels predicted by the MAMPEC model were significantly lower than those predicted for CL322,250 and no risks to the sediment compartment has been predicted. For tralopyril, the risk characterised in Table 2.8 suggests that the long-term risks within the OECD-EU commercial harbour and adapted marina (super yacht) would be unacceptable,

although risks in the shipping lane would be acceptable. In addition the risks in the areas adjacent to the OECD-EU commercial harbour and adapted marina (super yacht) would also be acceptable based on the PEC:PNEC values below.

Table 2.8 Tralopyril PEC:PNEC values for sediment (a) within and (b) in adjacent areas to OECD default MAMPEC environmental exposure scenarios and the amended adapted marina (super yacht) scenario

(a) Within;	% Application	PEC aquatic concentration (mg kg^{-1})			$PNEC_{aquatic}$ (mg kg^{-1})	PEC:PNEC
Commercial Harbour	**90**	**15 °C [OECD]**	**Suspended**	2.88E-03	0.00079	**3.6**
		9 °C [TGD]	**Suspended**	3.67E-03		**4.6**
Adapted marina (super yacht)	**90**	**15 °C [OECD]**	**Suspended**	9.03E-03		**11.4**
		9 °C [TGD]	**Suspended**	9.41E-03		**11.9**
Shipping Lane	**90**	**15 °C [OECD]**	**Suspended**	1.79E-05		0.02
		9 °C [TGD]	**Suspended**	1.83E-05		0.02

(b) Adjacent to;	% Application	PEC aquatic concentration (mg kg^{-1})			$PNEC_{aquatic}$ (mg kg^{-1})	PEC:PNEC
Commercial Harbour	**90**	**15 °C [OECD]**	**Suspended**	1.74E-04	0.00079	0.22
		9 °C [TGD]	**Suspended**	1.95E-04		0.25
Adapted marina (super yacht)	**90**	**15 °C [OECD]**	**Suspended**	7.46E-05		0.09
		9 °C [TGD]	**Suspended**	7.84E-05		0.10

2.2.2.6.2 Cumulative exposure

Consideration of the potential for cumulative or simultaneous multiple exposure routes have also been made. This has addressed direct inputs to the OECD-EU commercial harbour arising from application to large marine-going vessels (new build or maintenance and repair) combined with the in-service scenarios to provide an assessment of potential cumulative exposure. Results of the simultaneous multiple exposure assessment is presented below for tralopyril in surface water (Table 2.9). Since the PEC:PNEC ratio presented in earlier sections clearly indicated that the risks to the environment are predominantly due to the active substance rather than the metabolites, the simultaneous exposure assessment has only considered parent tralopyril. The detailed consideration of cumulative exposure in sediment included in Doc IIC also indicated that risks in the area adjacent to the OECD-EU commercial harbour would be

acceptable based on the standard MAMPEC simulations without any additional refinement and these have therefore been excluded from further consideration here. However, risk mitigation measures and risk refinement options to reduce tralopyril surface water exposure to acceptable levels have been considered and these are also included in Table 2.9 below. Further discussion of these refinements and risk mitigation measures is included in Section 3.4.3.3.4 of Doc IIB. These measures would also be expected to further reduce sediment exposure and exposure to any of the metabolites that may be formed.

For tralopyril, the risk characterised in Table 2.9 suggests that the long-term risks within and adjacent to the OECD-EU commercial harbour based on either the standard worst case or typical case application losses would be unacceptable. However the risks in the area adjacent to the OECD-EU commercial harbour would be acceptable based on the revised PEC:PNEC values for the refined assessments at Tier 3a and 3b (all based on typical case application losses combined with in-service losses). This refined tier includes refinement of the application factor and introduction of risk mitigation at two different levels (i.e. a fractional reduction of either 0.7 or 0.425) to reduce application losses. Based on survey information from CEPE and CESA, in order to achieve a fractional reduction in emissions of 0.425 it would be necessary to restrict application activities to professional boatyards where dock floor discipline, containment nets and good spraying practices were followed (see Table 2 of Doc IIB Section 3.4.3.3.4). The UK CA accepts that further discussion needs to take place on the exact mechanism for adopting risk mitigation in assessments of this kind and this discussion needs to involve the Commission as well as Working Group and CA level meetings. However the PEC:PNEC values above are considered sufficient to demonstrate that safe uses of tralopyril exist for the purposes of recommending Approval.

This assessment has concentrated on the worst-case simultaneous exposure events via application losses and in-service routes. As such the proposals for risk mitigation apply specifically to application activities. However if these losses can be acceptably mitigated, some consideration should also be given to the potential risks from the less worse case simultaneous exposure events via removal losses and in-service routes. Reference back to Table 3.4.8 of Doc IIB indicates that PECsw due to removal losses for the typical case defaults at Tier 2b (outside the OECD-EU commercial harbour) is 0.0008µg/l (taking into account the revised, increased Fa.i. old paint value of 0.9). If this is combined with the Tier 3 PECsw from in-service losses of 0.0005µg/l (assuming an application factor of 30 %) the corresponding combined PEC and PEC/PNEC ratios are 0.0013 µg/l and 0.76 respectively. Since the PEC/PNEC is less than 1, this indicates an acceptable risk without additional risk mitigation being needed to control removal losses. However, this is based on the typical case removal losses, which assumes paint is removed in a graving dock via high pressure washing followed by spot blast cleaning (compared with the worst case defaults where it is assumed paint is removed by full blast cleaning on an exposed floating dock or marine lift). Appropriate label phrases could be included to limit removal activities to situations comparable to those of the typical case defaults that result in acceptable risk assessments. For example, '*To protect the aquatic environment, professional removal of paint from large marine-going vessels must only be performed in a suitable graving dock via high pressure washing and spot blast cleaning only*'. As already highlighted above, the UK CA accepts that further discussion needs to take place on the exact mechanism for adopting risk mitigation in assessments of this kind and this discussion needs to involve the Commission as well as Working Group and CA level meetings.

Table 2.9 Tralopyril simultaneous multiple exposure following application activities and in-service losses (a) within and (b) adjacent to the OECD-EU Commercial Harbour

(a) Within;	**PEC aquatic concentration ($\mu g\ l^{-1}$)**			**$PNEC_{aquatic}$ ($\mu g\ l^{-1}$)**	**PEC:PNEC**
Commercial harbour (Tier 2a)	**9 °C [TGD] Total**	**Worst case**	0.181	**0.0017**	**106.6**
		Typical case	0.061		**36**
(b) Adjacent to;					
Commercial harbour (Tier 2b)	**9 °C [TGD] Total**	**Worst case**	0.0095		**5.59**
		Typical case	0.0032		**1.89**
Tier 3a (30 % application factor and **0.7** factor for risk mitigation of application losses)		**Typical case**	0.00170		1.0
Tier 3b (30 % application factor and **0.425** factor for risk mitigation of application losses)			0.00123		0.72

2.2.3. Assessment of endocrine disruptor properties

Available evidence at this time indicates that tralopyril does not have endocrine-disrupting properties (no effects on endocrine organs and/or reproduction were observed in standard toxicity studies to raise a concern for potential endocrine disruption).

2.3. Overall conclusions

The outcome of the assessment for tralopyril in product-type 21 is specified in the BPC opinion following discussions at the fifth meeting of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA web-site.

2.4. List of endpoints

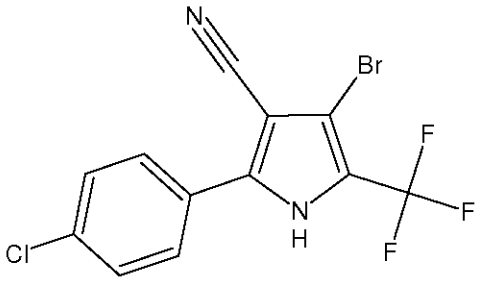
The most important endpoints, as identified during the evaluation process, are listed in Appendix I.

Appendix I: List of endpoints

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

Active substance (ISO Common Name)	Tralopyril
Product-type	21 (Antifouling Products)

Identity

Chemical name (IUPAC)	4-bromo-2-(4-chlorophenyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile
Chemical name (CA)	1H-Pyrrole-3-carbonitrile, 4-bromo-2-(4-chlorophenyl)-5-(trifluoromethyl)
CAS No	122454-29-9
EC No	-
Other substance No.	ZR107894 (Janssen code no.) AC303,268 (BASF code no.)
Minimum purity of the active substance as manufactured (g/kg or g/l)	≥ 975g/kg
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	There are no relevant impurities or additives.
Molecular formula	$C_{12}H_5BrClF_3N_2$
Molecular mass	349.5
Structural formula	

Physical and chemical properties

Melting point (state purity)	253.4 °C (purity: 98.4 %)
Boiling point (state purity)	> 400 °C (purity: 98.4 %)
Temperature of decomposition	No decomposition was observed below 400 °C
Appearance (state purity)	**Pure substance**: off-white powder with a slightly sweet, marzipan-like odour (purity: 98 %) **Technical grade**: pale yellow-brown powder with a slightly sweet, marzipan-like odour (purity: 94.6 %)
Relative density (state purity)	1.714 at 20 °C (purity: 98.4 %)
Surface tension	Not required due to low water solubility
Vapour pressure (in Pa, state temperature)	1.9×10^{-8} Pa at 20 °C (purity: 99.3 %) 4.6×10^{-8} Pa at 25 °C (purity: 99.3 %)
Henry's law constant (Pa m^3 mol^{-1})	3.91×10^{-5} $Pa.m^3.mol^{-1}$ (calculated)
Solubility in water (g/l or mg/l, state temperature)	At 20 °C: (purity: 99.3 %) 0.17 mg/L in unadjusted water (resultant pH of nominally 4.9) The active is not stable in seawater. At pH 6 and a purity of 98.94 % w/w:

Temperature (°C)	Results (mg/L)
10	0.083
20	0.168
30	0.205

Solubility in organic solvents (in g/l or mg/l, state temperature)	At 20 °C: (purity: 94.6 %) Acetone: 300.5 g/L Ethyl acetate: 236.0 g/L n-Heptane: 7.2 g/L Methanol: 109.1 g/L n-Octanol: 85.2 g/L Xylene:5.6 g/L
Stability in organic solvents used in biocidal products including relevant breakdown products	Tralopyril is stable in xylene (4 weeks at 40 ± 2 °C).
Partition coefficient (log P_{OW}) (state temperature)	log Pow = 3.47 (At 30 °C, purity: 99.3 %) The mobile phase was buffered to pH 5 to ensure tralopyril was tested in the non-ionised form.
Hydrolytic stability (DT_{50}) (state pH and temperature)	pH 5, 10 °C: DT50= 168 days pH 5, 9 °C: DT50= 155 days pH 5, 25 °C: DT50= 15 days
	pH 7, 10 °C: DT50= 69 hours pH 7, 9 °C: DT50= 75 hours pH 7, 25 °C: DT50= 8 hours
	Seawater, 10 °C: DT50= 15 hours

	Seawater, 9 °C: DT50= 16 hours Seawater, 25 °C: DT50= 3 hours
Dissociation constant	pKa = 7.08 at 26 °C
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	λ_{max}; Acidic conditions – 281.4 nm Neutral conditions – 281.9 nm Alkaline conditions – 223.9 nm – 303.4 nm (ε=16527 $M^{-1}cm^{-1}$)
Quantum yield of direct phototransformation in water at Σ > 290 nm	Reaction quantum yield of direct phototransformation was determined to be 4.93E-05Fluorescence quantum yield was determined to be 0.03
Flammability	No auto-ignition was observed up to the melting point. Not highly flammable.
Explosive properties	Not shock sensitive

Classification and proposed labelling

with regard to physical/chemical data	None.
with regard to toxicological data	T, Very toxic R26: Very toxic by inhalation R25: Toxic if swallowed R21: Harmful in contact with skin R48/25: Danger of serious damage to health by prolonged exposure if swallowed R48/20: Danger of serious damage to health by prolonged exposure if inhaled DANGER Acute Tox. 2 – Oral Acute Tox. 3 – Dermal Acute Tox. 2 - Inhalation STOT RE 1 – Oral STOT RE 2 – Inhalation H300: Fatal if swallowed H311: Toxic in contact with skin H330: Fatal if inhaled H372: Causes damage to organs through prolonged or repeated oral exposure H373: May cause damage to organs through prolonged or repeated inhalation exposure
with regard to fate and behaviour data	None.
with regard to ecotoxicological data	N, Dangerous for the environment R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment R55: Toxic to fauna R57: Toxic to bees DANGER Acute Aquatic 1 Chronic Aquatic 1 [Environmental warning symbol, warning label and an M

factor of 1000 is applicable] H400: Very toxic to aquatic life H410: Very toxic to aquatic life with long lasting effects

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	High Performance Liquid Chromatography - UV detection at 254 nm. The method was suitably validated.
Impurities in technical active substance (principle of method)	See Confidential Annex.

Analytical methods for residues

Soil (principle of method and LOQ)	Residue definition: Tralopyril only Analysis of marine sediment by LC-MS/MS. LOQ = 250µg/kg Further validation data as outlined in section 3.4 are required. For the current use a method for soil is not considered necessary.
Air (principle of method and LOQ)	A method of analysis is being developed.
Water (principle of method and LOQ)	Residue definition: Tralopyril only Natural seawater – LC-MS/MS. LOQ = 0.05µg/L For the current use a method for fresh water is not considered necessary. Further validation data as outlined in section 3.4 are required.
Body fluids and tissues (principle of method and LOQ)	Urine – LC-MS/MS. LOQ = 1 ng/mL Blood – LC-MS/MS. LOQ = 1 ng/mL Muscle tissue – LC-MS/MS. LOQ = 1 ng/g
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Not required
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Shellfish, non-edible fish tissue & edible fish tissue – LC-MS/MS. LOQ = 1 ng/g Further validation data as outlined in section 3.4 are required.

Chapter 3: Impact on Human Health

Read-across justification

Justification for the use of data generated on CL 303,630 in support of tralopyril	CL 303,630 is a metabolic pre-cursor of tralopyril. Oral data generated on CL 303,630 has been used in support of the following endpoints: toxicokinetics, sub-chronic toxicity, chronic toxicity, carcinogenicity, reproductive toxicity and neurotoxicity. The UK considers that the properties of tralopyril can reliably predicted by read-across to CL 303,630 for the following reasons: 1. Based on similar physicochemical properties and similar structures it can be assumed that the extent and speed of absorption via the oral route will be similar for CL 303,630 and tralopyril. 2. It has been demonstrated that a major and immediate metabolite of CL 303,630 is tralopyril. Thus, it can be predicted that the toxic properties of CL 303,630 and Tralopyril are likely to have similarities. The speed and extent of the conversion of CL 303,603 to tralopyril is not completely understood, but full knowledge of the comparative toxicokinetics is not crucial to the acceptance of the read across approach because there is good information on the comparative sub-chronic toxicity of the two substances. 3. Rat oral (dietary administration) sub-chronic studies are available for both CL 303,630 and tralopyril, which show that the repeat dose toxicity of the two substances is qualitatively similar. However, there appear to be quantitative differences as a comparison of the dose levels causing a key effect of neurohistopathological changes in male rats in 90-day studies indicate that equivalent N(L)OAELs for tralopyril are likely to be up to 10-fold lower than for CL 303,630.

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	Following single and repeat oral doses, CL 303,630 is absorbed (64-87 %) over approximately 8-hours and the extent of absorption appears to be dose dependent. The extent of tralopyril absorption has not been investigated, but on the basis of mainly calculated physicochemical properties it appears that absorption of the neutral forms for both CL 303,630 and tralopyril will be similar. For the purposes of risk assessment, an absorption value of 100 % by the oral route is proposed. This value is based on the observation that the degree of absorption appears to decrease with increasing dose and that human exposure to tralopyril in the product is likely to be less than 2 mg/kg, a dose at which 78-83 % absorption was observed. For the purposes of extrapolating between routes in animals studies it is proposed that a value of 70 % is used for doses of 20 mg/kg and 80 % is used for doses of 2 mg/kg.

Rate and extent of dermal absorption:	No information was available on the dermal absorption of the active substance. However, the ability of radio-labelled tralopyril to penetrate human skin was examined *in vitro* within a paint formulation containing 4.2 % w/w tralopyril (International Copper Free). A dermal absorption value of 2 % was obtained from this study. The rate of tralopyril absorption was measured hourly throughout this study and, since the rate of absorption was not affected by the drying of the paint formulation on the skin, the UK CA feel that a dermal absorption estimate of 2 % is appropriate to support tralopyril.
Rate and extent of inhalation absorption:	The physiochemical data on tralopyril and the significant number of deaths observed in the acute inhalation studies at low dose levels support a figure of 100 % for inhalation absorption.
Distribution:	CL 303,630 is widely distributed with radio-label detected in every tissue investigated.
Potential for accumulation:	There was no evidence for the bioaccumulation of CL 303,630
Rate and extent of excretion:	In the rat, elimination of CL 303,630 after oral administration occurs mainly in the faeces (comprising of unabsorbed and biliary excreted metabolites), but metabolites were also detected in the urine. The majority of excretion occurred within the first 48h and was practically complete within 168 h.
Toxicologically significant metabolite(s)	None

Acute toxicity

Rat LD_{50} oral	Rat (tralopyril): 28.7 mg/kg (combined) and a discriminating dose of 5 mg/kg
Rat LD_{50} dermal	Rat > 2000 mg/kg (test conducted with tralopyril) Guinea-pig: 520-700 mg/kg (test conducted with tralopyril)
Rat LC_{50} inhalation	Rat: < 0.5 mg/l (test conducted with tralopyril)
Skin irritation	Not classified (test conducted with tralopyril)
Eye irritation	Not classified (test conducted with tralopyril)
Skin sensitization (test method used and result)	Negative in a Buehler test (test conducted with tralopyril)

Repeated dose toxicity

Species/ target / critical effect	In oral developmental toxicity studies, delay in ossification of the nasal bone was considered the most sensitive marker of toxicity in rats. In subchronic and chronic oral studies, effects on bodyweight in dogs and vacuolation of the CNS in rats are considered to be the most sensitive marker of toxicity. Following dermal administration, increased liver weight was considered to the most sensitive marker of toxicity in rats.

	Following inhalation exposure, effects on the bodyweight of rats was considered the most sensitive marker of toxicity.
Lowest relevant oral NOAEL / LOAEL	$NOAEL_{acute}$: 10 mg/kg/day (rat developmental study with tralopyril) $LOAEL_{medium\text{-}term}$: 5 mg/kg/day (90-day rat study with tralopyril
Lowest relevant dermal NOAEL / LOAEL	$NOAEL_{acute/medium\text{-}term/chronic}$: 300 mg/kg/day equivalent to a systemic dose of 6 mg/kg bw/day (90-day rat study with tralopyril)
Lowest relevant inhalation NOAEL / LOAEL	$NOAEL_{acute/medium\text{-}term/chronic}$: 20mg/m^3 equivalent to a systemic dose of 5.8 mg/kg /day (90-day rat study with tralopyril)

Genotoxicity

	All studies were conducted with tralopyril. The result of an Ames study was equivocal due to an apparent increase in revertant rate in a single strain. The increase in mutation frequency was observed in only one strain. A repeat Ames study was unequivocally negative. The results of the *in vitro* mammalian cell gene mutation study and an *in vivo* micronucleus study were negative and no evidence of tumour formation was observed in two carcinogenicity studies conducted with CL 303,630 in rodents. The available data do not support classification for mutagenicity.

Carcinogenicity

Species/type of tumour	Tumour formation was not increased in either study conducted with CL 303,630 at the highest dose tested. Based on the arguments for read-across outlined in the toxicokinetic section, the UK CA feels that it is reasonable to conclude that tralopyril will also not be carcinogenic.
lowest dose with tumours	Not applicable

Reproductive toxicity

Species/ Reproduction target / critical effect	No treatment related effects on fertility
Lowest relevant reproductive NOAEL / LOAEL	NOAEL: 29 mg/kg/day (test conducted with CL 303,630)
Species/Developmental target / critical effect	In rat: the developmental toxicity manifested itself as an increase in the number of resorptions and a slight delay in development. At the top dose, these effects were observed in association with maternal toxicity (deaths and reduced bodyweight and bodyweight gain) and are likely to be a secondary non-specific consequence of the maternal toxicity. At the lower doses a slight delay in development was again observed, the extent of which was not considered severe enough to warrant classification. Rabbit: no treatment effects observed.
Developmental toxicity	
Lowest relevant developmental NOAEL / LOAEL	Rat: NOAEL: 5 10 mg/kg/day (test conducted with

	tralopyril) Rabbit: NOAEL: 30 mg/kg/day (highest dose tested) (test conducted with CL 303,630) Tralopyril equivalent NOAEL: 6 3 mg/kg/day (highest dose tested)

Neurotoxicity / Delayed neurotoxicity

Species/ target/critical effect	Histopathological effects of the CNS was observed following 1-year repeated administration to rats
Lowest relevant developmental NOAEL / LOAEL.	NOAEL: 3 mg/kg/day (test conducted with CL 303,630)

Summary	Value	Study	Safety factor
ADI (if residues in food or feed)	N/A	N/A	N/A
Oral AEL (acute)	0.08 mg/kg/day	Rat oral developmental study	100
Oral AEL (medium-term)	0.013 mg/kg/day	90-day rat oral study	300
Oral AEL (long-term)	0.007 mg/kg/day	90-day rat oral study	600
Dermal AEL (acute)	0.06 mg/kg/day	90-day rat dermal study	100
Dermal AEL (medium-term)	0.06 mg/kg/day	90-day rat dermal study	100
Dermal AEL (long-term)	0.03 mg/kg/day	90-day rat dermal study	200
Inhalation AEL (acute)	0.058 mg/kg/day	90-day rat inhalation study	100
Inhalation AEL (medium-term)	0.058 mg/kg/day	90-day rat inhalation study	100
Inhalation AEL (long-term)	0.029 mg/kg/day	90-day rat inhalation study	200
Acute AEClocal inhalation	0.27 mg/m^3	90-day rat inhalation study (LOAEC = 20 mg/m^3)	75
Medium AEClocal inhalation	0.27 mg/m^3	90-day rat inhalation study (LOAEC = 20 mg/m^3)	75
Long-term AEClocal inhalation	0.13 mg/m^3	90-day rat inhalation study (LOAEC = 20 mg/m^3)	150
Drinking water limit	N/A	N/A	N/A

ARfD (acute reference dose)	N/A	N/A	N/A

Acceptable exposure scenarios (including method of calculation)

Professional users

Exposure route: Combined dermal and inhalation (medium-term scenario)

Systemic NOAEL: 6 mg/kg bw/day (90-day rat dermal study)

Method of calculation: MOE and AEL

Task	Tier	MOE	Exposure/AEL
Sprayman applying International Copper Free to vessels in dockyards and slipways at high pressure (>100 bar) using airless spraying	Tier 2c	192	0.5
	Tier 2d	480	0.2
Potman mixing and loading International Copper Free into reservoirs for airless spraying in dockyards and slipways	Tier 2a	173	0.6
	Tier 2b	216	0.5
Professional applying International Copper Free by brush/roller	Tier 2a	121	0.8
	Tier 2b	242	0.4
Professional washing out brush/roller used to apply International Copper Free by brush/roller	Tier 2	4285	0.02
Combined exposure: professional application by brush/roller and cleaning of brush/roller	Tier 2a (application) + Tier 2 (brush/roller cleaning)	117	0.8
	Tier 2b (application) + Tier 2 (brush/roller cleaning)	229	0.4
Professionals removing coatings by abrasive blasting	Tier 2a	2000	0.05
	Tier 2b	2609	0.04

Intended uses	International Copper Free, is a liquid metal-free antifouling paint containing 4.17 % w/w tralopyril for application by professional operators.

Risks of local effects following inhalation exposure were characterised using the AEC of 0.27 mg/m^3 for medium-term exposure scenarios. Risks are considered acceptable if the external concentration is < 0.27 mg/ m^3. For airless spraying, the predicted external exposure concentration of tralopyril is 0.721 mg/ m^3; i.e., above the AEC. However, in this scenario the operators will be wearing RPE (as in the Tier 2c refinement), therefore the risks to human health as a result of local toxicity are acceptable. The risks for the other primary exposure scenarios listed above are acceptable.

No secondary exposure should occur as the sites of application and removal of International Copper Free will be inaccessible to the general public and other unprotected persons should be kept out of these sites.

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water

Hydrolytic stability (DT_{50}) (state pH and temperature)	pH 5, 10 °C: DT50= 169 days pH 5, 9 °C: DT50= 182 days (calculated) pH 5, 25 °C: DT50= 15 days
	pH 7, 10 °C: DT50= 69 hours pH 7, 9 °C: DT50= 75 hours (calculated) pH 7, 25 °C: DT50= 8 hours
	Seawater (pH7.9), 10 °C: DT50= 15 hours Seawater (pH7.9), 9 °C: DT50= 16 hours (calculated) Seawater (pH7.9), 25 °C: DT50= 3 hours
	pH 9, 10 °C: DT50= 12 hours pH 9, 9 °C: DT50= 13 hours (calculated) pH 9, 25 °C: DT50= 2 hours
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	Direct photolysis (pH 7): R107894: DT50= 8.9 hrs Indirect photolysis (pH 7 synthetic humic water): R107894: DT50= 5.1 hrs
Readily biodegradable (yes/no)	No, 7.73 % after 28 days
Biodegradation in seawater	
Distribution in water / sediment systems (active substance)	**Aerobic degradation of R107894 (21 °C):** Freshwater/sediment whole system: DT50= 12.75 days (26.19 d calculated at 12 °C) Seawater/sediment whole system: DT50= 0.34 day (0.89 d calculated at 9 °C) **% ^{14}C- recovery at end of test (freshwater):** 33.3 (water) 26.2 (sediment) 92.3 (system) **% ^{14}C- recovery at end of test (marine water):** 53.3 (water) 33.7 (sediment) 95.8 (system)
	Anaerobic degradation of R107894 (21 °C): Freshwater/sediment: DT50= 35.46 days, (72.6 d calculated at 12 °C); Seawater/sediment: DT50= 0.68 day, (1.78 d calculated at 9 °C) **% ^{14}C- recovery at end of test (freshwater):** 26.3 (water) 22.9 (sediment) 100.4 (system) **% ^{14}C- recovery at end of test (marine water):** 57.7 (water)

	22.5 (sediment) 97.0 (system)
Distribution in water / sediment systems (metabolites)	**Aerobic degradation of R107894 degradation products > 10 % ^{14}C- recovery** Freshwater/sediment: Max 48.2 % CL322,250 on day 7 in water Seawater/sediment: Max 71.9 % CL322,250 on day 7 in water
	Anaerobic degradation of R107894 degradation products > 10 % ^{14}C- recovery Freshwater/sediment: Max 21.1 % CL322,250 on day 30 in water; Max 23.4 & 12.2 % unknown metabolite B in water & sediment respectively on wk 52. Seawater/sediment: Max 44.9 & 14.4 % CL322,250 on day 7 in water & sediment respectively; Max 55.8 & 19.9 % unknown metabolite B in water & sediment respectively on wk 39.
Non-extractable residues	**Aerobic degradation of R107894 % ^{14}C- recovery** Freshwater/sediment: Max 36.4 % non-extractable residues in sediment on day 30 Seawater/sediment: Max 19.5 & 10.8 % unknown metabolite B in water & sediment respectively on day 30
	Anaerobic degradation of R107894 % ^{14}C- recovery Freshwater/sediment: Max 61 % non-extractable residues in sediment on wk 26. Seawater/sediment: Max 17 % non-extractable residues in sediment on wk 52.

Route and rate of degradation in soil

Laboratory studies (range or median, with number of measurements, with regression coefficient)	No test performed, n.a. DT_{50lab} (20°C, aerobic):
	DT_{90lab} (20°C, aerobic):
	DT_{50lab} (10°C, aerobic):
	DT_{50lab} (20°C, anaerobic):
	degradation in the saturated zone:
Non-extractable residues	
Mineralization (aerobic)	
Field studies (state location, range or median with number of measurements)	DT_{50f}:
	DT_{90f}:
Anaerobic degradation	
Soil photolysis	
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	
Soil accumulation and plateau concentration	

Adsorption/desorption

Ka , Kd Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	R107894: Freshwater: Ka= 450-335 l/kg, Kd= 599-568 l/kg (n=2) Ka_{oc} =20440-16733 l/kg (mean = 18586.5 l/kg), Kd_{oc} = 27229-28353 l/kg Seawater : Ka= 26-196 l/kg, Kd= 40-299 l/kg (n=2) Ka_{oc} =3582-5588 l/kg mean = 4585 l/kg), Kd_{oc}=5658-8543 l/kg
	CL322,250: Freshwater: Ka= 132-383 l/kg, Kd= 165-295.5 l/kg (n=2) Ka_{oc} = 6016-19167 l/kg (mean = 11459 l/kg), Kd_{oc}= 7500-14850 l/kg Seawater : Ka= 7-114 l/kg, Kd= 11-131.5 l/kg (n=2) Ka_{oc} =1000-3265 l/kg (mean = 2079 l/kg), Kd_{oc}=1571-3757 l/kg

Fate and behaviour in air

Direct photolysis in air	No test performed, n.a.
Quantum yield of direct photolysis	
Photo-oxidative degradation in air	Latitude: ..... Season: ..... DT_{50} .....
Volatilization	

Monitoring data, if available

Soil (indicate location and type of study)	
Surface water (indicate location and type of study)	
Ground water (indicate location and type of study)	
Air (indicate location and type of study)	

Chapter 5: Effects on Non-target Species

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

Species	Time-scale	Endpoint	Toxicity

Fish

Species	Test substance	Time-scale	Endpoint	Toxicity
Cyprinodon variegatus	R107894	96 h	LC50	26 µg l^{-1}
Cyprinodon variegatus	CL322,250	96 h	LC50	>0.95 mg l^{-1}
Cyprinodon variegatus	CL325,195	96 h	LC50	>16 mg l^{-1}
Cyprinodon variegatus	CL322,248	96 h	LC50	>89mg l^{-1}
Lepomis macrochirus	R107894	96 h	LC50	3.2 µg l^{-1}
Lepomis macrochirus	CL322,250	96 h	LC50	1.2 mg l^{-1}
Oncorynchus mykiss	R107894	96 h	LC50	1.3 µg l^{-1}
Oncorynchus mykiss	CL322,250	96 h	LC50	0.52 mg l^{-1}
Cyprinodon variegatus	R107894	34 days	NOEC	4.3 µg l^{-1}
Cyprinodon variegatus	CL322,250	34 days	NOEC	0.24 mg l^{-1}
Cyprinodon variegatus	CL325,195	34 days	NOEC	1.3 mg l^{-1}
Danio rerio	R107894	33 days	NOEC	0.17 µg l^{-1}
Danio rerio	CL322,250	35 days	NOEC	0.069 mg l^{-1}
Danio rerio	CL325,195	34 days	NOEC	0.911 mg l^{-1}

Invertebrates

Species	Test substance	Time-scale	Endpoint	Toxicity
Daphnia magna	R107894	48 h	EC50	1.50 µg l^{-1}

Daphnia magna	CL322,250	48 h	EC50	0.50 mg l^{-1}
Crassostrea virginica	R107894	96 h	EC50	0.66 µg l^{-1}
Crassostrea virginica	CL322,250	96 h	EC50	0.29 mg l^{-1}
Crassostrea virginica	CL325,195	96 h	EC50	>14 mg l^{-1}
Americamysis bahia	R107894	96 h	LC50	0.98 µg l^{-1}
Americamysis bahia	CL322,250	96 h	LC50	0.55 mg l^{-1}
Americamysis bahia	CL325,195	96 h	LC50	12 mg l^{-1}
Americamysis bahia	CL322,248	96 h	LC50	4.6 mg l^{-1}
Daphnia magna	R107894	21 days	NOEC	0.20 µg l^{-1}
Daphnia magna	CL322,250	21 days	NOEC	0.30 mg l^{-1}
Americamysis bahia	R107894	28 days	NOEC	0.25 µg l^{-1}
Americamysis bahia	CL322,250	28 days	NOEC	0.082 mg l^{-1}

Algae

Species	Test substance	Time-scale	Endpoint	Toxicity
Anabaena flos-aquae	R107894	48 h	E_bC50	n.a. mg l^{-1}
			E_rC50	n.a. mg l^{-1}
			NOE_rC	0.070 mg l^{-1}
Anabaena flos-aquae	CL322,250	72 h	E_bC50	>0.83 mg l^{-1}
			E_rC50	>0.83 mg l^{-1}
Anabaena flos-aquae	CL322,248	72 h	E_bC50	>1.0 mg l^{-1}
			E_rC50	>1.0 mg l^{-1}
Anabaena flos-aquae	CL325,195	72 h	E_bC50	1.3 mg l^{-1}
			E_rC50	>8.4 mg l^{-1}
Navicula pelliculosa	R107894	48 h	NOErC	0.00073 mg l^{-1}
Navicula pelliculosa	CL322,250	72 h	E_bC50	>0.93 mg l^{-1}
			E_rC50	>0.93 mg l^{-1}

Navicula pelliculosa	CL322,248	72 h	E_bC50 E_rC50	>0.98 mg l^{-1} >0.98 mg l^{-1}
Navicula pelliculosa	CL325,195	72 h	E_bC50 E_rC50	1.3 mg l^{-1} 1.5 mg l^{-1}
Pseudokirchneriella subcapitata	R107894	72 h	E_bC50 E_rC50	0.0091 mg l^{-1} 0.012 mg l^{-1}
Skeletonema costatum	R107894	72 h	EC50	0.0027 mg l^{-1}
Skeletonema costatum	CL322,250	72 h	EC50	0.66 mg l^{-1}
Skeletonema costatum	CL322,248	72 h	E_bC50 E_rC50	1.21 mg l^{-1} 3.8 mg l^{-1}

Microorganisms

Species	Test substance	Time-scale	Endpoint	Toxicity
Ready biodegradation	R107894	28 days	NOEC	78.8 mg l^{-1}

Aquatic plants

Species	Test substance	Time-scale	Endpoint	Toxicity
Lemna gibba	R107894	7 days	EC50	0.088 mg l^{-1}
Lemna gibba	CL322,250	7 days	EC50	>0.99 mg l^{-1}
Lemna gibba	CL322,248	7 days	EC50	>0.93 mg l^{-1}
Lemna gibba	CL325,195	7 days	EC50	>15 mg l^{-1}

Sediment organisms

Species	Test substance	Time-scale	Endpoint	Toxicity
Leptocheirus plumulosus	R107894	10 days	LC50	1.1 mg Kg^{-1}
Leptocheirus plumulosus	CL322,250	10 days	LC50	>70 mg Kg^{-1}
Leptocheirus plumulosus	CL322,248	10 days	LC50	>75 mg Kg^{-1}
Leptocheirus plumulosus	CL325,195	10 days	LC50	>27 mg Kg^{-1}
Hyalella azteca	R107894	10 days	LC50	2.2 mg Kg^{-1}
Hyalella azteca	CL322,250	10 days	LC50	>35 mg Kg^{-1}
Hyalella azteca	CL322,248	10 days	LC50	>37 mg Kg^{-1}
Hyalella azteca	CL325,195	10 days	LC50	>49 mg Kg^{-1}

Effects on earthworms or other soil non-target organisms

Acute toxicity to ……..	No tests performed, not applicable
Reproductive toxicity to ……	

Effects on soil micro-organisms

Nitrogen mineralization	No tests performed, not applicable
Carbon mineralization	

Effects on terrestrial plants

Acute toxicity to plants (Annex IIIA, point XIII……)	R107894, Inhibition of seedling emergence of Oryza sativa, 14 days EC25=>0.17 mg l^{-1}, NOEC= 0.17 mg l^{-1}

Effects on terrestrial vertebrates

Acute toxicity to mammals	
Acute toxicity to birds	
Dietary toxicity to birds	Anas platyrhinchos, 5 day exposure LC50: R107894 =10.8 mg Kg^{-1}; CL322,250 =962 mg Kg^{-1}; CL325,248 =>5620 mg Kg^{-1}
Reproductive toxicity to birds	

Effects on honeybees

Acute oral toxicity	No tests performed, not applicable
Acute contact toxicity	

Effects on other beneficial arthropods

Acute oral toxicity	No tests performed, not applicable
Acute contact toxicity	
Acute toxicity to ……..	

Bioconcentration

Bioconcentration factor (BCF)	<3.2 ml g^{-1}.
Depration time (DT_{50}) (DT_{90})	Not determined as BCF was too low.
Level of metabolites (%) in organisms accounting for > 10 % of residues	Not determined.

Chapter 6: Other End Points

Not applicable.

Appendix II: List of Intended Uses

Tralopyril has been evaluated for its intended use as a marine Antifouling Product (PT21) on surfaces subject to immersion (vessels and structures).

Product Type	Product Type 21 (Antifouling Prodcuts)
Object and/or situation	Application to parts of ships, boat hulls and static structures that will be submerged in the marine environment. There will be no application to boats under 25 m in overall length, so only large marine-going vessels and super yachts will be treated.
Product name	International Copper Free.
Packaging	International Copper Free is packaged in 20 litre steel drums or in 750 ml and 2.5 litre tinplate cans. These are lined with an epoxy-phenolic coating.
Categories of User	Professional operators only
Organisms controlled	Broad range of marine animal and algal fouling species.
Formulation type	International Copper Free is a solvent-based mobile liquid antifouling paint.
Concentration in formulation	4.17 % w/w
Application method / kind	To be applied by airless spray and from time to time by brush/roller. All surfaces are treated while they are out of the water.
Applied amount per treatment	Application rate varies on a case-by-case basis, depending on vessel speed, vessel trading route, vessel activity and the predicted time between dry-dockings. Theoretical application rates are 1 litre product (41.7 ml tralopyril) 4.4 m^{-2}, 125 µm dry film thickness (airless spray) and 1 litre product (41.7 ml tralopyril) 10.5 m-2, 50 µm dry film thickness (brush and roller).
Application number min/max	In service for ships, 2 coats of product will be applied to give a total Dry Film Thickness (DFT) of 250 µm.
Application interval (min)	A total DFT of 250 µm will give an in-service lifetime of 3 years.
Storage	Store in a well-ventilated place, away from sources of heat and direct sunlight. Store on concrete or other impervious floor. Keep container tightly closed. Containers that are opened must be carefully resealed to prevent leakage. Prevent unauthorised access.

Data supporting the active substance for its use against the intended target organisms have demonstrated sufficient efficacy for Approval to be recommended.

To date, there are no known resistance issues when using tralopyril against the target organisms.

Appendix III: List of studies

Data protection is claimed by the applicant in accordance with Article 60 of Regulation (EU) No 528/2012.

Reference	Author	Date	Study title	Data Protection claimed	Data Owner
IIA, IIIA A2.8, A4	Knox III, D.E.	2011 Amended 2012	- Econea Technical, Preliminary Analysis. Eurofins / Product Safety Laboratories Laboratory Study Number 32442. Janssen Study Number AGR4539, GLP, Unpublished.	Y	Janssen
IIA 4.2.1.2	Mookerjee, P.K.	2011	- QSAR Evaluation of the Ecotoxicity of tralopyril Photolytic Degradation Products Using Experimental and ECOSAR Predicted Data - Accelerand LLC, Flemington, NJ 08822, USA. - Report No. AGR 4527 - GLP, Unpublished	Y	Janssen
A2.6 Confidential	Bleiman, P., Lodewyckx, D.	2011	Manufacturing Directions Report for Econea Technical. Janssen PMP. Janssen Report Number MDR 11-03 (290611). Unpublished	Y	Janssen PMP, division of Janssen Pharmaceutica N.V.
A2.7 Confidential	Lodewyckx, D.	2011	Product Specification Report for Econea Technical (Amended). Janssen PMP. Original Janssen Report Number PSR 11-11 (160911) Amended Laboratory Stusy No. 32442, Janssen study No. 4539. Unpublished	Y	Janssen PMP, division of Janssen Pharmaceutica N.V.
A2.8 Confidential	Knox III, D.E	2011 Amended 2012	Econea Technical, Preliminary Analysis. Eurofins / Product Safety Laboratories Laboratory Study Number 32442. Janssen Study Number AGR4539, GLP, Unpublished	Y	Janssen PMP, division of Janssen Pharmaceutica N.V.
A3.	Foster, B.	2012	- Analytical method validation and evaluation of water solubility. - Smithers Viscient (ESG) Ltd. Otley Road, Harrogate, North Yorkshire HG3 1PY, UK - Study Number 8261677. - GLP, Unpublished.	Y	Janssen
A3.1.1	Ristorcelli, D.	2001a	- R107894: Determination of Physico-Chemical Properties - Covance Laboratories Ltd. - Janssen Pharmaceutica NV Report No. 1073/48-D2149 - GLP, Unpublished	Y	Janssen
A3.11	Daemen, W.	2006	- Thermal stability, burning behaviour, shock sensitivity - Janssen Pharmaceutica NV Report No. 2006/253A - Not GLP, Unpublished	Y	Janssen
A3.15	Möller	2011	- ECONEA Technical, Determination of physico-chemical properties, Explosive Properties EC A.14 - Consilab Gesellschaft fur Anlagensicherheit mbH, Germany - Report number: CSL-11-0173.01 - GLP, Unpublished	Y	Janssen

A3.17	Bates, M.	2006	- R107894: Evaluation of the Ambient Temperature Storage Stability - Covance Laboratories Ltd. - Janssen Pharmaceutica NV Report No. 1073/063-D2149 - GLP, Unpublished	Y	Janssen
A3.17	Meinerling, M.	2007	- Expert Statement on the Oxidizing Properties of ECONEA - IBACON GmbH - Janssen Pharmaceutica NV Project 39921209 - Unpublished	Y	Janssen
A3.2	Cox, P. and Ristorcelli, D.	2001	- R107894: Determination of the Physico-Chemical Properties (pH, pKa, and EC Tests A4, A6 and A8) - Covance Laboratories Ltd. - Janssen Pharmaceutica NV Report No. 1073/41-D2141 - GLP, Unpublished	Y	Janssen
A3.2.1	Bates, M.	2007	- R107894: Calculation of Volatility (Henry's Law Constant) - Covance Laboratories Ltd. - Janssen Pharmaceutica NV Report No. 1073/120 - Unpublished	Y	Janssen
A3.3	De Meyer, K.	2008	- Certificate of Analysis. Tralopyril, purified active substance - Janssen Pharmaceutica NV Report No. AF2612007 - Unpublished	Y	Janssen
A3.4	Cleeren, D.	2008	- Infra red spectrum of R107894 - Johnson & Johnson Pharmaceutical Research & Development Report No. TC-TA Result 08-060 - Not GLP, unpublished	Y	Janssen
A3.4	Drewicz, G.A.	1993	- Analytical Data for the Identification and Purity Assignment of CL 303,268 Primary Analytical Standard AC7185-69-1 - American Cyanamid Company Report No. APBR 256 - Unpublished	Y	BASF
A3.4	Halfpenny, L.	2008	- Determination of Fluorescence Quantum Yield and Molar Extinction Coefficient of Econea Technical (Tralopyril) - Intertek ASG, Manchester, UK - Report number 1312235, - GLP, Unpublished	Y	Janssen
A3.5	Ristorcelli, D.	2001b	- CL325,195, CL322,250 and CL322,248: Determination of solubility in artificial sea water and in buffered water at pH 7 - Covance Laboratories Ltd. - Janssen Pharmaceutica NV Report No. 1073/52-D2149 - Unpublished	Y	Janssen
A3.8	Kempen, T. Van den Heuvel, H. De Meyer, K.	2007	- Chemical stability of ECONEA® (tralopyril) in xylene - Janssen Pharmaceutica NV Report No. 07005 - Not GLP, Unpublished	Y	Janssen

A3.9	Van den Heuvel, H.	2004	- Determination of the partition coefficient of different metabolites of ECONEA at pH8 - Janssen Pharmaceutica NV Report No. 04094 - Unpublished	Y	Janssen
A3.11	Quirijnen, J.	2009	- Flammability - Janssen Pharmaceutica NV - Report No. 2009/127B - Not GLP, Unpublished	Y	Janssen
A4	Bleiman, P., Lodewyckx, D.	2011	- Manufacturing Directions Report for Econea Technical. Janssen PMP. Janssen Report Number MDR 11-03 (290611). Unpublished	Y	Janssen
A4	Lodewyckx, D.	2011	- Product Specification Report for Econea Technical (Amended). Janssen PMP. Original Janssen Report Number PSR 11-11 (160911) Amended Laboratory Stusy No. 32442, Janssen study No. 4539. Unpublished	Y	Janssen
A4	Yang, H.	2002	- Preliminary analysis and certification of ingredient limits for the technical grade of AC 303268. BASF Agro Research, Princeton, NJ. Report No. APBR 1212.	Y	BASF
A4.1/01	Yang, H.	2000	- Validation of the High Performance Liquid Chromatographic Method M-3408 to Assay for CL 303268 in the Technical Grade Active Ingredient (TGAI) - BASF Agro Research Report No. APBR 1109 - GLP, Unpublished	Y	BASF
A4.1/02	Yang, H.	2001	- Validation of High Performance Liquid Chromatographic Method M-3397.03 to Assay for the Minor Components in CL 303268 Technical Grade Active Ingredient - BASF Agro Research Report No. APBR 1129 - GLP, Unpublished	Y	BASF
A4.1/03	Millen, W.G.,	2001	- Validation of HRGC Method M-3467.01 to Assay for [redacted] in the Technical Grade of AC 303268; - BASF Agro Research, Princeton New Jersey, USA, - Report No.APBR1153 - GLP, unpublished	Y	BASF
A4.1/04	Yang, H.,	2000	- Validation of the Ion Chromatographic Method M-3417.01 to Assay for [redacted] in the CL 303268 Technical Grade Active Ingredient (TGAI) - BASF Agro Research, Princeton New Jersey, USA, - Report No. APBR 1130, - GLP, unpublished	Y	BASF
A4.1/05	Rajamoorthi, K	1997	- Quantitative Analysis by Nuclear Magnetic Resonance Spetroscopy; Cyanamid, Princeton New Jersey, USA, - Report No. M-2103.01 (appendix in	Y	BASF

			report APBR 1212) - Unpublished		
A4.1/06	Bielawski, M.W	1998	- Coulometric Karl Fischer determination for water in solid and liquid samples; - Cyanamid, Princeton New Jersey, USA, - Report No. M-2372.02 (appendix in report APBR 1212) - unpublished	Y	BASF
A4.2/01	[redacted]	2001	- R107894 – Early Life-Stage Toxicity Test with Sheepshead Minnow (*Cyprinodon variegatus*) [redacted] - GLP, Unpublished	Y	Janssen
A4.2/02	Hoberg, J.R.	2001	- R107894 - Toxicity to Duckweed, Lemna gibba - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6104 (AGR337) - GLP, Unpublished	Y	Janssen
A4.2/03	Mackie, J.A.	1999	- The Aerobic Degradation of [^{14}C]-R107894 in two water/sediment systems - Inveresk Research - Janssen Pharmaceutica NV Report No. 16787 - GLP, Unpublished	Y	Janssen
A4.2/04	Dix, M.E.,	2009	- Validation of the Analytical Method for the Determination of R107894, CL-322,250 and CL-322,248 in Natural Seawater following OPPTS Guideline 850.7100 - Springborn Smithers Laboratories, Wareham, Massachusetts, - Report No. 13751.6167 (Janssen No.: AGR 4090-A). - unpublished	Y	Janssen Pharmaceutica NV
A4.2/05	Dix, M.E.,	2009	- Validation of the Analytical Method for the Determination of R107894, CL-322,250 and CL-322,248 in Marine Sediment following OPPTS Guideline 850.7100 - Springborn Smithers Laboratories, Wareham, Massachusetts, - Report No. 13751.6168 (Janssen No.: AGR 4097). - GLP, unpublished	Y	Janssen Pharmaceutica NV
A4.2/06	[redacted]	2010	- Method Development for Tralopyril in Rat Blood, Urine, and Muscle Tissue; [redacted] - GLP, Unpublished	Y	Janssen Pharmaceutica NV
A4.2/07	[redacted]	2010	- Method Development for Tralopyril in Fish and Shell Fish Tissue; [redacted]	Y	Janssen Pharmaceutica NV

			- GLP, Unpublished		
A5.1	Kirby, M., Clare, A.S.	2007	- Toxicity of Econea 028 to larvae of the barnacle, *Balanus amphitrite*. Newcastle University, Report No. not specified, 07th May 2007 (unpublished).	Y	International Paint Ltd.
A5.10	De Witte, L., Bosselaers, J.	2006a	- Dose screening results against algae and brine shrimp, obtained with tralopyril. Internal report Janssen PMP, IV/18/2006, Beerse, unpublished.	Y	Janssen
A5.11	De Witte, L., Bosselaers, J.	2004	- Antifouling characteristics of test and reference compounds applied on PVC-boards and exposed in the Oosterschelde. Internal report Janssen PMP, AF/05/2004, Beerse, unpublished.	Y	Janssen
A5.12	De Witte, L., Bosselaers, J.	2006b	- Antifouling activity of 26 New Nautical Coatings paint formulations applied to PVC boards and exposed on rafts in the Eastern Scheldt estuary. Internal report Janssen PMP, AF/01/2006, Beerse, unpublished.	Y	Janssen
A5.13	De Witte, L., Bosselaers, J.	2006c	- Antifouling activity of 13 calcium metabolism modifiers, one quorum sensing inhibitor and one repellent exposed on rafts in the Eastern Scheldt estuary. Internal report Janssen PMP, AF/02b/2006, Beerse, unpublished.	Y	Janssen
A5.14	De Witte, L., Roymans, A.	2005	- Algal toxicity test. Internal report Janssen PMP, IV/14/2005, Beerse, unpublished.	Y	Janssen
A5.15	Van der Flaas, M., De Witte, L., Willems, W.	2006	- Algal toxicity test. Internal report Janssen PMP, IV/21/2006, Beerse, unpublished.	Y	Janssen
A5.16	De Witte, L., Bosselaers, J.	2006d	- Ballast water biocidal activity of tralopyril and three reference compounds against eight bacteria in sea water. Internal report Janssen PMP, IV/20/2006, Beerse, unpublished.	Y	Janssen
A5.2	De Witte, L., Roymans, A., Bosselaers, J.	2005	- Laboratory in vitro toxicity assay on *Artemia salina*. Internal report Janssen PMP, IV/13/2005, Beerse, unpublished.	Y	Janssen
A5.3	Mackie, G.L.	1995a	- Short- and long-term efficacy of CL303268 and CJ301814 for control of zebra mussels. Confidential report from Water Systems Analysts, Guelph, unpublished	Y	Janssen
A5.4	Mackie, G.L.	1995b	- Efficacy of CL303268 for preventing byssal attachment of zebra mussels. Confidential report from Water Systems Analysts, Guelph, unpublished	Y	Janssen
A5.5	Dionne, E.	2001	- R107894 - Acute toxicity to Eastern Oysters (*Crassostrea virginica*) under flow-through conditions. report from Springborn Laboratories, Wareham, unpublished.	Y	Janssen
A5.6	Cafarella, M.A.	2006	- R107894 - Acute toxicity to Eastern Oyster (*Crassostrea virginica*) under flow-through conditions. report from Springborn Smithers Laboratories, Wareham, unpublished.	Y	Janssen
A5.7	Hoberg, J.R.	2003	- R107894 - Acute toxicity to the freswater	Y	Janssen

			diatom, *Navicula pelliculosa*. report from Springborn Smithers Laboratories, Wareham, unpublished.		
A5.8	Van der Kerken, K.	2002	- Alga, growth inhibition test effect of R107894 technical on the growth of *Skeletonema costatum*. Lisec study n° WE-06-270, Genk, unpublished.	Y	Janssen
A5.9	Van der Flaas, M., Willems, W., De Witte, L.	2002	- Killing speed of two Econea 028 formulations using *Artemia salina* in a micro well dose experiment. Internal report Janssen PMP, AF/02/2002, Beerse, unpublished	Y	Janssen
A6.1.1/01	[redacted]	1994	- Oral LD_{50} Study in Albino Rats with AC 303, 268 Technical [redacted] - GLP, Unpublished	Y	BASF
A6.1.1/02	[redacted]	2001a	- R107894 Technical Acute Oral Toxicity (Fixed Dose Procedure) Test in Rats [redacted] - GLP, Unpublished	Y	Janssen
A6.1.2	[redacted]	2001b	- R107894 technical: Acute Dermal Toxicity (LD_{50}) Test in Rats [redacted] - GLP, Unpublished	Y	Janssen
A6.1.3/01	[redacted]	2002	- R107894 Technical: Acute Inhalation Toxicity Study in Rats - Report amendment 1 [redacted] - GLP, Unpublished	Y	Janssen
A6.1.3/02	[redacted]	2006	- R107894: Acute Inhalation Toxicity Study in Rats – limit test. [redacted] - GLP, Unpublished	Y	Janssen
A6.1.4/01	[redacted]	2002	- R107894 Technical: Acute dermal irritation test in rabbits [redacted] - GLP, Unpublished	Y	Janssen
A6.1.4/02	[redacted]	2005	- R107894: Primary Eye Irritation Study in Rabbits [redacted] - GLP, Unpublished	Y	Janssen
A6.1.5	[redacted]	2002	- R107894 Technical: Buehler Test in Guinea Pigs for Delayed Skin Sensitisation Potential [redacted]	Y	Janssen

			[redacted] - GLP, Unpublished		
A6.2	[redacted]	1994	- CL 303,630 Metabolism of Carbon-14 Labeled CL 303,630 in the Rat, [redacted] - GLP Unpublished.	Y	BASF
A6.2	Mirbach, M.J.	2006	- Qualitative Comparison of the Potential for Systemic Absorption of Tralopyril and CL 303,630 Based on their Physical Chemical Properties - Landis Kane Consulting (LKC) - Janssen Pharmaceutica NV Report No. 06-quebec-02 - Not GLP, Unpublished	Y	Janssen
A6.2/03	[redacted]	1994	- Biological Fate of MK-242 Absorption, Distribution and Excretion in Rats, [redacted] - GLP Unpublished.	Y	BASF
A6.2/04	[redacted]	1994	- Biological Fate of MK-242 Metabolism in Rats, [redacted] - GLP Unpublished.	Y	BASF
A6.3.1	[redacted]	2004a	- R 107894 Range-finding Study in Sprague Dawley Rats – Administration in the Diet for 4 Weeks [redacted] - GLP, Unpublished	Y	Janssen
A6.3.2	[redacted]	2005	- R107894: Dermal toxicity study (28-day repeat dermal toxicity study in rats) [redacted] - GLP, Unpublished	Y	Janssen
A6.4.1	[redacted]	2004b	- R 107894 Subchronic toxicity study in Sprague Dawley rats – Administration via the diet over 3 months and recovery period of 4 weeks. [redacted] - GLP, Unpublished and	Y	Janssen
	[redacted]	2005	- Pathology Peer Review Statement Subchronic toxicity study in Sprague Dawley rats – Administration via the diet over 3 months and recovery period of 4 weeks [redacted] - GLP, Unpublished	Y	Janssen

A6.4.1/01	[redacted]	1993	- 90-day toxicity study with AC 303,630 in purebread beagle dogs [redacted] - GLP unpublished	Y	BASF
A6.4.1/02	[redacted]	1993	- AC 303,630: A 13-Week Dietary Toxicity Study in the Albino Rat [redacted] - GLP unpublished	Y	BASF
A6.4.1/04	[redacted]	1994	- One year Dietary toxicity study with AC 303,630 in purebreac beagle dogs [redacted] - GLP, Unpublished	Y	BASF
A6.4.2/01	[redacted]	2006a	- R 107894 Dermal toxicity study (90-day repeat dermal application study in rats) [redacted] - GLP, Unpublished	Y	Janssen
A6.4.2/02	[redacted]	2006b	- Amendment to Report R 107894 Dermal toxicity study (90-day repeat dermal application study in rats) [redacted] - GLP, Unpublished	Y	Janssen
A6.4.3	[redacted]	2006	- A 90-day combined nose-only inhalation toxicity and neurotoxicity study of R107894 in rats. [redacted] - GLP, Unpublished	Y	Janssen
A6.6/A6.8	Cotterill, JV, Price, N and Kelly, MJ	2013	- IN SILICO ASSESSMENT OF MAMMALIAN TOXICITY OF TWO IMPURITIES OF TRALOPYRIL WITH PARTICULAR REGARD TO MUTAGENICITY AND FERTILITY ENDPOINTS; The Food and Environment Research Agency, Sand Hutton, York, YO41 1LZ, UK; Unpublished report, FERA Project Number: W5ZZ3002.2, Janssen Study Number: AGR 5118.	Y	Janssen
A6.6.1	Mulligan, E.	1994	- Microbial Mutagenicity Plate Incorporation Assay of CL 303,268 - American Cyanamid Co., Agricultural Research Division - Janssen Pharmaceutica NV Report No. 94-02-001 - GLP, Unpublished	Y	BASF
A6.6.1	May, K.	2014	- TRALOPYRIL Bacterial Reverse Mutation Test; Huntingdon Life Sciences, Eye Research Centre, Eye, Suffolk, IP23 7PX, UK; unpublished report no.	Y	Janssen

			IMB0086, AGR 5097		
A6.6.3	[redacted]	2004a	- In vitro gene mutation test with R 107894 in CHO cells (HPRT locus assay) [redacted] - GLP, Unpublished	Y	Janssen
A6.6.4	[redacted]	2004b	- Cytogenetic study in vivo with R 107894 in the mouse micronucleus test single oral administration [redacted] - GLP, Unpublished	Y	Janssen
A6.7/01	[redacted]	1994	- A chronic Dietary Toxicity and Oncogenicity Study with AC 303,630 in Rats [redacted] - GLP, Unpublished	Y	BASF
A6.7/02	[redacted]	1994	- A chronic Dietary Toxicity Study and Oncogenicity Study with Ac 303,630 in Mice [redacted] - GLP, Unpublished	Y	BASF
A6.8.1	[redacted]	2004	- R107894 – Prenatal Developmental Toxicity Study in Sprague Dawley Rats – Oral Administration (Gavage) [redacted] - GLP, Unpublished	Y	Janssen
A6.8.2	[redacted]	1994	- A Two Generation (one-Litter) Reproduction Study with AC 303,630 in Rats [redacted] - GLP, Unpublished	Y	BASF
A6.8/01	[redacted]	1993	- An oral Developmental Toxcity (Embryo-Fetal Toxicity/Terogenicity) definitive Study with Ac 202,630 in Rats [redacted] - GLP Unpublished.	Y	BASF
A6.9/01	[redacted]	1994	- An acute neurotoxicity study with AC 303,630 in rats [redacted] - GLP, Unpublished	Y	BASF
A6.9/02	[redacted]	1994	- A One-Year Dietary Neurotoxicity Study with AC 303,630 in Rats [redacted]	Y	BASF

			[redacted] - GLP, Unpublished		
A7.1.1.1.1/01	Milligan, F.M., Williams S.G.P. and McGuire G.M.	1997	- Identification of hydrolytic degradation products of [^{14}C]-R107894 - Inveresk Research - Janssen Pharmaceutica NV Report No. 15365 - GLP, Unpublished	Y	Janssen
A7.1.1.1.1/01	Milligan, F.M., Williams S.G.P. and McGuire G.M.	1997	- Identification of hydrolytic degradation products of [^{14}C]-R107894 - Inveresk Research - Janssen Pharmaceutica NV Report No. 15365 - GLP, Unpublished	Y	Janssen
A7.1.1.1.1/02	Mackie, J.A.	1997	- Determination of the hydrolytic stability of [^{14}C]-R107894 - Inveresk Research - Janssen Pharmaceutica NV Report No. 15348 - GLP, Unpublished	Y	Janssen
A7.1.1.1.1/02	Mackie, J.A.	1997	- Determination of the hydrolytic stability of [^{14}C]-R107894 - Inveresk Research - Janssen Pharmaceutica NV Report No. 15348 - GLP, Unpublished	Y	Janssen
A7.1.1.1.2	Lentz, N.R.	2007	- Non-GLP Photolysis of R107894 and CL322,250 in Sterile pH 5 Buffer and Non-GLP Indirect Photolysis of R107894 in Sterile Synthetic Humic Water (SHW) - Springborn Smithers Laboratories - Janssen Pharmaceutica NV Report No. 13751.61.62 - Not GLP, Unpublished	Y	Janssen
A7.1.1.2.1	Zhao, Y.	2007	- Biodegradation Test of R107894 - Supervision and Test Center for Pesticide Safety Evaluation and Quality Control, China - Janssen Pharmaceutica NV Report No. G0640A0269 (AGR3509) - GLP, Unpublished	Y	Janssen
A7.1.1.1.2/02	McLaughlin, S.P.	2011	- [14C]Tralopyril (R107894) - Indirect Photodegradation in Water with Artificial Sunlight, Following OPPTS Guideline 835.5270 - Smithers Viscient (formerly Springborn Smithers Laboratories), 790 Main Street, Wareham, Massachusetts 02571-1037 - Report No. 13751.6170 - GLP, Unpublished.	Y	Janssen
A7.1.2.2.2/01	Mackie, J.A.	1998a	- The Aerobic Degration of [^{14}C]-R107894 in two water/sediment systems - Inveresk Research - Janssen Pharmaceutica NV Report No. 16787 - GLP, Unpublished	Y	Janssen
A7.1.2.2.2/01	Mackie, J.A.	1998a	- The Aerobic Degration of [^{14}C]-R107894 in two water/sediment systems - Inveresk Research	Y	Janssen

			- Janssen Pharmaceutica NV Report No. 16787 - GLP, Unpublished		
A7.1.2.2.2/02	Mackie, J.A.	2000	- The Anaerobic Degration of [^{14}C]-R107894 in two water/sediment systems - Inveresk Research - Janssen Pharmaceutica NV Report No. 17832 - GLP, Unpublished	Y	Janssen
A7.1.2.2.2/03	Best, S.A. and McGuire, G.M.	1999	- Identification of Unknown Component Present in a Day 30 Surface Water Following Application of [^{14}C]-R107894 to Loamy Sand Sediment - Inveresk Research - Janssen Pharmaceutica NV Report No. 17802 - GLP, Unpublished	Y	Janssen
A7.1.3	Mackie, J.A.	1998b	- Adsorption/desorption of [^{14}C]-R107894 in sediments - Inveresk Research - Janssen Pharmaceutica NV Report No. 15715 - GLP, Unpublished	Y	Janssen
A7.1.4	Mackie, J.A.	1999	- Adsorption/desorption of the hydrolysis products of [^{14}C]-R107894 in sediments - Inveresk Research - Janssen Pharmaceutica NV Report No. 16693 - GLP, Unpublished	Y	Janssen
A7.4.1.1/01	[redacted]	2001a	- R107894 - Acute toxicity to Sheepshead Minnow (*Cyprinodon variegatus*) Under Flow-Through Conditions [redacted] - GLP, Unpublished	Y	Janssen
A7.4.1.1/02	[redacted]	2001b	- CL322,250 - Acute toxicity to Sheepshead Minnow (*Cyprinodon variegatus*) Under Flow-Through Conditions [redacted] - GLP, Unpublished	Y	Janssen
A7.4.1.1/03	[redacted]	2001c	- CL325,195 - Acute toxicity to Sheepshead Minnow (*Cyprinodon variegatus*) Under Flow-Through Conditions [redacted] - GLP, Unpublished	Y	Janssen
A7.4.1.1/04	[redacted]	2006a	- CL322,248 - Acute toxicity to Sheepshead Minnow (*Cyprinodon variegatus*) Under Static Conditions [redacted] - GLP, Unpublished	Y	Janssen
A7.4.1.1/05	[redacted]	2005a	- R 107894 - Acute toxicity to Bluegill Sunfish (*Lepomis macrochirus*) Under	Y	Janssen

			Flow-Through Conditions [redacted] - GLP, Unpublished		
A7.4.1.1/06	[redacted]	2005b	- CL 322,250 - Acute toxicity to Bluegill Sunfish (*Lepomis macrochirus*) Under Flow-Through Conditions [redacted] - GLP, Unpublished	Y	Janssen
A7.4.1.1/07	[redacted]	2005c	- R 107894 - Acute toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Flow-Through Conditions [redacted] - GLP, Unpublished	Y	Janssen
A7.4.1.1/08	[redacted]	2005d	- CL 322,250 - Acute toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Flow-Through Conditions [redacted] - GLP, Unpublished	Y	Janssen
A7.4.1.2/01	Cafarella, M.A.	2005a	- R107894 – Acute toxicity to Water Fleas (*Daphnia magna*) Under Flow-Through Conditions - Springborn Laboratories - Janssen Pharmaceutica NV Report No. 13751.6144 (AGR 921) - GLP, Unpublished	Y	Janssen
A7.4.1.2/02	Cafarella, M.A.	2005b	- CL 322,250 - Acute toxicity to Water Fleas (*Daphnia magna*) Under Flow-Through Conditions - Springborn Laboratories - Janssen Pharmaceutica NV Report No. 13751.6151 (AGR 925) - GLP, Unpublished	Y	Janssen
A7.4.1.3/01	Hoberg, J.R.	2003a	- R107894 – Toxicity to the Freshwater Blue-Green Alga, *Anabaene flos-aquae* - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6137 (AGR390) - GLP, Unpublished	Y	Janssen
A7.4.1.3/02	Hoberg, J.R.	2003b	- CL322,250 - Toxicity to the Freshwater Blue-Green Alga, *Anabaena flos-aquae* - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6138 (AGR 389) - GLP, Unpublished	Y	Janssen
A7.4.1.3/03	Hoberg, J.R.	2003c	- CL322,248 - Toxicity to the Freshwater Blue-Green Alga, *Anabaena flos-aquae* - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6139 (AGR478) - GLP, Unpublished	Y	Janssen
A7.4.1.3/04	Hoberg, J.R.	2003d	- CL325,195 - Toxicity to the Freshwater	Y	Janssen

			- Blue-Green Alga, *Anabaena flos-aquae* - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6140 (AGR388) - GLP, Unpublished		
A7.4.1.3/05	Hoberg, J.R.	2003e	- R107894 - Toxicity to the Freshwater Diatom, *Navicula pelliculosa* - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6133 (AGR391) - GLP, Unpublished	Y	Janssen
A7.4.1.3/06	Hoberg, J.R.	2003f	- CL322,250 - Toxicity to the Freshwater Diatom, *Navicula pelliculosa* - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6134 (AGR392) - GLP, Unpublished	Y	Janssen
A7.4.1.3/07	Hoberg, J.R.	2003g	- CL322,248 - Toxicity to the Freshwater Diatom, *Navicula pelliculosa* - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6135 (AGR479) - GLP, Unpublished	Y	Janssen
A7.4.1.3/08	Hoberg, J.R.	2003h	- CL325,195 - Toxicity to the Freshwater Diatom, *Navicula pelliculosa* - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6136 (AGR393) - GLP, Unpublished	Y	Janssen
A7.4.1.3/09	Hoberg, J.R.	2005a	- R107894 – Toxicity to the Freshwater Green Alga, *Pseudokirchneriella subcapitata.* - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6146 (AGR1025) - GLP, Unpublished	Y	Janssen
A7.4.1.3/10	Hoberg, J.R.	2005b	- R107894 - Acute Toxicity to the Marine Diatom, *Skeletonema costatum*, Under Static Conditions. - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6147 (AGR1026) - GLP, Unpublished	Y	Janssen
A7.4.1.3/11	Hoberg, J.R.	2005c	- CL 322,250 - Acute Toxicity to the Marine Diatom, *Skeletonema costatum*, Under Static Conditions - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6154 (AGR1027) - GLP, Unpublished	Y	Janssen
A7.4.1.3/12	Van der Kerken, K.	2002	- CL 322,248 – Alga, growth inhibition test effect of CL 322,248 on the growth of *Skeletonema costatum* - Lisec - Janssen Pharmaceutica NV Report No. WE-06-272 (AGR309) - GLP, Unpublished	Y	Janssen
A7.4.1.4	Mackie, J.A.	1998c	- The effect of R107894 on water/sediment microflora	Y	Janssen

			- Inveresk Research - Janssen Pharmaceutica NV Report No. 16484 - GLP, Unpublished		
A7.4.2	[redacted]	2011	- Bioconcentration study of R107984 in carp [redacted] GLP, Unpublished.	Y	Janssen
A7.4.3.2/01	[redacted]	2001a	- R107894 - Early Life-Stage Toxicity Test with Sheepshead Minnow (*Cyprinodon variegatus*) [redacted] - GLP, Unpublished	Y	Janssen
A7.4.3.2/02	[redacted]	2001b	- CL322,250 - Early Life-Stage Toxicity Test with Sheepshead Minnow (*Cyprinodon variegatus*) [redacted] - GLP, Unpublished	Y	Janssen
A7.4.3.2/03	[redacted]	2001c	- CL325,195 – Early Life-Stage Toxicity Test with Sheepshead Minnow (*Cyprinodon variegatus*) [redacted] - GLP, Unpublished	Y	Janssen
A7.4.3.2/04	[redacted]	2003	- R107894 - Early Life-Stage Toxicity Test with Zebra Fish (*Danio rerio*) [redacted] - GLP, Unpublished	Y	Janssen
A7.4.3.2/05	[redacted]	2006b	- CL322,250 - Early Life-Stage Toxicity Test with Zebra Fish (*Danio rerio*) [redacted] - GLP, Unpublished	Y	Janssen
A7.4.3.2/06	[redacted]	2002	- Fish, Early-life Stage Toxicity Test of CL325,195 [redacted] - GLP, Unpublished	Y	Janssen
A7.4.3.4/01	Sousa, J.V.	2001d	- R107894 - Life-Cycle Toxicity Test with Mysids (*Americamysis bahia*) - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6107 (AGR336) - GLP, Unpublished	Y	Janssen
A7.4.3.4/02	Cafarella, M.A.	2005c	- CL 322,250 - Life-Cycle Toxicity Test with Mysids (*Americamysis bahia*) - Springborn Smithers Laboratories, Inc. - Janssen Pharmaceutica NV	Y	Janssen

			Report No. 13751.6153 (AGR927) - GLP, Unpublished		
A7.4.3.4/03	Cafarella, M.A.	2005d	- R107894 – Full Life-Cycle Toxicity Test with Water Fleas, *Daphnia magna*, Under Flow-Through Conditions - Springborn Smithers Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6145 (AGR922) - GLP, Unpublished	Y	Janssen
A7.4.3.4/04	Cafarella, M.A.	2005e	- CL322,250 - Full Life-Cycle Toxicity Test with Water Fleas, *Daphnia magna*, Under Flow-Through Conditions - Springborn Smithers Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6152 (AGR926) - GLP, Unpublished	Y	Janssen
A7.4.3.5.1/01	Putt, A.E.	2001c	- R107894 – Toxicity to Marine Amphipods (*Leptocheirus plumulosus*) During a 10-Day Sediment Exposure - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6106 (AGR332) - GLP, Unpublished	Y	Janssen
A7.4.3.5.1/02	Putt, A.E.	2001d	- CL322,250 - Toxicity to Marine Amphipods (*Leptocheirus plumulosus*) During a 10-Day Sediment Exposure - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6110 (AGR333) - GLP, Unpublished	Y	Janssen
A7.4.3.5.1/03	Putt, A.E.	2001e	- CL322,248 - Toxicity to Marine Amphipods (*Leptocheirus plumulosus*) During a 10-Day Sediment Exposure - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6113 (AGR334) - GLP, Unpublished	Y	Janssen
A7.4.3.5.1/04	Putt, A.E.	2001f	- CL325,195 - Toxicity to Marine Amphipods (*Leptocheirus plumulosus*) During a 10-Day Sediment Exposure - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6117 (AGR335) - GLP, Unpublished	Y	Janssen
A7.4.3.5.1/05	Cafarella, M.A.	2001a	- R107894 – Toxicity to Amphipods (*Hyalella azteca*) During a 10-Day Sediment Exposure - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV, - Report No.13751.6105 (AGR340) - GLP, Unpublished	Y	Janssen
A7.4.3.5.1/06	Cafarella, M.A.	2001b	- CL322,250 - Toxicity to Amphipods (*Hyalella azteca*) During a 10-Day Sediment Exposure - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6109 (AGR341) - GLP, Unpublished	Y	Janssen
A7.4.3.5.1/07	Cafarella, M.A.	2001c	- CL322,248 - Toxicity to Amphipods	Y	Janssen

			(*Hyalella azteca*) During a 10-Day Sediment Exposure - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6112 (AGR342) - GLP, Unpublished		
A7.4.3.5.1/08	Cafarella, M.A.	2001d	- CL325,195 - Toxicity to Amphipods (*Hyalella azteca*) During a 10-Day Sediment Exposure - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6116 (AGR343) - GLP, Unpublished	Y	Janssen
A7.4.3.5.2/01	Hoberg, J.R.	2001a	- R107894 – Toxicity to Duckweed, *Lemna gibba* - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6104 (AGR344) - GLP, Unpublished	Y	Janssen
A7.4.3.5.2/02	Hoberg, J.R.	2001b	- CL322,250 - Toxicity to Duckweed, *Lemna gibba* - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6108 (AGR338) - GLP, Unpublished	Y	Janssen
A7.4.3.5.2/03	Hoberg, J.R.	2001c	- CL322,248 - Toxicity to Duckweed, *Lemna gibba* - Springborn Laboratories Inc., - Janssen Pharmaceutica NV Reprot No. 13751.6111 (AGR339) - GLP, Unpublished	Y	Janssen
A7.4.3.5.2/04	Hoberg. J.R.	2001d	- CL325,195 - Toxicity to Duckweed, *Lemna gibba* - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6115 (AGR344) - GLP, Unpublished	Y	Janssen
A7.4.3/01	Cafarella, M.A.	2006a	- R107894 - Acute Toxicity to Eastern Oysters (*Crassostrea virginica*) under Flow-Through Conditions - Springborn Smithers Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6157 (AGR1176) - GLP, Unpublished	Y	Janssen
A7.4.3/02	Dionne, E.	2001a	- CL322,250 - Acute Toxicity to Eastern Oysters (*Crassostrea virginica*) under Flow-Through Conditions - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6123 (AGR364) - GLP, Unpublished	Y	Janssen
A7.4.3/02	Dionne, E.	2001a	- CL322,250 - Acute Toxicity to Eastern Oysters (*Crassostrea virginica*) under Flow-Through Conditions - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6123 (AGR364) - GLP, Unpublished	Y	Janssen
A7.4.3/03	Dionne, E.	2001b	- CL325,195 - Acute Toxicity to Eastern	Y	Janssen

			Oysters (*Crassostrea virginica*) under Flow-Through Conditions - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6126 (AGR363) - GLP, Unpublished		
A7.4.3/03	Dionne, E.	2001b	- CL325,195 - Acute Toxicity to Eastern Oysters (*Crassostrea virginica*) under Flow-Through Conditions - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6126 (AGR363) - GLP, Unpublished	Y	Janssen
A7.4.3/04	William, L.	2001d	- R107894 - Acute Toxicity to Mysids (*Americamysis bahia*) under Flow-Through Conditions - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6118 (AGR371) - GLP, Unpublished	Y	Janssen
A7.4.3/05	Putt, A.E.	2001a	- CL322,250 - Acute Toxicity to Mysids (*Americamysis bahia*) under Flow-Through Conditions - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6121 (AGR370) - GLP, Unpublished	Y	Janssen
A7.4.3/06	Putt, A.E.	2001b	- CL325,195 - Acute Toxicity to Mysids (*Americamysis bahia*) under Flow-Through Conditions - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6124 (AGR369) - GLP, Unpublished	Y	Janssen
A7.4.3/07	Sayers, L.E.	2006b	- CL322,248 - Acute Toxicity to Mysids (*Americamysis bahia*) under Static Conditions - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6160 (AGR1179) - GLP, Unpublished	Y	Janssen
A7.5.1.3	Teixeira, D.	2001	- R107894 – Determination of Effects on Seedling Emergence of Rice (*Oryza sativa*) - Springborn Laboratories, Inc. - Janssen Pharmaceutica NV Report No. 13751.6127 (AGR362) - GLP, Unpublished	Y	Janssen
A7.5.3.1.1/01	[redacted]	2005a	- R107894: A dietary LC50 study with the mallard. [redacted] - GLP, Unpublished	Y	Janssen
A7.5.3.1.1/02	[redacted]	2005b	- CL 322250: A dietary LC50 study with the mallard. [redacted] - GLP, Unpublished	Y	Janssen

A7.5.3.1.1/03	[redacted]	2005c	- CL 322248: A dietary LC50 study with the mallard. [redacted] GLP, Unpublished	Y	Janssen
A8.1/02	[redacted]	1993	- An Oral Developmental Toxicity (Embryo-Fetal Toxicity/Terogenicity) Definitive Study with AC 303,630 in Rabbits [redacted] - GLP, Unpublished	Y	BASF
IIB 3.4.3.1	Mookerjee, P.K.	2011	- QSAR Evaluation of the Ecotoxicity of tralopyril Photolytic Degradation Products Using Experimental and ECOSAR Predicted Data - Accelerand LLC, Flemington, NJ 08822, USA. - Report No. AGR 4527 - GLP, Unpublished	Y	Janssen
B3	Wong, D.K.H.	2006	- International Copper Free Anti-Fouling Paint: Evaluation of Physical Properties, Storage Stability and Certificate of Analysis - Charles River Laboratories Report No. 26301 - GLP, Unpublished	Y	International Paint
B4 4.1/01	Wong D K H	2001	- Econea 028: Validation of methodology for the assay of Econea 028 - Charles River Laboratories Study No 26278 - GLP, Unpublished	Y	International Paint
B4 4.1/02	Wright E, Ristorcelli D.	2001	- Zinc Pyrithione: Validation of the Analytical Method for Analysis in Antifouling Paints. - Charles River Laboratories Study Number 1485/009-D2149 - GLP, Unpublished	Y	International Paint
B5.1	Chapman J.	2006	- International Paint Ltd: Antifouling Paint Efficacy Report; International Copper Free. International Paint Ltd., Felling, U.K. Sept. 2006. Unpublished.	Y	International Paint Ltd.
IIB Environment	OECD	2004	Emission Scenario Documents (ESDs); '*An Emission Scenario Document for Antifouling Products in OECD countries*'		
Section 6 B6.3	[redacted]	2005	International Copper Free: Skin sensitization study in guinea pigs [redacted] GLP/Unpublished	Yes (New First)	International Paint
Section 6 B6.1.3	[redacted]	2006	International Copper Free: Acute Inhalation Toxicity Study in Rats [redacted] GLP/Unpublished	Yes (New First)	International Paint

Section 6 B6.2/01	[redacted]	2006	International Copper Free: Acute Dermal Irritation Test in Rabbits [redacted] GLP/Unpublished	Yes (New First)	International Paint
Section 6 B6.4/01	Roper C S,	2002	The In Vitro Percutaneous Absorption of Radiolabelled Zinc Pyrithione in Two Paint Preparations Through Human Skin Inveresk Research, UK. Report Number 20499 GLP/Unpublished	Yes (New First)	International Paint
Section 6 B6.4/02	Toner F Crow L F Roper C S	2005	The In Vitro Percutaneous Absorption of Radiolabelled Econea 028 in a single Paint formulation Through Human Skin - Inveresk Research, UK. Report Number 25468 GLP/Unpublished	Yes (New First)	International Paint
Section 6 B6.1.2	[redacted]	2006	International Copper Free Acute Dermal Toxicity (Limit) Test in Rats [redacted] GLP/Unpublished	Yes (New First)	International Paint
Section 6 B6.1.1	[redacted]	2006	International Copper Free: Acute Oral Toxicity (Acute Toxic Class) Test in Rats [redacted] GLP/Unpublished	Yes (New First)	International Paint
Section 7 B7.1/02	Tunink, A.	2008	Determination of the Leach Rate of Organic Biocides from One Paint Color, Code No. LAg 2007 023 – Blue, in Substitute Ocean Water (15°C) ABC Laboratories, Inc., 7200 E. ABC Lane, Columbia, Missouri 65202 Report No. 63313-2 GLP, Unpublished	Y	Janssen
Section 7 B7.1/03	Tunink, A.	2008	Determination of the Leach Rate of Organic Biocides from One Paint Color, Code No. LAg 2007 023 – Blue, in Substitute Ocean Water (5°C) ABC Laboratories, Inc., 7200 E. ABC Lane, Columbia, Missouri 65202 Report No. 63313-1 GLP, Unpublished	Y	Janssen
Section 7 B7.1/04	Tunink, A.	2008	Determination of the Leach Rate of Organic Biocides from One Paint Color, Code No. LAg 2007 023 – Blue, in Substitute Ocean Water ABC Laboratories, Inc., 7200 E. ABC Lane, Columbia, Missouri 65202 Report No. 63312-1 GLP, Unpublished	Y	Janssen
Section 7 B7.1/01	Tunink, A.	2009	Determination of the Leach Rate of Organic Biocides at Three Different Temperatures from the antifouling paint Code No. Lag 2008 036 – Blue, in Substitute Ocean Water ABC Laboratories, Inc., 7200 E. ABC Lane, Columbia, Missouri 65202	Y	Janssen

			Report No. 65299 GLP, Unpublished		