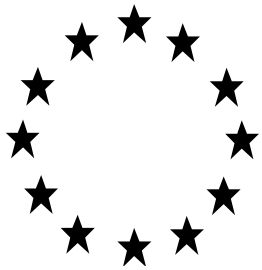
Directive 98/8/EC concerning the placing biocidal products on the market

Inclusion of active substances in Annex I or IA to Directive 98/8/EC

Assessment Report



Alphachloralose

Product-type 14 (rodenticide)

30 May 2008

Annex I - PT

Alphachloralose (PT 14)

Assessment report

Finalised in the Standing Committee on Biocidal Products at its meeting on 30 May 2008 in view of its inclusion in Annex I to Directive 98/8/EC

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 Alphachloralose as product-type 14 (rodenticide), carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of biocidal products on the market[1], with a view to the possible inclusion of this substance into Annex I to the Directive.

Alphachloralose (CAS no.15879-93-3) was notified as an existing active substance, by Rentokil Initial plc and Physalys, hereafter referred to as the applicants, in product-type 14.

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

In accordance with the provisions of Article 7(1) of that Regulation, PT was designated as Rapporteur Member State to carry out the assessment on the basis of the dossier submitted by the applicant. The deadline for submission of a complete dossier for Alphachloralose as an active substance in product-type 14 was 28 March 2004, in accordance with Article 9(2) of Regulation (EC) No 1451/2007.

On 28 March, 2004 competent authorities received a dossier from the applicant. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation on 28 September 2004.

On 14 November, 2006, the Rapporteur Member State submitted, in accordance with the provisions of Article 14(4) and (6) of Regulation (EC) No 1451/2007, to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report. The Commission made the report available to all Member States by electronic means on 24 November, 2006. The competent authority report included a recommendation for the inclusion of Alphachloralose in Annex I to the Directive for PT 14.

In accordance with Article 16 of Regulation (EC) No 1451/2007, the Commission made the competent authority report publicly available by electronic means on 21 December, 2006. This report did not include such information that was to be treated as confidential in accordance with Article 19 of Directive 98/8/EC.

In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by the Commission. Revisions agreed upon were presented at technical (TMIII07) and competent authority meetings and the competent authority report was amended accordingly.

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

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

On the basis of the final competent authority report, the Commission proposed the inclusion of Alphachloralose in Annex I to Directive 98/8/EC and consulted the Standing Committee on Biocidal Product on 30 May 2008.

In accordance with Article 15(4) of Regulation (EC) No 1451/2007, the present assessment report contains the conclusions of the Standing Committee on Biocidal Products, as finalised during its meeting held on 30 May 2008.

1.2. Purpose of the assessment report

This assessment report has been developed and finalised in support of the decision to include Alphachloralose in Annex I to Directive 98/8/EC for product-type 14. The aim of the assessment report is to facilitate the authorisation in Member States of individual biocidal products in product-type 14 that contain Alphachloralose. In their evaluation, Member States shall apply the provisions of Directive 98/8/EC, in particular the provisions of Article 5 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 at the Commission website[3], shall be taken into account.

However, where conclusions of this assessment report are based on data protected under the provisions of Directive 98/8/EC, such conclusions may not be used to the benefit of another applicant, unless access to these data has been granted.

1.3. Overall conclusion in the context of Directive 98/8/EC

The overall conclusion from the evaluation is that it may be expected that there are products containing Alphachloralose for the product-type 14, which will fulfil the requirements laid down in Article 10(1) and (2) of Directive 98/8/EC. This conclusion is however subject to:

i. compliance with the particular requirements in the following sections of this assessment report,

ii. the implementation of the provisions of Article 5(1) of Directive 98/8/EC, and

iii. the common principles laid down in Annex VI to Directive 98/8/EC.

Furthermore, these conclusions were reached within the framework of the uses that were proposed and supported by the applicant (see Appendix II). Extension of the use pattern beyond those described will require an evaluation at product authorisation level in order to establish whether the proposed extensions of use will satisfy the requirements of Article 5(1) and of the common principles laid down in Annex VI to Directive 98/8/EC.

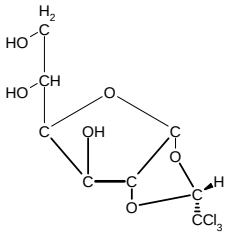
3 http://ec.europa.eu/comm/environment/biocides/index.htm

2. OVERALL SUMMARY AND CONCLUSIONS

2.1. Presentation of the Active Substance

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

Identity

CAS No.	15879-93-3
EINECS No.	240-016-7
IUPAC name	(R)-1,2-O-(2,2,2-Trichloroethylidene)-α-D-glucofuranose
Common name; synonyms	Chloralose; Alphachloralose,α-D-glucochloralose, glucochloral, Anhydroglucochloral
Molecular mass	309.54
Molecular formula	$C_8H_{11}Cl_3O_6$
Structural formula	
Purity	≥ 825 g/kg * of alphachloralose
Isomers	Mixture of α and β isomers.

*The specification for purity (≥97% w/w) is based on the combined concentration of both isomers.

This isomeric composition of Chloralose is made up of ≥ 85% alphachloralose and ≤15% betachloralose.

ßetachloralose was proven to have no activity.

Alphachloralose does not contain other impurities above or equal to the concentration limit of 0.1 %w/w.

Physico-Chemical Properties

Alphachloralose does not exhibit hazardours physical-properties. It is a white to yellowish white powder with no discernible odour and with a melting point of 176.6ºC. It is slightly volatile, has a low vapour pressure (0.0083 Pa at 25ºC), and a low Henry's Law constant. It is readily soluble in water, soluble organic solvents, it is thermally stable, not flammable and should not be considered to have explosive or oxidising properties. There is no specific packaging material which is known to be incompatible with Alphachloralose.

Methods of Analysis

The methods of analysis of the active substance, as manufactured, has been validated and shown to be sufficiently specific, accurate and precise. A method of analysis for the ß isomer, present at a quantity ≤ 15% w/w, was also validated.

An analytical method for determining the concentration of the active substance in the biocidal product was submitted and validated on the basis of linearity, accuracy, precision and specificity.

A LC/MS/MS method was developed for the analysis of alphachloralose and betachloralose in surface water and drinking water with a limit of quantification of 0.1 µg/L.

A GC-MS method was submitted for the identification and quantification of residues of both isomers derivatised with Tri-Sil Z in soil, with a limit of quantification of 0.05 mg/kg.

Analytical methods for the determination of residues of alphachloralose derivatised with Tri-sil Z in/on food or feedingstuffs were developed. GC-MS and GC-ECD methods were used on cucumber, meat, oil-seed rape and lemon.A GC-ECD method was used on wheat. Validation parameters were only fulfilled for cucumber, therefore the tested methods are proposed to be used only for monitoring and control purposes. Since the proposed use pattern for chloralose does not involve use in food and feed areas, a validated method must be asked, if relevant, at the product authorization stage.

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) avoiding unnecessary suffering of target organisms 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 Member States in granting or reviewing authorisations, and to apply adequately the provisions of Article 5(1) of Directive 98/8/EC and the common principles laid down in Annex VI of that Directive, the intended uses of the substance, as identified during the evaluation process, are listed in Appendix II.

2.1.3. Classification and Labelling

2.1.3.1 Proposed for active substance

Classification	Xn N  
Class of danger	Harmful, Dangerous for the environment
R phrases	R20/22 – Harmful by inhalation and if swallowed. R50/53 – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
S phrases	S2 – Keep out of the reach of children. S13 – Keep away from food, drink and animal feedingstuffs. S29 – Do not empty into drains. S46 – If swallowed, seek medical advice immediately and show this container or label. S60 – This material and its container must be disposed of as hazardous waste. S61 – Avoid release to the environment. Refer to special instructions/safety data sheet.

2.1.3.2 Proposed for biocidal products

2.1.3.2.1 Alphablock (professional use)

Classification	N 
Class of danger	Dangerous for the Environment.
R phrases	R50/53 – Very toxic to aquatic organisms, may cause long term adverse effects in the aquatic environment
S phrases	S60 – This material and its container must be disposed of as hazardous waste. S61 – Avoid release to the environment. Refer to special instructions/Safety data sheets.

2.1.3.2.2 Alphakil Block (non-professional use, amateurs)

Classification	N 
Class of danger	Dangerous for the Environment.
R phrases	R50/53 – Very toxic to aquatic organisms, may cause long term adverse effects in the aquatic environment
S phrases	S29 – Do not empty into drains. S61 – Avoid release to the environment. Refer to special instructions/Safety data sheets.

Alphakil Block is only 10 g (2 x 5g blocks) in total, which is significantly less than the 125 ml ≡ 125 g quoted as the threshold for a small quantity in Directive 1999/45/EC. Accordingly, it's not necessary to indicate on the label the R phrases or the S phrases.

2.2. Summary of the Risk Assessment

2.2.1. Human Health Risk Assessment

2.2.1.1 Critical endpoints

Chloralose is an acute central nervous system (CNS) depressant. High acute doses lead to a reduction in body temperature, marked respiratory inhibition and death. Repeat dose toxicity at doses above sub-acute NOAEL (20mg/kg bw/day) and subchronic NOAEL (15 mg/kg bw/day) showed evident CNS depression effects, within 10-20 minutes.

2.2.1.2 Toxikocinetics

After oral administration of Chloralose, to rats at least 80% of the substance is rapidly absorbed, widely distributed, metabolised and excreted. The plasma half-life in rats is between 8.8-12.6 hours. Elimination from the body is not significantly influenced by dose, occurring via urine in the low level at approx. 60% and high level at 70% and faeces in low level at approx. 30% and high level at 20%, in the first 24h after dosing. Urine metabolite examinations showed that chloral hydrate is the main metabolite of Chloralose accounting for about 40% of the identified components, at 24h. In faeces, α, ß chloralose were quantified as the most relevant components, at comparable proportions, respectively 16% and 11%, at 24h.

Toxikocinetics evaluation indicates that Chloralose and its metabolites are unlikely to bioaccumulate in mammals.

2.2.1.3 Human Health Hazard of the active substance

Chloralose was harmful in the acute toxicity studies carried out in rats by oral and inhalative exposure with LD/C 50s of 341 mg/kg and more than 1.99 mg/L respectively. No adverse effects were observed following an acute dermal exposure of 2000 mg/kg. It is not corrosive, does not induce skin or eye irritation and is not a skin sensitiser.

Repeated oral administration of Chloralose in rats (28d and 90d studies) demonstrated critical neurological adverse effects (e.g. prostration, spastic locomotion, drowsiness and piloerection) used for NOAEL setting at 15mg/kg bw/day based on the 90d study results.

These effects proved to be reversible under the study conditions and confirmed a.s. pharmacological mode of action (CNS depression). Human and veterinary use of the substance and its metabolite (chloral hydrate) as sedative and hypnotic drugs confirm that the primary effect of alphachloralose is on the CNS causing sedation. Reading across from its main metabolite, chloral hydrate, it is concluded that delayed neurotoxicity is not a critical endpoint.

The results of the two developmental toxicity studies in rats and rabbits suggest a non species difference for maternal toxicity to Chloralose with a $NOAEL_{maternal\ toxicity}$ 15 mg /kg bw/day based on sedation effects and alterations in body weight and food consumption. A $NOAEL_{foetal\ toxicity}$ 15 mg/kg bw/day was established based on reduced birth weights. These effects are secondary to CNS depression; hence it was considered that a developmental toxicity classification for Chloralose toxicity is not required. Both alphachloralose and chloral hydrate have therapeutic use, without known history of paediatric susceptibility or other reproductive toxicity. WHO 2005 evaluation on chloral hydrate in infants and conclude that developmental toxicity, including

developmental neurotoxicity, and immunotoxicity are not critical effects. It was concluded that reproductive toxicity is not a critical effect of alphachloralose.

The active substance tested negative in all *in vitro* genotoxicity studies. Reading across from chloral hydrate, it was concluded that similar to chloral hydrate, alphachloralose is an aneugenic agent of very low potency. Supporting evidence from two carcinogenicity (non guideline) studies with mice and dogs both concluded an absence of carcinogenicity potency for alphachloralose. There is no evidence of carcinogenicity in humans despite therapeutic use and long follow-up time. Reading across from chloral hydrate, in which the carcinogenicity potential of this metabolite was evaluated by the US-EPA, IPCS, IARC, and more recently WHO found chloral hydrate to be carcinogenic in mice but not in rats. The evaluations of these organizations all stated that the potential carcinogenicity in mice (occurring only after hepatotoxicity is evident), is of highly questionable relevance to man. More recently, there is now evidence that peroxisome proliferation is postulated as a mechanism of hepatic change with chloral hydrate. Since humans and other primates are less responsive than rats and mice in terms of peroxisomal proliferation, the rodent tumourigenicity of chloral hydrate is therefore of doubtful significance to man. Hence, it was concluded that there was no CMR concerns for chloral hydrate nor for alphachloralose.

2.2.1.4 Human Health Hazard of the product

The only components of the product that are classified as harmful according to Directive 67/548/EEC, are the active ingredient, Chloralose and the taste aversant,. The latter is classified as harmful by inhalation. The active substance is classified as R20/22 Harmful by inhalation and if swallowed. Using the conventional method these hazards do not carry through to the product thus Alphablock and Alphakil Block are not classified as hazardous for health under EC Directive 1999/45. Once formulated into the product, the exposure route of concern will be dermal, the fact that this route is not classified as a route of concern for Chloralose nor for the taste aversant is reassuring. Maximum dermal penetration of Chloralose from the formulated product was 3.11%.

No acute testing on the product has been carried out. It was considered that the information above on the active substance provides adequate assurance and is sufficient to mean that a separate acute toxicity tests involving further animal experiments are not necessary for Annex I inclusion.

2.2.1.5 AOEL (Acceptable Operator Exposure Level) and MOE (Margin Of Exposure)

The risk assessment was performed using both the AOEL and MOE approach. For each group of users (professionals and non-professionals) an acute, medium and long term AOEL were set. Due to the fast metabolism and low bioaccumulative potential as well as the rapid onset of the adverse effect of alphachloralose and the reversible nature of this effect, an extra AF for the long term AOEL calculation was not justified and therefore medium and long term AOEL have the same value.

2.2.1.5.1 Setting of AOEL and MOEref for professional users

A medium/long term AOEL of 0.15 mg/kg bw/day and MOEref of 100 were set based on the rat sub-chronic NOAEL of 15 mg/kg bw/day and the assessment factor (AF) of 100 (10 for interspecies variation and 10 for intraspecies variation since this is a worker population)

An acute AOEL of 0.2 mg/kg bw/day and an acute MOEref of 100 were set based on the rat sub-acute NOAEL of 20 mg/kg bw/day and an AF of 100 (factor of 10 for interspecies and 10 for intraspecies variation as described in the repeat dose above).

2.2.1.5.2 Setting of AOEL and MOEref for non-professional users

Although non-professionals are not expected to use the rodenticide bait on a daily basis, medium/long term AOEL of 0.15 mg/kg bw/day and a MOEref of 100 were set based on the sub-chronic NOAEL (15 mg/kg bw/day) above and an AF of 100 (factor of 10 for interspecies variation and another 10 for intraspecies variation)

An acute AOEL of 0.2 mg/kg bw/day and an acute MOEref of 100 were set based on the sub-acute NOAEL (20 mg/kg bw/day), with an AF of 100 (as described in the repeat dose above).

2.2.1.5.3 Setting of AOEL and MOEref for indirect exposures

The acute AOEL of 0.2 mg/kg bw/day and acute MOEref of 100 described for non-professional users were also used for this scenario.

2.2.1.6 Exposure and risk from use of the representative product

2.2.1.6.1 Professional Users

There is a risk that professional users may be exposed to Chloralose via the skin during normal use of the product as a rodenticide. Inhalation and oral exposure are negligible and not assessed further. Operator exposure was calculated based on measured data. The total systemic dermal exposure for unprotected (i.e. no glove use) operators during normal use of the product (Alphablock) was calculated for two different methods of loading and placing bait blocks into boxes [Alpha Rapid (Trays) and Alpha Rapid (Winged insert)].

Total systemic operator dermal exposure of Chloralose per day for each scenario is 0.025 mg/kg bw/day and 0.015 mg/kg bw/day respectively. Professional use of Alphablock has high safety margins for repeated exposure effects with MOE values of 600 and 1000 respectively, MOE values for acute exposures are 800 and 1333 respectively, indicating high safety margins for acute exposure to Alphablock. Risk characterisation using the AOEL approach indicates that repeat and acute exposures are below the AOEL.

2.2.1.6.2 Non-professional users

Alphakil Block is a ready for use Chloralose product for non-professional use only. Exposure to the active substance is significantly reduced since the product consists of a plastic tamper resistant outer box which is pre-baited with two bait blocks prior to sale or supply. Boxes are for single use only. There is however, a risk that non-professional users may be exposed to Chloralose via the skin during normal use of the product as a rodenticide. Inhalation and oral exposure are negligible and not assessed further. The worst case dermal exposure was estimated to be 0.0041 mg/kg bw/day, which is well below the medium/long term AOEL and acute AOEL. Risk characterisation based on the MOE approach also indicates that normal use of Alphakil Blocks by non-professionals has a high safety margins for both repeat (MOE of 3658) and acute (MOE 4878) exposures.

2.2.1.6.3 Indirect exposures

Total systemic indirect/secondary acute exposure of adult and child handling dead mice and infant transient mouthing of bait with the use of rodenticide baits containing 4% Chloralose were estimated to be 0.021 mg/kg bw/day, 0.082 mg/kg bw/day, and 0.04 mg/kg bw/day respectively. These exposures have high safety margins with MOE values of 952, 244, 500 respectively.

Infant mouthing of unsecured bait (i.e. not in bait box) resulted in a total systemic exposure of alphachloralose of 20 mg/kg bw/day. This exposure scenario exceeds the safety reference values indicating a significant health risk. However, as the product is only to be used in tamper resistant bait boxes with a bittering agent, this scenario is very unlikely to occur.

It was concluded that there is an acceptable level of risk to professional users and non-professionals users that may be indirectly exposed to the rodenticide baits in tamper resistant bait boxes containing 4% w/w Alphachloralose presented in this assessment.

2.2.2. Environmental Risk Assessment

2.2.2.1. Fate and distribution in the environment

Chloralose is not expected to undergo abiotic degradation by hydrolysis or photolysis in water. If present in air it is expected to be quickly degraded by photo-oxidation. It was not readily biodegradable under the conditions of the Closed Bottle Test and not inherently biodegradable under the conditions of the Zahn-Wallens/EMPA Test.

It can be classified very mobile in sand/ loamy sand soil, mobile in sandy clay loam, clay and loamy sand soils and moderately mobile in clay loam/ clay soil. Due to its low adsorption onto soils and being readily soluble in water, Chloralose is expected to move from soil into water.

As it is intended to be indoor use only, and taken into account mice behaviour, release to soil of this substance can be considered negligible.

Nevertheless, as it is non biodegradable and hydrolytically stable, and due to its low adsorption onto soils, contamination of surface and groundwater may eventually occur and therefore this emission scenario is considered in the assessment performed.

An assessment of n-octanol/water partition coefficient and adsorption capacity indicated that Chloralose is not likely to bioaccumulate in aquatic or terrestrial species.

2.2.2.2. Effects assessment

Based on the evaluation of hazards for the aquatic environment, Chloralose is very toxic to aquatic organisms. Two studies, both with a reliability factor of 2, were performed on each of the three trophic levels of the base set (fish, Daphnia and algae).

$PNEC_{aquatic}$ was calculated from the geometric mean of the most sensitive species EC_{50}, *Daphnia magna*, applying an assessment factor of 1000. The $PNEC_{aquatic}$ is 0.099 μg/L. Chloralose showed low toxicity to microrganisms, with EC_{10} of 702.89 mg/L. $PNEC_{microorganisms}$ was determined as 70.29 mg/L, applying an assessment factor of 10 to the EC_{10} value.

No further testing was submitted given the intended use of Chloralose present in product Alphablock – indoor use only in a tamper resistant bait box.

2.2.2.3. PBT assessment

Chloralose can be regarded as potentially persistent (P) or very persistent (vP) in marine environment. However, given its low log K_{ow}, it's not considered to potentially fulfil the B criterion. The T criterion is fulfilled due to the classification as very toxic to aquatic organisms and as harmful with danger of serious damage to health by prolonged exposure.

Since the active substance does not clearly fulfil the B criterion, Chloralose is not considered to be a PBT or a vPvB substance, according to the TGD on Risk Assessment (2003).

2.2.2.4. Exposure assessment

Aquatic compartment

Given the use pattern of Chloralose – indoor use only – the route of exposure to the environment being considered is through waste disposal of unspent product. Given the properties of the active substance (low vapour pressure, high solubility in water, not degradable, very mobile), and the fact that the formulated product is a solid, the most important route of environmental emission from landfill sites for Chloralose would be leaching with water. Leachate produced from the landfill is therefore collected and treated on a STP before being either discharged or re-cycled.

The model of a sanitary landfill included on RIVM report 601450009 – Emission scenarios for all 23 product types of the Biocidal Products Directive (EU Directive 98/8/EC) – was followed in order to calculate for a certain year the maximum quantities of Chloralose loads to percolating water, from the first year after the start of utilisation of the landfill up to 5 years after closure, leading to a total of 20 years.

Based on worst case assumptions the following maximum predicted environmental concentrations (PEC) of Chloralose in the aquatic compartment were determined:

$PEC_{STP} = 7.72 \times 10^{-6}$ mg/L (on year 12)

$PEC_{surface\ water} = 7.72 \times 10^{-7}$ mg/L (on year 12)

$PEC_{groundwater} = 7.64 \times 10^{-5}$ mg/L (on year 20)

An assessment of a PEC for sediment was not carried out since log K_{ow} for Chloralose, 0.85±0.03, is below the trigger value of 3, according the TGD on Risk Assessment (2003).

Atmosphere

Due to the low vapour pressure and low Henry's law constant it is not likely that Chloralose will be present in the atmosphere at a relevant extent and if present in air it is expected to be quickly degraded by photo-oxidation.

Terrestrial compartment

There is no likely scenario for Chloralose to enter the terrestrial environment. Chloralose is for indoor use only so there is no direct application. On the other hand, is unlikely that a mouse would venture outdoors after consuming the bait due to the fast acting nature of the active substance and even if it did it is likely that the Chloralose would have already been metabolised at least at some extension. The only other foreseeable route of entry to the terrestrial environment may be during disposal. Disposal of unused bait and collected rodent bodies will be to landfill. This has been considered in detail and, besides the fact that a fraction of the leachate can penetrate into the subsoil of the landfill, it's not likely that the substance remains in the soil due to its mobility properties.

Primary and secondary poisoning

The primary poisoning hazard may be related to grain-eating birds because birds are more susceptible to this active substance than rodents and other mammals that are bigger than mice (TGD on Risk Assessment, 2003). Chloralose is to be used indoors and the opportunity for primary poisoning to non-targets is negligible. The biocidal product is presented in a tamper-resistant bait box as a non-spill wax block formulation. It is therefore not attractive to granivorous passerine and corvid species.

There is unlikely to be an issue of secondary poisoning since a limited exposure to the environment is expected. Chloralose is for indoor use only and immobilisation of mice occurs shortly after bait consumption. Reference should also be made to ESD (2003), which states that the target animal, the mouse, will not eat large portions of the poison bait due to its rapid narcotic effect. Mammal predators may catch a poisoned mouse but with LD_{50} values no less than 100 mg/kg for cats and dogs, a secondary poisoning risk is considered negligible.

2.2.2.5. Risk characterisation

Risk in the aquatic compartment (including sediment)

The route of exposure to the environment considered was through waste disposal of unspent product in landfill. Given the properties of Chloralose (vapour pressure, solubility in water, not degradable, very mobile), and the fact that the formulated product is a solid, the most important route of environmental emission from landfill sites would be leaching with water to the STP, surface water and groundwater. The determined PEC/PNEC ratios for those compartments through the landfill life cycle (utilization period of 15 years plus 5 years after closure) are all below 1 indicating no risk to aquatic biota.

No risk characterization was performed for sediment since, as in accordance with the TDG on Risk Assessment (2003), log K_{ow} is well below the trigger value of ≥3.

Risk in the atmosphere

Chloralose has low vapour pressure and is not intended to be sprayed or fumigated. It is formulated into a non volatile solid being occurrence in air highly unlikely. Moreover, significant phototransformation in air due to hydroxyl radicals would be expected. It is also highly unlikely that will have any impact either on global warming, on ozone depletion or on acidification.

Risk in the terrestrial compartment

Under normal conditions of use, the exposure of Chloralose to the terrestrial environment will be negligible, when it is used in the rodenticide product Alphablock. There is no mechanism by which the active substance can be released directly into the terrestrial ecosystem because it is only for use indoors in discrete tamper resistant bait boxes. Other routes such as from rodent urine, faeces or carcasses and from disposal of unused bait have been considered and found to be insignificant.

Disposal of unused bait and collected rodent bodies will be to landfill and, besides the fact that a fraction of the leachate can penetrate into the subsoil of the landfill, it's not likely that the substance remains in the soil due to its mobility properties. Furthermore, as indicated by its log Kow and Henry's law constant, the substance is expected to remain in the water phase of the STP and no exposure is expected to occur to agricultural soil, via STP slurry.

Risk for primary and secondary poisoning

The primary poisoning hazard may be related to grain-eating birds because birds are more susceptible to this active substance than rodents and other mammals that are bigger than mice (TGD on Risk Assessment, 2003). Chloralose is to be used indoors and the opportunity for primary poisoning to non-targets is negligible. The biocidal product is presented in a tamper-resistant bait box as a non-spill wax block formulation. It is therefore not attractive to granivorous passerine and corvid species.

An assessment of n-octanol/water partition coefficient, adsorption capacity and molecular mass indicated that Chloralose is not likely to bioaccumulate in aquatic or terrestrial species, which leads to a negligible risk of secondary poisoning.

2.2.3. List of endpoints

In order to facilitate the work of Member States in granting or reviewing authorisations, and to apply adequately the provisions of Article 5(1) of Directive 98/8/EC and the common principles laid down in Annex VI of that Directive, the most important endpoints, as identified during the evaluation process, are listed in Appendix I.

3. DECISION

3.1. Background to the Decision

On the basis of the proposed and supported uses and the evaluation conducted as summarised in Sections 2.1-2.8, it can be concluded that the proposed use of alphachloralose under specified conditions fulfil the safety requirements laid down in Article 5(1) (b), (c) and (d) of Directive 98/8/EC. It is therefore proposed to include alphachloralose in Annex I of the Directive.

The exposure scenario related to infant mouthing of unsecured bait (i.e. not in tamper resistant bait boxes) exceeds the safety reference values indicating a significant health risk. So, the products are only to be used in tamper resistant bait boxes with a bittering agent, although this scenario is very unlikely to occur.

3.2. Decision regarding Inclusion in Annex I

Alphachloralose shall be included in Annex I to Directive 98/8/EC as an active substance for use in product-type 14 (Rodenticide) subject to the following condition:

- minimum purity of 825 g/kg, in the biocidal product as placed on the market;

Although, Member States shall ensure that authorisations are subject to the following specific provisions:

(1) The nominal concentration of the active substance in the products shall not exceed 40 g/kg.

(2) Products shall contain an aversive agent and a dye.

(3) Only products for use in tamper resistant and securely closed bait boxes shall be authorised.

3.3. Elements to be taken into account by Member States when authorising products

The conclusions of this assessment report are based on data relating to the indoor use of solid blocks containing alphachloralose in tamper resistant bait boxes by professional user and solid blocks containing alphachloralose in tamper resistant bait boxes ready-for-use by non-professional user.

Products cannot be authorised for outdoor use unless data is submitted to demonstrate that the product will meet the requirements of Article 5 and Annex VI, if necessary by the application of appropriate risk mitigation measures.

The active substance, although is manufactured as a powder and has been evaluated as such, it is not used in this physical state in neither of the representatives products submitted in the dossier. Therefore, the risks for the environment and human health in powder formulations were not assessed for the purpose of annex I inclusion of alphachloralose.

Information on full two year shelf life study and the auto-ignition temperature of alphachloralose should be submitted at the latest when applying authorization of the biocidal product for the first time after Annex I inclusion.

No field studies were performed, but at this stage sufficient information was provided. However for product authorisation at national level field trials should be presented.

The participant shall make sure that the IUCLID file is in line with the final version of the CA Report.

3.4. Requirement for further information

It is considered that the evaluation has shown that sufficient data have been provided to verify the outcome and conclusions, and permit the proposal for the inclusion of alphachloralose in Annex I to Directive 98/8/EC, as active substance for use as a rodenticide (product-type 14).

3.5. Updating this Assessment Report

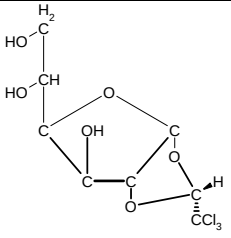
This assessment report may need to be updated periodically in order to take account of scientific developments and results from the examination of any of the information referred to in Articles 7, 10.4 and 14 of Directive 98/8/EC. Such adaptations will be examined and finalised in connection with any amendment of the conditions for the inclusion of Alphachloralose in Annex I to the Directive.

Appendix I: List of endpoints

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

Active substance (ISO Common Name)	Alphachloralose. Also known as α-D-glucochloralose; glucochloral; anhydroglucochloral; chloralosane.
Product-type	14 - Rodenticide

Identity

Chemical name (IUPAC)	(R)-1,2-O-(2,2,2-Trichloroethylidene)-α-D-glucofuranose
Chemical name (CA)	Chloralose
CAS No	15879-93-3
EC No	240-016-7
Other substance No.	None known.
Minimum purity of the active substance as manufactured (g/kg or g/l)	The specification of the purity is ≥ 97% w/w. The minimum purity of alphachloralose is 825g/kg.
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	This isomeric composition is made up of ≥85% alphachloralose and ≤15% betachloralose. ß isomer was found to have no activity. There are no others impurities present at 0.1% or higher.
Molecular formula	$C_8H_{11}Cl_3O_6$
Molecular mass	309.54
Structural formula	

Physical and chemical properties

Melting point (state purity)	176.6°C (97% w/w purity)
Boiling point (state purity)	Not applicable as alphachloralose decomposes immediately after melting.
Temperature of decomposition	182.0°C
Appearance (state purity)	Solid (powder), white to yellowish white and odourless (97% w/w purity)
Relative density (state purity)	0.7739 at 20°C (97% w/w purity)
Surface tension	50.076 +/- 0.045 mN/m (at 20°C) The surface tension of a 1 g/L aqueous sample solution of alphachloralose was determined.
Vapour pressure (in Pa, state temperature)	0.00883 Pa (at 25°C, calculated from the regression curve derived by plotting Log P vs. 1/T).
Henry's law constant (Pa m^3 mol^{-1})	5.65 x 10^{-4} Pa. M^3. mol^{-1}
Solubility in water (g/l or mg/l, state temperature)	pH 5: 4.86 g/l
	pH 7: 4.84 g/l
	pH 9 4.73 g/l The assay was conducted at 24°C.
Solubility in organic solvents (in g/l or mg/l, state temperature)	Solubility in n-hexane 20°C - 0.8 g/l 40°C - 1.0 g/l
	Solubility in 2-Propanol 20°C - 13.2 g/l 40°C - 24.8g/l
Stability in organic solvents used in biocidal products including relevant breakdown products	Not applicable. There are no organic solvents used in the representative product.
Partition coefficient (log P_{OW}) (state temperature)	Mean partition coefficient 0.85 +/- 0.03 at 22-26°C (room temperature)
Hydrolytic stability (DT_{50}) (state pH and temperature)	pH 4 and 50° C: hydrolytically stable.
	pH 7 and 50° C: hydrolytically stable.
	pH 9 and 50° C: hydrolytically stable.

Dissociation constant	Not applicable.
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	CONFIDENTIAL information - data provided separately The spectrum was consistent with the accepted structure of alphachloralose.
Photostability (DT_{50}) (aqueous, sunlight, state pH)	Not applicable due to UV absorption maxima.
Quantum yield of direct phototransformation in water at Σ > 290 nm	Not applicable due to UV absorption maxima.
Flammability	Not flammable.
Explosive properties	Not explosive.

Proposed Classification and Labelling

with regard to toxicological data	R20/22 – Harmful by inhalation and if swallowed.
with regard to ecotoxicological data	R50/53 – Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method)	The method consists of a dissolution of alphachloralose reference material in methanol followed by determination using HPLC with a 5 µm, 100Å, C-18, 250 x 3.0 mm column and with a photodiode array detector. The linearity and accuracy of the method were determined using external calibration solutions. LOQ is 5% (w/w).
Impurities in technical active substance (principle of method)	The method consists of a dissolution of betachloralose reference material in methanol followed by determination using HPLC with a 5 µm, 100Å, C-18, 250 x 3.0 mm column and with a photodiode array detector. The linearity and accuracy of the method were determined using external calibration solutions. LOQ is 5% (w/w).

Analytical methods for residues

Soil (principle of method and LOQ)	The analytical procedure consisted of extraction with acetone followed by liquid/liquid partition in dichloromethane. The extracts were then derivatised by Tri-Sil Z, reconstituted in hexane and then analysed by GC-MS using a SGE BPX5 column. LOQ is 0.05 mg/kg.

Air (principle of method and LOQ)	Waived
Water (principle of method and LOQ)	The method performed was analysis of alphachloralose and betachloralose standards, extracted from drinking water and surface water by retention on a C_{18} solid phase extraction cartridge and elution with acetone after drying. The extract was dissolved in HPLC mobile phase followed by determination by LC/MS/MS with mulitple reaction monitoring (MRM). LOQ is 0.1 μg/L.
Body fluids and tissues (principle of method and LOQ)	Waived
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	The analytical procedures consisted of extraction from cucumber, wheat, oil-seed rape and lemon with solvent followed by a clean up procedure, if appropriate, and determination by GC-ECD and GC-MS (except on wheat which was only by GC-ECD). The extracts were then derivatised by Tri-Sil Z. Quantification of extracts was performed by linear or quadratic regression using peak areas of external calibration standards or peak area ratios using an internal standard. LOQ of 0.01 mg/kg validated for cucumber.
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	The analytical procedures consisted of extraction from meat with solvent followed by a clean up procedure, if appropriate, and determination by GC-ECD and GC-MS. The extracts were then derivatised by Tri-Sil Z. Quantification of extracts was performed by linear or quadratic regression using peak areas of external calibration standards or peak area ratios using an internal standard. No LOQ validated.

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals

Rate and extent of oral absorption:	An absorbed fraction of at least 80% of the administered dose was calculated based on the urine (and cage washings) excretion of [14C]-alphachloralose and its metabolites. Chromatographic analysis of urine and faeces indicated the presence unchanged alphachloralose and six chromatographically polar metabolites including trichloroacetic acid, chloral hydrate and conjugate derivatives. Radioactivity in blood and plasma was detected 15 mins after dosing, peaking at 30 mins for females and 60 mins for males.
Rate and extent of dermal absorption:	The ability of Alphachloralose in the formulated product to penetrate the skin was tested in an *in vitro* radiolabelled study. The product was held in contact with dermatomed human skin for 8 hours. During a period of 24 hours the maximum dermal penetration of Alphahloralose was 3.11%. In this test system the recovery of the test compound was 100% of the applied dose.
Distribution:	Distribution was evaluated quantitatively using the technique of whole-body autoradiography. Greatest concentrations were measured in the gastrointestinal tract, liver, kidney, urinary bladder and lachrymal glands. Tissues in which the tissue:blood ratios were higher than unity were: adrenal gland, caecum mucosa, cartilage, ex-orbital and intra-orbital lachrymal gland, kidney, large intestine mucosa, liver, lung, myocardium, nasal mucosa, pancreas, pituitary gland, salivary gland, small intestine contents and mucosa, spleen, stomach contents and mucosa, tongue, and urinary bladder. Alphachloralose was below the limit of quantification in all tissues analysed after 168 hours except for the large intestine contents.
Potential for accumulation:	Alphachloralose and its metabolites are unlikely to bioaccumulate in mammals. The plasma half-life in rats is between 8.8-12.6 hours.
Rate and extent of excretion:	Radioactivity excreted in urine samples accounted

	for the higher proportion of dose in all rat groups. Radioactivity was mostly excreted via urine and faeces with 70-80% eliminated in the first 24 hours after dosing. Negligible dose was excreted in expired air.
Toxicologically significant metabolite(s)	Proportions of radioactive components in urine and faeces extract were determined using HPLC with on-line radioactivity detection. Chromatographic analysis of both indicated the presence of unchanged alphachloralose and six chromatographically polar metabolites including trichloroacetic acid, chloral hydrate and conjugate derivatives. Urine metabolite examinations showed that chloral hydrate is the main metabolite of Alphachloralose accounting for about 40% of the radioactive components.

Acute toxicity

Rat LD_{50} oral	The oral LD_{50} Males: 611 mg/kg; Females: 212 mg/kg Oral LD_{50} combined: 341 mg/kg.
Rat LD_{50} dermal	The acute dermal LD_{50} is >2000 mg/kg.
Rat LC_{50} inhalation	LC50 is > 1.99 mg/L (the highest concentration at which the actual exposure is certain).
Skin irritation	Alphachloralose is considered as non-irritant when administered by cutaneous route in rabbits.
Eye irritation	Alphachloralose is considered as non-irritant when administered by ocular route in rabbits.
Skin sensitization (test method used and result)	According to the maximisation method established by Magnusson and Kligman, no cutaneous reactions attributable to the sensitisation potential of Alphachloralose was observed in guinea pigs. It is concluded that is not a skin sensitiser in guinea pigs.

Repeated dose toxicity

Species/ target / critical effect	Sprague-Dawley Crl CD (SD) BR / reduced body weight and clinical signs.
Lowest relevant oral NOAEL / LOAEL	Subacute NOAEL (28d study): 20mg/kw bw/day based on CNS depression in both sexes, at next dose level (80 mg/kg bw/day). Subchronic NOAEL (90d study): 15mg/kg bw/day based on CNS depression in both sexes, at the next dose level (60 mg/kg bw/day).
Lowest relevant dermal NOAEL / LOAEL	Not tested. Justifications were provided.
Lowest relevant inhalation NOAEL / LOAEL	Not tested. Justifications were provided.

Genotoxicity

Reverse Mutation Assay on Bacteria

Chloralose did not induce any significant increase in the number of revertants, with or without S9 mix, in any of the 5 strains tested.

In vitro Mammalian Cytogenicity Test

Chloralose at all tested dose levels (0.25, 0.5 and 1.0 mg/mL of culture) does not possess chromosomal aberration induction potential to human lymphocytes both without and with metabolic activation (5% v/v and 30% v/v S9 mix).

In vitro gene mutation assay in mammalian cells.

Chloralose at concentrations up to 500 μg/mL is not mutagenic to the *hgprt* locus of CHO-K1 cells under the conditions used in this assay.

The genotoxicity of chloral hydrate (metabolite of concern) has been extensively studied and concluded to be an aneugenic agent of very low potency. Reading across from chloral hydrate, it was concluded that alphachloralose is also an aneugenic agent of very low potency.

Carcinogenicity

Species/type of tumour	Carcinogenicity test not performed. Justifications were provided.

	Supporting evidence from two carcinogenicity (non guideline) studies with mice and dogs both concluded an absence of carcinogenicity potency for alphachloralose. There is no evidence of carcinogenicity in humans despite therapeutic use and long follow-up time. Reading across from chloral hydrate, in which the carcinogenicity potential of this metabolite was evaluated by the US-EPA, IPCS, IARC, and more recently WHO found chloral hydrate to be carcinogenic in mice but not in rats. The evaluations of these organizations all stated that the potential carcinogenicity in mice (occurring only after hepatotoxicity is evident), is of highly questionable relevance to man. More recently, there is now evidence that peroxisome proliferation is postulated as a mechanism of hepatic change with chloral hydrate. Since humans and other primates are less responsive than rats and mice in terms of peroxisomal proliferation, the rodent tumourigenicity of chloral hydrate is therefore of doubtful significance to man. Hence, it was concluded that there was no carcinogenicity concerns for chloral hydrate nor for alphachloralose.
lowest dose with tumours	Carcinogenicity test not performed. Justification were provided.

Reproductive toxicity

Species/ Reproduction target / critical effect	Two-generation reproduction study was not performe Justification were provided. Evidence from the subacute and subchronic studies show that alphachloralose exposure to rats does not result in adverse morphological effects on reproductive male and female organs and accessory tissues up to concentrations well above the critical NOAEL and in the presence of clear CNS depression effects. Both alphachloralose and its main metabolite, chloral hydrate, have therapeutic use, without known history of paediatric susceptibility or other reproductive toxicity. WHO evaluation on chloral hydrate in infants and conclude that developmental toxicity, including developmental neurotoxicity, and immunotoxicity are not critical effects.

	It was concluded that reproductive toxicity is not a critical effect of alphachloralose.
Lowest relevant reproductive NOAEL / LOAEL	See above.
Species/Developmental target / critical effect	See below.
Developmental toxicity	
Lowest relevant developmental NOAEL / LOAEL	The results of the two developmental toxicity studies with alphachloralose in rats and rabbits suggest a non species difference for maternal toxicity with a $NOAEL_{maternal\ toxicity}$ of 15 mg /kg bw/day based on sedation effects and alterations in body weight and food consumption. A $NOAEL_{foetal\ toxicity}$ of 15 mg Chloralose/kg bw/day was set based on reduced birth weights. As these effects are secondary to CNS depression. It was considered that a developmental toxicity classification for Alphachloralose toxicity is not required.

Neurotoxicity / Delayed neurotoxicity

Species/ target/critical effect	Neurotoxicity effects of chloralose were addressed in several studies, which show transient and reversible CNS depression effects with no apparent neuropathology changes. Based on these studies, neurotoxicity was concluded to be the critical effect from from which the acute NOAEL at 20 mg/kg bw/day (Doc IIIA_A6.3.1) and sub-chronic NOAEL at 15mg/kg bw/day (Doc IIIA_A6.4.1a) were derived and used in the RA. .
Lowest relevant developmental NOAEL / LOAEL.	See above.

Other toxicological studies

.....	No other toxicological studies carried out.

Medical data

.....	Alphachloralose and its metabolite (chloral hydrate) were have been used as sedative, hypnotic, anesthetic agents and management of alcohol withdrawal symptoms in humans. Adult oral dose to alphachloralose is reported to be 150-300mg administered after meals, while the dose for children to be 37-150 mg. Adverse effects

following medical use included: vomiting, tremors, ataxia, mental confusion, and very seldom leukopenia and eosinophilia. There is also no literature data available from occupational surveillance on adverse health effects of Chloralose. There are over 20 acute poisonings by Chloralose reported in the literature, but fatal cases are rare.

Intake of chloral hydrate from pharmaceutical exposure is about 17 mg/kg BW for a 60kg adult and 29 mg/kg bw for a 35kg child (assuming dose of 1g). The LOAEL is 12.5 mg/kg bw/day based on the recommended sedative dose. There is no evidence of carcinogenicity or reproductive toxicity in humans despite therapeutic use and long follow-up time.

As chloral hydrate can be formed as a by-product of the chlorination of water, public exposure to chronic low levels of chloral hydrate and its breakdown products are not uncommon. Surveys in Canada and the USA report mean concentrations of 1.2-8.4ug/l and 5ug/l respectively. The maximum level reported is 46 ug/l. Human exposure from drinking water is less than 1 ug/kg bw/day (assuming the maximum concentration). There is no data indicating adverse health effects from these chronic exposures.

Summary	Value	Study	Safety factor
Non-professional user			
ADI (acceptable daily intake, external long-term reference dose)	Not applicable, as not intended for use on food or feed.		
AOEL-S (Operator Exposure)			
Acute A(O)EL	0.2 mg/kg bw/day	Doc IIIA_A6.3.1	100
Medium A(O)EL	0.15 mg/kg bw/day	Doc IIIA_A6.4.1	100
Long Term A(O)EL	0.15 mg/kg bw/day	Doc IIIA_A6.4.1	100
ARfD (acute reference dose)	Not applicable, as not intended to be applied in foodstuffs.		
Professional user			

Reference value for inhalation (proposed OEL)	-	-	-
Reference value for dermal absorption	3.11%.	Doc IIIB 6.4	-

Acceptable exposure scenarios (including method of calculation)	
Professional users	The worst case scenario risk characterization was bait blocks of solid wax used in tamper resistance bait boxes. Operator lifts 10g blocks from "chocolate-box" type tray. This involves pushing the block from the bottom of the tray, and lifting out with hands. Block is then placed in a tamper resistant bait box and placed where mouse activity is evident. Manipulations of the boxes are done without gloves. An operator visits 2 sites per day to load 15 boxes, clean-up 14 boxes and dispose of 6 per site. This worst case scenario has MOE values of 600 for repeat exposures and 800 for acute exposures, indicating safe product use. See Doc IIC for calculation details.
Non-professional users	The worst case scenario risk characterization was pre-loaded bait blocks of solid wax used in tamper resistance bait boxes. Operator has no direct access to bait blocks inside the tamper resistant bait box. Bait boxes are single use, and are not for re-filling. Manipulations of the boxes are done without gloves. TNGs default values were used for this use pattern. MOE values for the worst case exposure scenario are 3658 for repeat exposures and 4878 for acute exposures indicating safe product use. See Doc IIC for calculation details.
Indirect exposure as a result of use	TNGs default values were used for these use patterns. MOE values for adult and child handling dead mice and infant transient mouthing of bait with the use of rodenticide baits containing 4% chloralose were 952, 244, 500 respectively, indicating safe scenarios. The scenario of infant mouthing unsecured bait resulted in an unsafe use with a MOE of 1. However due to use in tamper resistant bait box with an aversive agent, this scenario was considered unlikely to occur. See Doc IIC for calculation details.

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	Results at 50° C
	pH 4:+0.5% (Average % change in chloralose)
	pH 7:+0.1% (Average % change in chloralose)
	pH 9:-3.3% (Average % change in chloralose) The half-life at these pH values can be expected to exceed one year at 25° C. Chloralose is hydrolytically stable and is not likely to hydrolyse under the environmental conditions. Degradation products: not applicable.
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	No light is absorbed above 194.5 nm in the spectrum of chloralose (no UV absorbance in the sun light region). So chloralose is not degradable by direct phototransformation and is assumed to be stable against photolysis in water.
Readily biodegradable (yes/no)	No. Result: < 17% after 28 days.
Biodegradation in seawater	Waived.
Non-extractable residues	Waived.
Distribution in water / sediment systems (active substance)	Waived.
Distribution in water / sediment systems (metabolites)	Waived.

Route and rate of degradation in soil

Mineralization (aerobic)	Waived.
Laboratory studies (range or median, with number of measurements, with regression coefficient)	DT_{50lab} (20°C, aerobic): Waived.
	DT_{90lab} (20°C, aerobic): Waived.
	DT_{50lab} (10°C, aerobic): Waived.
	DT_{50lab} (20°C, anaerobic): Waived.
	Degradation in the saturated zone: Waived.
Field studies (state location, range or median with number of measurements)	DT_{50f}: Waived.
	DT_{90f}: Waived.
Anaerobic degradation	Waived.

Soil photolysis	Waived.
Non-extractable residues	Waived.
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	Waived.
Soil accumulation and plateau concentration	Waived.

Adsorption/desorption

Ka , Kd Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	Ka from 0.44 to 0.84 cm^3/g Ka_{oc} from 5.49 to 120.00 cm^3/g Kd and Kd_{oc} not available since calculated desorption values were negative. No pH effects observed. Chloralose is considered very to moderately mobile in soil.

Fate and behaviour in air

Direct photolysis in air	Waived.
Quantum yield of direct photolysis	Waived.
Photo-oxidative degradation in air	The estimated half-live for the hydroxyl reactions in air is 3.191 hours (calculated with AOPWIN, v1.91). Half-life for ozone in air has not been estimated.
Volatilization	Vapour pressure: 0.00883 Pa at 25° C. Henry's law constant: 0.58×10^{-4} $Pa.m^3.mol^{-1}$ Chloralose is not expected to volatilise to air in significant quantities.

Monitoring data, if available

Soil (indicate location and type of study)	Not available.
Surface water (indicate location and type of study)	Not available.
Ground water (indicate location and type of study)	Not available.
Air (indicate location and type of study)	Not available.

Chapter 5: Effects on Non-target Species

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

Species	Time-scale	Endpoint	Toxicity
Fish			
Rainbow Trout, *Oncorhynchus mykiss*	96 hours	LC_{50} 2.4 mg/L	Toxic (Directive 67/548/EEC)
Rainbow Trout, *Oncorhynchus mykiss*	96 hours	LC_{50} 5.01 mg/L	
Invertebrates			
Daphnia magna	48 hours	EC_{50} 0.027mg/L	Very toxic (Directive 67/548/EEC)
Daphnia magna	48 hours	EC_{50} 0.36mg/L	
Algae			
Selenastrum capricornutum	72 hours	NOE_rC 0.02 mg/L E_rC_{50} 0.52 mg/L	Very toxic (Directive 67/548/EEC)
Pseudokirchneriella subcapitata	72 hours	NOE_rC 0.13 mg/L E_rC_{50} 4.90 mg/L	
Microorganisms			
Heterogeneous sample of bacteria, found naturally in domestic sewage	3 hours	EC_{20} 1699.63 mg/L EC_{10} 702.89 mg/L	Low toxicity

Effects on earthworms or other soil non-target organisms

Acute toxicity…..……..	Waived
Reproductive toxicity……	Waived

Effects on soil micro-organisms

Nitrogen mineralization	Waived
Carbon mineralization	Waived

Effects on terrestrial vertebrates

Acute toxicity to mammals	Waived
Acute toxicity to birds	Waived
Dietary toxicity to birds	Waived
Reproductive toxicity to birds	Waived

Effects on honeybees

Acute oral toxicity	Waived
Acute contact toxicity	Waived

Effects on other beneficial arthropods

Acute oral toxicity	Waived
Acute contact toxicity	Waived

Bioconcentration

Bioconcentration factor (BCF)	Bioconcentration factor not measured. BCF_{fish} = 1.05 (calculated according to TGD, eq. 74, using experimentally determined log Kow value of 0.85). $BCF_{earthworm}$ = 0.92 (calculated according to TGD, eq. 82d, using experimentally determined log Kow value of 0.85).
Depration time (DT_{50}) (DT_{90})	n.a.
Level of metabolites (%) in organisms accounting for > 10 % of residues	n.a.

Chapter 6: Other End Points

There are no other relevant data available on Chloralose which has not been summarised elsewhere in this document.

Appendix II: List of Intended Uses

Object and/or situation (a)	**Member State or Country**	**Product name**	**Organisms controlled** (c)	**Formulation**		**Application**			**Applied amount per treatment**			**Remarks:** (m)
				Type (d-f)	Conc. of as (i)	method kind (f-h)	number min max (k)	interval between applications (min)	g as/L min max	water L/m^2 min max	g as/m^2 min max	
Rodents	EU	Alpha block	*house mouse (*Mus musculus code I.1.1.3*)*	Solid, ready to use fat based block	4% w/w	Bait	Blocks are positioned 2 per bait station and placed as required.	-	Boxes containing 2 x 10g blocks should be placed at each baiting point. The baiting points should be inspected frequently and bait replaced until no more is taken. The actual number of baiting points is decided on a case by case basis dependant on many factors including size of area to be treated, size of mouse infestation.			Professional use Indoor use only
Rodents	EU	Alphakil Block	*house mouse (*Mus musculus code I.1.1.3*)*	Solid, ready to use fat based block	4% w/w	Bait	Blocks are positioned 2 per bait station and placed as required.	-	Boxes containing 2 x 5g blocks should be placed at each baiting point. The baiting points should be inspected frequently and bait replaced until no more is taken. The actual number of baiting points is decided on a case by case basis dependant on many factors including size of area to be treated, size of mouse infestation.			Non-professional use (general public) Indoor use only

Chloralose has been evaluated for its use as a rodenticide (product type 14) for the control of house mouse (*Mus musculus code I.1.1.3*). In its use as a rodenticide, is presented as ready-to-use bait at a concentration of 4 % w/w, in a tamper resistant bait box, for indoor use only. Two variants of the representative product have been submitted, for professional use (Alphablock) and for amateur use (Alphakil Block).

A total of 5 trials were performed in laboratory on Albino TO mice to evaluate the acceptance, palatability and efficacy of Alphablock (4% w/w). Complete mortality was accomplish in 29 ½ hours. Trials showed that efficacy is not affected by temperature in the range used (16° C and 21° C). The palatability is unaffected when using two week accelerated aged samples.

One study was conducted in indoor pens using Oakleaze wild mice using Alphablock (4% w/w). 85% of mortality was achieved.

No field studies were performed, but at this stage sufficient information was provided. However for product authorisation at national level field trials should be presented.

In its application as a rodenticide, laboratory studies have demonstrated a sufficient degree of efficacy of Chloralose (4% w/w) against mice.

Convulsive effects prior to insensibility have been reported when using Chloralose as a pesticide. Convulsions are suggestive of extreme distress but these occur in relatively few animals. According to human data these convulsions are of shorter duration and far less extreme, than those induced by strychnine. Animals that ingest non-lethal doses of Chloralose rapidly recover. Regarding this Chloralose can be considered to be a relatively humane rodenticide for control of mice.

Appendix III: List of studies

Data protection is claimed by the applicant in accordance with Article 12.1(c) (i) and (ii) of Council Directive 98/8/EC for all study reports marked "Y" in the "Data Protection Claimed" column of the table below. For studies marked Yes(i) data protection is claimed under Article 12.1(c) (i), for studies marked Yes(ii) data protection is claimed under Article 12.1(c) (ii). These claims are based on information from the applicant. It is assumed that the relevant studies are not already protected in any other Member State of the European Union under existing national rules relating to biocidal products. It was however not possible to confirm the accuracy of this information.

Section No / Reference No	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company Report No.** **GLP (where relevant)** **(Un)Published**	**Data Protection Claimed (Yes/No)**	**Owner**
III A2.1 A2.2 A2.4.1 A2.4.2 A2.4.3 A2.5.1 A2.5.2 A2.5.3	Budavari S, O'Neil MJ, Smith A, Heckelman PE Kinneary JF	1996	Entry for Alphachloralose, The Merck Index An Encyclopedia of Chemicals, Drugs and Biologicals. Twelfth Edition Page 295 Merck Research Laboratories, ISBN 0911910-12-3 Published	No	PUB
III A2.6	Vxx QA	1998	Mode operatoire de fabrication alpha chloralose pur Reference RAL FAB 007 Gestionnaire TAE. RAL Edition 01 Applicant's reference number ALPHCHL 207 Not GLP Unpublished	Yes	Oxx (Pxx)
III A2.7	Rxx Rxx	1993	Certificat D'Anayse. Reference RAL PG 506 - ENR 004, RAL.PF 007 dated 4 Mars 93, Applicant's reference number ALPHCHL 209 Not GLP Unpublished	Yes	Oxx (Pxx)
III A2.8	Exx Axx	1999	Analyse Alphachloralose dated 30/11/1999 Applicant's reference number ALPHCHL 206 Not GLP Unpublished	Yes	Oxx (Pxx)
III A2.8	Chem Service Pesticide Standards	2001	Comparison of Alphachloralose and Betachloralose isomers. From:www.chemservice.com/ps	No	PUB

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			2001_cat.pdf ALPHCHL 162 Published		
III A2.8_03	Rxx Ixx pxx	2005	Relative efficacy of alphachloralose and betachloralose, two isomers of chloralose, in the Alpha Rapid Bait Block Formulation. Applicant's reference number ALPHCHL 267 GLP Unpublished	Yes	Oxx (Rxx Ixx pxx)
III A2.10 III B6.6 Key study	Sxx PJ	2005	Validation of an analytical method for the determination of residues of alphachloralose in cotton gloves; Sxx Lxx Lxx Study Number SYN/4901 Applicant's reference number ALPHCHL 273 GLP Unpublished	Yes	Oxx (Pxx)
III A2.10 B6.6 Doc IIC Key study	Cxx J G	2005	Analytical method for the determination of Residues of Alphachloralose in Cotton Gloves; Dosimeters from an Operator Exposure Trial Conducted with Three Types of Rodent Baits Study No. SYN/4902 Applicant's reference number ALPHCHL 311 GLP Unpublished.	Yes	Oxx (Rxx Ixx pxx)
III A3.1.1	Vxx Y	2002	Melting Point of Alphachloralose Jxx Rxx Fxx study number 3641 Applicant's reference number ALPHCHL 183 GLP Unpublished	Yes	Oxx (Pxx)
III A3.1.1 A3.1.2	Bxx D	2003	Physico/chemical Testing on a Sample of Alphachloralose Report No.11499/35903 for Pxx Applicant's reference number ALPHCHL 187 GLP Unpublished	Yes	Oxx (Pxx)

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III A3.1.1 A3.1.2 A3.4(2) A3.4(3) A3.4(4) A3.5 A3.7a A3.9 A3.10 A3.11 A3.13 A3.15 A3.16 A6.4.1a A6.6.2 A7.1.1.1.1 A7.1.1.2.1 A7.1.1.2.2 A7.1.3 A7.2.3.1-1	Rxx Ixx pxx	2005	Determination of Chloralose in Chloralose Technical Material by Reverse Phase Liquid Chromatography Report PC277 Applicant's reference number ALPCHL 314 GLP Unpublished	Yes	Oxx (Rxx Ixx pxx)
III A3.1.3	Sxx TG	2002	Relative Density of Alphachloralose Jxx Rxx Fxx study number 3642 Applicant's reference number ALPHCHL 184 GLP Unpublished	Yes	Oxx (Pxx)
III A3.2	Sxx V	2002	Vapour Pressure of Alphachloralose Jxx Rxx Fxx study number 3945 Applicant's reference number ALPHCHL 185 GLP Unpublished	Yes	Oxx (Pxx)
IIIA3.4(1) A4.1 Key study	Cxx Sxx Lxx	2004	Validation of Analytical Methodology for the Determination of Alphachloralose and Betachloralose in Alphachloralose Technical Grade Material Study No. PGD-143 Applicant's reference number ALPCHL 225 Unpublished	Yes	Oxx (Pxx)
IIIA3.4(2)	Sxx Lxx	2004	Alphachloralose: Determination	Yes	Oxx

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A3.4(3) A3.4(4)			of Spectra SPL Project No. 1617/005 Applicant's reference number ALPHCHL 226 Unpublished		(Pxx)
III A3.5	Sxx TG	2004	Water Solubility of Alphachloralose at pH 5,7 and 9 Jxx Rxx Fxx study number 3643 Applicant's reference number ALPHCHL 220 GLP Unpublished	Yes	Oxx (Pxx)
III A3.7	Rxx Ixx pxx	2004	Determination of Solubility of Chloralose Report PC226 Applicant's reference number ALPHCHL 244 GLP Unpublished	Yes	Oxx (Rxxl)
III A3.7a	Sxx T. G.	2004	Fat Solubility of Alphachlo-ralose Jxx Rxx Fxx Study number 3661, report date 11/09/2004 Applicants reference number ALPHCHL257 GLP Unpublished	yes	Oxx (Rxx)
III A3.9	Sxx TG	2002	Partition Coefficient of Alphachloralose Jxx Rxx Fxx study number 3644 Applicant's reference number ALPHCHL 186 GLP Unpublished	Yes	Oxx (Pxx)
III A3.10 A3.16	Bxx D	2003	Physico/chemical Testing on a Sample of Alphachloralose Report No.11499/35903 for Pxx Applicant's reference number ALPHCHL 187 GLP Unpublished	Yes	Oxx (Pxx)
III A3.11	Sxx TG	2002	Flammability of Alphachloralose Jxx Rxx Fxx study number 3662 Applicant's reference number ALPHCHL 188 GLP Unpublished	Yes	Oxx (Pxx)

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III A3.11	Sxx TG	2002	Auto-ignition Temperature of Alphachloralose Jxx Rxx Fxx study number 3663 Applicant's reference number ALPHCHL 190 GLP Unpublished	Yes	Oxx (Pxx)
III A3.13	Sxx TG	2002	Surface Tension of Alphachlorasole Jxx Rxx Fxx study number 3660 Applicant's reference number ALPHCHL 189 GLP Unpublished	Yes	Oxx (Pxx)
III A3.15	Cxx Txx	2003	Physico/chemical Testing on a Sample of Alphachloralose Report No. J121791L.R01/03-Explosivity (3 Tests) Applicant's reference number ALPHCHL 213 GLP Unpublished	Yes	Oxx (Pxx)
IIIA3.17.1	Rxx Ixx pxx	2005	Technical Committee Report PC 05/06. Accelerated Shelf Life: Chloralose Technical Project 298/19 Applicants reference ALPHCHL 299 GLP Unpublished	Yes	Oxx (Rxx Ixx)
III A4.1 Key study	Jxx A	2005	Determination of LOQ for Alphachloralose and Betachloralose in Alphachloralose Technical Grade Material Study No. PGD- 193/25 Applicant's reference number ALPHCHL 313 Not GLP Unpublished	Yes	Oxx (Rxx)
IIIA4.2a-3 Key study	Jxx A	2005	Validation of Analytical Methodology for the Determination of Alphachloralose in Soil Cxx Sxx Lxx Study No. PGD-185	Yes	Oxx (Pxx)

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			Applicant's reference number ALPHCHL 268 GLP Unpublished		
IIIA4.2a-4 Key study	Wxx S	2005	Validation of Analytical Methodology for the Determination of Betachloralose in Soil Cxx Sxx Lxx Study No. PGD-216 Applicant's reference number ALPHCHL 308 GLP Unpublished	Yes	Oxx (Pxx)
IIIA4.2c-1	Jxx Rxx Fxx	2003	Method Validation for Determination of Alphachloralose Active Ingredient Content in Water Reference for Study No 3930 (Refer Jxx Rxx Fxx Study No. 3787) Applicant's reference number ALPHCHL 238 Unpublished	Yes	Oxx (Pxx)
IIIA4.2c-1	Cxx Bxx Rxx	2004	Acute toxicity study of Alphachloralose in Rainbow trout, *Oncorhynchus mykiss* Jxx Rxx Fxx study number 3930 Applicants reference number ALPHCHL 227 GLP Unpublished	Yes	Oxx (Pxx)
IIIA4.2c-2 Key study	Cxx, J G	2005	Development and Validation of an Analytical Method for the Determination of Residues of Alpha-Chloralose and Beta-Chloralose in Drinking Water and Surface Water by LC/MS Study No. SYN/4905 Applicant's reference number ALPHCHL 309 GLP Unpublished	Yes	Oxx (Pxx)
III A4.2d	Odam E.M., Wardall H.P., Bailey S., Findlay	1984	Determination of Alphachloralose residues in Vertebrate tissues by Gas-Liquid Chromatography, Analyst Vol.	No	PUB

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			109: 1335-1338 Applicant's reference number ALPHCHL 258 and 176 Published		
III A4.3-3	Txx G	2005	Validation of Analytical Methodology to Determine Rodenticides in Food Matrices Cxx Sxx Lxx Study No. PGD-180 Applicant's reference number ALPHCHL 300 GLP Unpublished	Yes	Oxx (Pxx)
III A5 A6.12.8 A6.13 A8.5.4 III B5	Meehan AP	1984	Rats and Mice Their Biology and Control Pages 215-218 The Rentokil Library Rentokil Ltd, Felcourt East Grinstead West Sussex RH19 2JY Published	No	PUB
III A5	Environmental Protection Agency (EPA)	2000	Toxicological Review of Chloral hydrate. In support of Summary Information on the Integrated Risk Information System (IRIS) August 2000, EPA/635/R-00/006 ALPHCHL 167 Published	No	PUB
III A6.1.1 Key study	Dxx Jxx S	1995	Acute Oral Toxicity in Rats: Alphachloralose Cxx Ixx Txx Study Number 10201 Applicant's reference number ALPHCHL 192 GLP Unpublished	Yes	Oxx (Pxx)
III A6.1.2 Key study	Cxx J	1993	Acute Dermal Toxicity in Rats: Alphachloralose Cxx Ixx Txx Study Number 10202 Applicant's reference number ALPHCHL 193 GLP Unpublished	Yes	Oxx (Pxx)
IIIA6.1.3a Key study	Gxx D R	2005	Acute Inhalation Toxicity (Nose Only) Study In The Rat Sxx Lxx Lxx Project Number: 1617/006 Applicant's reference number	Yes	Oxx (Pxx)

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			ALPHCHL 271 GLP Unpublished		
IIIA6.1.3b	BxxD	2005	Physico/Chemical Testing on a sample of Alphachloralose Cxx Txx Lxx Report No.12799R1V1/04 Applicant's reference number ALPHCHL 265 GLP Unpublished	Yes	Oxx (Pxx)
IIIA6.1.4a Key study	Cxx J	1993	Acute Dermal Irritation in Rabbits: Alphachloralose Cxx Ixx Txx Study Number 10203 Applicant's reference number ALPHCHL 194 GLP Unpublished	Yes	Oxx (Pxx)
IIIA6.1.4b Key study	Cxx J	1993	Acute Eye Irritation in Rabbits: Alphachloralose Cxx Ixx Txx Study Number 10204 Applicant's reference number ALPHCHL 195 GLP Unpublished	Yes	Oxx (Pxx)
III A6.1.5 Key study	Dxx Jxx S	1995	Skin Sensitisation Test in Guinea Pigs (Maximisation Method of Magusson B and Kligman AM): Alphachloralose Cxx Ixx Txx Study Number 10205 Applicant's reference number ALPHCHL 196 GLP Unpublished	Yes	Oxx (Pxx)
III A6.2a A6.4.1b A6.5 A6.8.2[a] Key study	Bxx H	2004	Chloralose: Toxicokinetic Study in the Rat. Bxx Rxx Lxx Study Number RTK/01 Applicants reference number ALPHCHL 259 Unpublished	yes	Oxx (Pxx)
III A6.2a	Rozman KK, Klaassen CD	2001	Absorption, Distribution and Excretion of Toxicants. Chapter	No	PUB

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			5 (in) Klaassen CD (ed) Cassarett and Doull's Toxicology, The Basic Science of Poisons (6th ed). New York: McGraw-Hill		
III A6.2a A6.3.1 A6.4.1b A6.5 A6.6.7d A6.7a A6.8.2a CH	US EPA	2000	Toxicological Review of Chloral Hydrate. EPA/635/R-00/006. US Environment Protection Agency, Washington DC.	No	PUB
III A6.2b CH	Frederic A. Beland, Thomas C. Schmitt, John F. Young	1998	Metabolism of Chloral hydrate in mice and rats after single and multiple doses; Journal of Toxicology and Environmental Health, Part A, 54:209-226	No	PUB
III A6.3.1 CH	Miller, RR; Greenblatt, DJ	1979	Clinical effects os Chloral hydrate in hospitalized medical patients; J Clin Pharmacol 19:669-674	No	PUB
A6.3.1 CH	Kauffmann BM, White KL et al	1982	Humoral and cell-mediated immune status in mice exposed to Chloral hydrate; Environmental Health Perspectives, 44:147-151	No	PUB
III A6.3.1 CH	Sandres VM, Kauffmann BM et al	1982	Toxicology of Chloral hydrate in mouse; Environmental Health Perspectives:44:137-146	No	PUB
III A6.3.1	Fxx C	1995	4-week toxicity study by oral route in rats: Alphachloralose Cxx Ixx Txx Study Number 10284 Applicant's reference number ALPHCHL 197 GLP Unpublished	Yes	Oxx (Pxx)
IIIA6.4.1a A6.7a A6.8.2a A6.9[a] Key study	Kxx H	2003	Repeated Dose 90-day Oral Toxicity Study of Alphachloralose in Rats Jxx Rxx Fxx Applicant's reference number ALPHCHL 166 GLP Unpublished	Yes	Oxx (Pxx)

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IIIA6.4.1b A6.5 A6.7a A6.8.2a	O'Neil, M J *et al*	2001	"The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals" 13th Edn. Merck & Co, Inc./White House Station. ISBN 0911910-13-1 (2080 chloral hydrate, 2081 α-chloralose)	No	PUB
IIIA6.4.1b A6.5 A6.7a A6.8.2a	Harvey SC	1980	Hypnotics and Sedatives. (In) Gilman AG, Goodman LS, Rall TW et al (eds) The Pharmacological Basis of Therapeutics, 6th Edn. 339-75. MacMillan, New York.	No	PUB
IIIA6.4.1b A6.5 A6.7a A6.8.2a	Roberts T, Hutson D (Eds)	1999	"Metabolic Pathways of Agrochemicals". Royal Society of Chemistry/ Cambridge.	No	PUB
IIIA6.4.1b A6.5 A6.7a A6.8.2a CH	Benson, R	2000	"Chloral Hydrate" Concise International Chemical Assessment Document No 25. International Programme on Chemical Safety, Geneva. (http://www.inchem.org/documents/cicads/cicads/cicad25.htm)	No	PUB
IIIA6.4.1b A6.5 A6.7a A6.8.2a CH	IARC	1995	Chloral and Chloral Hydrate. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. 63, 245-269	No	PUB
IIIA6.4.1b A6.7a A6.8.2a	Thomas H M, Simpson D, Prescott L F	1988	The toxic effects of Alpha-Chloralose. Human Toxicol. 2, 285-287.	No	PUB
IIIA6.4.1b A6.5 A6.7a A6.8.2a	Clarke E G C, Clarke M L	Unknown	Veterinary Toxicology. P231. London/Bailliere Tindall.	No	PUB
IIIA6.4.1b A6.5 A6.7a A6.8.2a A6.12.2a	-	Nov. 1999	http://www.biam2.org/www/Sub2970.html#SubIndic Chloralose, Banque de Données Automatisée sur les Médicaments (BAIM)	No	PUB
IIIA6.4.1b A6.5 A6.7a A6.8.2a	Holzgrefe H H, Everitt J M, Wright E M	1987	"Special Topic Overview: Alphachloralose as a canine anaesthetic" LAS 37 (5) 587-595.	No	PUB
IIIA6.4.1b	Crossland J	1980	"Lewis's Pharmacology", 5th	No	PUB

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A6.5 A6.7a			Edn. p510 Edinburgh: Churchill Livingstone		
IIIA6.4.1b A6.5 A6.7a	-	-	Yale University, veterinary clinical services. http://info.med.yale.edu/yarc/vcs/anesthesiaeffect.htm#Chloralose	No	PUB
IIIA6.4.1b A6.5	Moser VC., Mc Cormick.JP., Creason. JP., Mac Phail. RC.	1988	Comparison of Chlordimeform and Carbaryl Using a Functional Observational Battery. Environmental and Applied Toxicology 11, pp. 189 – 206.	No	PUB
IIIA6.4.1b A6.5	Tempe J D, Kurtz D	1972	"Acute chloralose intoxication". Concours Med 94 (5) 801-813	No	PUB
IIIA6.4.1b A6.5	Hamouda C, Amamou M et al	2001	"Graded classification of acute chloralose poisoning: 509 cases". Presse Med. Jun 16-23; 30 (21) 1055-8	No	PUB
IIIA6.4.1b A6.5	Thomas H M, Simpson D, Prescott LF	1988	"The toxic effects of Alpha-chloralose". Human Toxicol. 7 285-287	No	PUB
IIIA6.4.1b A6.5	Grad G, Witten ML et al	1988	Intravenous chloralose is a safe anaesthetic for longitudinal use in beagle puppies. Lab Anim Sci 38(4): 422-425	No	PUB
IIIA6.4.1b A6.5 A6.7a	Innes JMR, Ulland BM et al	1969	Bioassay of Pesticides and Industrial Chemicals for Tumourigenicity in Mice: A Preliminary Note. J. Nat.Cancer Inst. 42 1101-1114	No	PUB
IIIA6.4.1c	Daniel F. B. Robinson M., Stober J. A., Page N. P., Olson G. R.	1992	Ninety-Day Toxicity Study of Chloral Hydrate in the Sprague-Dawley Rat. Drug and Chemical Toxicology. 15(3), 217-232 (1992). Published Applicant's reference number ALPHCHL 287.	No	PUB
III A6.6.1 Key study	Mxx B	1994	Reverse Mutation Assay on Bacteria Salmonella Typhimurium: Alphachloralose Cxx Ixx Txx Study Number 10200 Applicant's reference number ALPHCHL 198 GLP Unpublished	Yes	Oxx (Pxx)

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III A6.6.2 Key study	Sxx R J	2002	In Vitro Mammalian Chromosome Abberation Test of Alphachloralose with Human Lymphocytes Jxx Rxx Fxx study number 3650 Applicant's reference number ALPHCHL 199 GLP Unpublished	Yes	Oxx (Pxx)
III A6.6.3 Key study	Sxx V K	2003	In Vitro Mammalian Cell Gene Mutation Test of Alphachloralose Using CHO-K1 Line Jxx Rxx Fxx study number 4245 Applicant's reference number ALPHCHL 200 GLP Unpublished	Yes	Oxx (Pxx)
IIIA6.6.7b CH	Haworth S., Lawlor T., Mortelmans K., Speck W., Zeiger E.	1983	Salmonella Mutagenicity Test Results for 250 Chemicals. Environmental Mutagenesis Supplement 1:3-142 (1983) Published / Applicant's reference number ALPHCHL 286	No	PUB
IIIA6.6.7c CH	Harrington-Brock k., Doerr C. L., Moore M. M.	1998 CH	Mutagenicity of three disinfection by-products: di- and trichloroacetic acid and chloral hydrate in L5178Y / TK+/- -3.7.2C mouse lymphoma cells. Mutation research 413(1998) 265-276 / Published / Applicant's reference number ALPHCHL 285.	No	PUB
IIIA6.6.7d CH	Lynch A.M. Parry J.M..	1993	The cytochalasin-B micronucleus / kinetochore assay in vitro: Studies with 10 suspected aneugens. Mutation Research, 287 (1993) 71-86. Published / Applicant's reference number ALPHCHL 283	No	PUB
IIIA6.6.7d	Russo A, Levis AJ	1992	Detection of aneuploidy in male germ cells of mice by means of a meiotic micronucleus assay; Mutat.Res. 281:187-191	No	PUB
IIIA6.6.7d CH	George MH, Kilburn S, Moore T et al	2000	The carcinogenicity of chloral hydrate administered in drinking water to the male B6C3F1 mouse	No	PUB

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			and F344/N rat; Toxicol.Pathol. 28:610-618		
IIIA6.6.7e CH	J.W.Allen, B.W.Collins, P.A.Evasky	1994	Spermatid micronucleus analyses of trichloroethylene and chloral hydrate effects in mice, Mutation Research, 323(1-2): 81-88. Published	No	PUB
IIIA6.6.7f CH	P. Leopoldi	1993	In vivo studies on chemically induced aneuploidy im mouse somatic and germinal cells, Mutation Research, 287: 119-130	No	PUB
IIIA6.6.7g CH	M. Ikbal	2004	The assessment of genotoxic effects in lymphocyte cultures of infants treated with chloral hydrate, Mutation Research, 564: 159-164	No	PUB
III A6.7a	MacGregor DB, Pangrekar J et al	1994	A reexamination of the low Prevalence of Carcinogens in an Early carcinogen screen; Regul. Toxicol. Pharmacol. 19:97-105	No	PUB
III A6.7a	-	-	Carcinogenicity potency database, available at: http://potency.berkeley.edu/search.html	No	PUB
III A6.7b CH	Leuschner J., Beuscher N.	1998	Studies on the Mutagenic and Carcinogenic Potential of Chloral Hydrate. Arzneim.-Forsch./Drug Research. 48 (II), 961-968 (1998). Published. ALPHCHL 281.	No	PUB
III A6.7c CH	NTP Technical Report	2002	The Toxicology and Carcinogenesis studies of chloral hydrate in B6C3F1 mice, NTP TR 502, NIH Publication n.º 2-4436	No	PUB
III A6.7d	Innes JRM et al	1969	Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in mice: A preliminary note; J. Nat. Cancer Inst. 42:1101-1141/1969 / Not GLP/ Published. ALPHCHL 178	No	PUB
IIIA6.8.1a Key study	Mxx V Pxx	2004	Prenatal Developmental Toxicity Study Of Alphachloralose In Rats	yes	Oxx (Pxx)

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			Jxx Rxx Fxx study Number: 3890 Applicant's reference number ALPHCHL 255 GLP unpublished		
IIIA6.8.1b Key study	Gxx Ixx	2004	Prenatal Developmental Toxicity (Teratogenicity) Study of Alphachloralose In Rabbits Jxx Rxx Fxx Study Number 3891 Applicant's reference number: ALPHCHL 256 GLP unpublished	yes	Oxx (Pxx)
IIIA6.8.2a	-	-	International Conference on harmonization of Technical Requirements for registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Maintenance of the ICH Guideline on Toxicity to male Fertility. An addendum to the ICH Tripartite Guideline on Detection of Toxicity to Reproduction for Medicinal Products, S5B(M). Available at: http://www.ich.org/MediaServer.jser?MODE=GLB	No	PUB
IIIA6.8.2b CH	Kallman M. J., Kaempf G. L., Balster R. L..	1984	Behavioural Toxicity of Chloral in Mice: An Approach to Evaluation. Neurobehavioral Toxicology and Teratology. Vol. 6 p. 137-146, 1984. Published / Applicants reference number ALPHCHL 282	No	PUB
IIIA6.8.2c CH	Klinefelter G. R., Suarez J. D., Roberts N. L., DeAngelo A. B.	1995	Preliminary screening for the potential of drinking water disinfection byproducts to alter male reproduction. Reproductive Toxicology, Vol 9. No. 6 p. 571-578, 1995./ Applicants reference number ALPHCHL 276 / published	No	PUB
III A6.9b CH	Kallman M. J., Kaempf G. L., Balster R.	1984	Behavioral Toxicity of Chloral in Mice: An Approach to Evaluation. Neurobehavioral	No	PUB

Section No / Reference No	Author(s)	Year	Title Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/No)	Owner
	L.		Toxicology and Teratology. Vol. 6 p. 137-146, 1984. / Published / ALPHCHL 282		
III A6.10a TCE	Peter Scheibler, Anita Kronfeld, Peter Illes, Clemens Allgaier	1999	Trichloroethanol impairs NMDA receptor function in rat mesencephalic and cortical neurones. European Journal of Pharmacology Vol 366p R1-R2 Elsevier Science B.V.	No	PUB
III A6.10b CH	Kauffmann B, White K, Sanders V, Douglas K, Sain L, Borzelleca F, Munson A.	1982	Humoral and Cell-Mediated Immune Status in Mice exposed to chloral hydrate. Environmental Health Perspectives Vol 44, p 147-151. Applicants reference ALPHCHL 284	No	PUB
III A6.11	Wxx S	2003	Alphachloralose: Proposal for Data Waiver - Carcinogenicity/chronic Toxicity Studies in Rodents Project no. re08903 Applicant's reference number ALPHCHL 210 Unpublished	Yes	Oxx (Pxx)
III A6.11	Fxx C	1995	4-week toxicity study by oral route in rats: Alphachloralose Cxx Ixx Txx Applicant's reference number ALPHCHL 197 GLP Unpublished	Yes	Oxx (Pxx)
III A6.11	Kxx H	2003	Repeated Dose 90-day Oral Toxicity Study of Alphachloralose in Rats Jxx Rxx Fxx Applicant's reference number ALPHCHL 166 GLP Unpublished	Yes	Oxx (Pxx)
IIIA6.12.1	Mxx B	2003	Medical Monitoring for Alphachloralose at Atofina Applicant's reference number ALPHCHL 212 Unpublished	Yes	Oxx (Pxx)
III	-	-	Chloralose, Banque de Données	No	PUB

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A6.12.2a			Automatisée sur les Médicaments (BAIM) database, available at : http://www.biam2.org/www/Sub2970.htm#SubIndic last updated November 1999.		
III A6.12.2a A6.12.5b	H.M. Thomas, D. Simpson, and L.F. Prescott.	1988	The toxic effects of alpha-chloralose. Hum. Toxicol. 7: 285–287	No	PUB
III A6.12.2a	P. Kintz, S. Doray, V. Cirimele, and B. Ludes.	1999	Testing for alphachloralose by headspace-GC/MS. A case report. Forensic Sci. Int. 104: 59–63.	No	PUB
III A6.12.2a	F. Flesch, P. Kintz, P. Reydel, C. Tournoud, A. Jaeger, and B. Ludes.	2000	Chloralose: 49 clinical cases over a 30-year period (in French). Ann. Toxicol. Anal. 12: 157–158.	No	PUB
III A6.12.2b CH	Zahedi A, Grant M, Wong D.	1999	Successful treatment of chloral hydrate cardiac toxicity with propranolol	No	PUB
III A6.12.2c CH	Ludwigs U,, Divino C. J,, Magnusson A., Berg A.	1996	Suicidal Chloral Hydrate Poisoning. Södersjukhuset, Stockholm, Sweden. Clinical Toxicology, 34(1), 97-99	No	PUB
III A6.12.2d CH	Miller R, Greenblatt D	1979	Clinical Effects of Chloral Hydrate in Hospitalized Medical Patients. Journal of Clinical. Pharmacology. Vol.19 669-674.	No	PUB
III A6.12.4b CH	R. Poon, J. Nakai, A. Yagminas, F. Benoit, D. Moir, I. Chu and V.E. Valli.	2002	*Subchronic Toxicity of Chloral Hydrate on rats: a drinking water study. Journal of Applied Toxicology, 22, 227-236 (2002)* Published / Applicants reference number ALPHCHL 279.	No	PUB
IIIA6.12.4 CH	R, Poon Nadeau B, Chu I.	2000	Biochemical Effects of Chloral Hydrate on Male Rats Following 7-day Drinking Water Exposure. Journal of Applied Toxicology. 20, 455-461/ Applicants reference number ALPHCHL 277.	No	PUB

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III A6.12.4c CH	George M, Moore T, Kilburn S, Olson G, DeAngelo A	2000	Carcinogenicity of Chloral Hydrate Administered in Drinking Water to the Male F344/N Rat and Male B6C3F$_1$ Mouse. Toxicologic Pathology, Vol 28, no 4, pp 610-618/ Applicants reference number ALPHCHL 278.	No	PUB
III A6.12.5a	Savin S et al.	2003	Journal of Analytical Toxicology, Vol 27:156-161	No	PUB
III A6.12.5a A6.12.7 A6.12.8 A8 A9	Physalys SARL	2003	Safety Data Sheet for Chloralose dated 28/03/2003 Revision 04. / Published.	No	PUB
III A6.12.5b	H.M.Thomas, D.Simpson,L. F.Prescott	1988	The toxic effects of Alpha-Chloralose; Regional Poisoning Treatment Centre and University Department of Clinical Chemistry, The Royal Infirmary Edinburgh. Human Toxicity, 7:285-287. Applicants Reference ALPHCHL 293.	No	PUB
IIIA6.12.5	Gaulier J, Merle G, Lacassie E, Courtiade B, Haglund P, Marquet P,	2001	Fatal Intoxications with Chloral Hydrate. Journal of Forensic Science. 46 (6) 1507-1509. Applicants Reference ALPHCHL 292	No	PUB
IIIA6.12.8	Rentokil Initial plc	2002	Treatment of Domestic Animals Affected by Rentokil Initial Rodenticides / Vets chart / Published.	No	PUB
III A6.13	Timm RM	1994	Description of Active Ingredients: Alphachloralose Prevention and Control of Wildlife Damage 1994. From: http://wildlife.tamu.edu/publications/NebraskaExtension/CWDPDF/PESTCHEM/ACTIVE.PDF Published. Applicant's reference number ALPHCHL 163	No	PUB
III A6.13	Dxx Jxx S	1995	Acute Oral Toxicity in Rats: Alphachloralose Cxx Ixx Txx	Yes	Oxx (Pxx)

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			Study Number 10201 Applicant's reference number ALPHCHL 192 GLP Unpublished		
III A6.13	Agricultural Compounds and Veterinary Medicines Group for ERMA New Zealand	1995	Controlled Pesticides Alphachloralose for Bird Control From: http://www.nzfsa.govt.nz/acvm/publications/notes/alphacl-study-notes.pdf / Published. Applicant's reference number ALPHCHL 164	No	PUB
III A7.1.1.1.1	Sxx A	2004	Hydrolysis of Alphachloralose as a Function of pH Jxx Rxx Fxx study number 3993 Applicant's reference number ALPHCHL 218 GLP Unpublished	Yes	Oxx (Pxx)
III A7.1.1.1.1-1 Key study	Rxx Ixx pxx	2005	Hydrolysis of Chloralose as a Function of pH Project 248/18 Txxl Cxx Report PC 05/05 Applicants reference number ALPHCHL 296 GLP Unpublished	Yes	Oxx (Rxx)
III A7.1.1.1.1-2	Pxx Jxx Sxx & Cxx, Jxx Gxx	2005	Evaluation of Gas Chromatography for the Determination of Alphachloralose Sxx Lxx Lxx Study number SYN/4903 Applicants reference number ALPHCHL 295 GLP Unpublished	Yes	Oxx (Pxx)
III A7.1.1.2.1 Key study	Kxx P	2002	Ready Biodegradability of Alphachloralose Jxx Rxx Fxx study number 3646 Applicant's reference number ALPHCHL 201 GLP Unpublished	Yes	Oxx (Pxx)
III A7.1.1.2.2	Sxx Lxx	2004	Alphachloralose: Assessment of Inherent Biodegradability,	Yes	Oxx (Pxx)

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Key study			Modified Zahn-Wellens/EMPA Test Sxx Pxx Lxx Project Number: 1617/004 Applicant's reference number ALPHCHL 242 GLP Unpublished		
III A7.1.2.1.1 A7.1.2.2.1 A7.1.2.2.2 A7.1.4 A7.2.1 A7.2.2.4 A7.2.3 A7.2.3.1 A7.2.3.2 A7.4.3 A7.4.3.1 A7.4.3.2 A7.4.3.3.2 A7.4.3.4 A7.4.3.5 A7.4.3.5.1 A7.4.3.5.2 A7.5.1.1 A7.5.1.2 A7.5.1.3 A7.5.2.1 A7.5.2.2 A7.5.4.1 A7.5.5 A7.5.5.1 A7.5.6 A7.5.7.1 A8.5.3 Doc IIC	Sxx S	2004	Environmental Exposure Assessment - Alphablock Applicant's reference number ALPHCHL 217 Unpublished	Yes	Oxx (Rxx)
III A7.1.2.2.1 A7.1.2.2.2 A7.2.1 A7.2.2.4 A7.2.3 A7.2.3.1 A7.2.3.2 A7.4.3	Rentokil Ltd	1993	Technical Committee Report No. 93/26 A brief review of the effect of alphachloralose on mice and other animals (abstracted from work conducted by Rentokil) ALPHCHL 235 GLP UnPublished	No	ORG (Rentokil)

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A7.4.3.1 A7.4.3.2 A7.4.3.3.2 A7.4.3.4 A7.4.3.5 A7.4.3.5.1 A7.4.3.5.2 A7.5.1.1 A7.5.1.2 A7.5.1.3 A7.5.2.1 A7.5.2.2 A7.5.4.1 A7.5.5 A7.5.5.1 A7.5.6 A7.5.7.1 B5					
III A7.1.3 Key study	Jxx Rxx Fxx	2004	Adsorption-desorption of alphachloralose in different types of soils Jxx Rxx Fxx Study Number 3955 ALPHCHL 248 GLP Unpublished	Yes	Oxx (Pxx)
III A7.2.3.1-1	Jxx Rxx Fxx	2004	Adsorption-desorption of alphachloralose in different types of soils Jxx Rxx Fxx Study Number 3955 ALPHCHL 248 GLP Unpublished	Yes	Oxx (Pxx)
III A7.3.1 Key study	US EPA	2002	http://www.epa.gov/oppt/exposure/docs/episuitedl.htm	No	PUB
III A7.4.1.1-1 Key study	Cxx, Bxx Rxx	2004	Acute toxicity study of Alphachloralose in Rainbow trout, *Oncorhynchus mykiss* Jxx Rxx Fxx study number 3930 Applicants reference number ALPHCHL 227 GLP Unpublished	Yes	Oxx (Pxx)
III A7.4.1.1-2	Pxx Ixx	2005	Acute toxicity study of Alphachloralose in Rainbow trout, *Oncorhynchus mykiss*	Yes	Oxx (Pxx)

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Key study			Jxx Rxx Fxx study number 5559 Applicants reference number ALPHCHL 327 GLP Unpublished		
III A7.4.1.2-1 Key study	Nxx A	2002	48h EC50 Acute Immobilisation Study of Alphachloralose in Daphnia magna JRF study number 3638 Applicant's reference number ALPHCHL 202 GLP Unpublished	Yes	Oxx (Pxx)
III A7.4.1.2-2 Key study	Dxx Yxx Pxx	2005	48h EC50 Acute Immobilisation Study of Alphachloralose in Daphnia magna JRF study number 5560 Applicant's reference number ALPHCHL 323 GLP Unpublished.	Yes	Oxx (Pxx)
III A7.4.1.3-1 Key study	Kxx Rxx Kxx	2002	Alga (Selenastrum capricornutum), Growth Inhibition Test with Alphachloralose JRF study number 3637 Applicant's reference number ALPHCHL 203 GLP Unpublished	Yes	Oxx(Pxx)
III A7.4.1.3-2 Key study	Sxx Rxx	2005	Alga (Selenastrum capricornutum), Growth Inhibition Test with Alphachloralose JRF study number 5558 Applicant's reference number ALPHCHL 326 GLP Unpublished	Yes	Oxx (Pxx)
A7.4.1.4 Key study	Pxx Dxx	2002	Activated Sludge, Respiration Inhibition Test of Alphachloralose JRF study number 3645 Applicant's reference number. ALPHCHL 204 GLP Unpublished	Yes	Oxx (Pxx)

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III A7.5.3.1.1 A7.5.3.1.2 A7.5.3.1.3	Pxx Ixx	2004	Waiver: Avian Toxicity Studies Primary and Secondary Poisoning Issues Applicant's reference number ALPHCHL 237 Unpublished	Yes	Oxx (Rxx)
III B3.7 B5 Doc IIB	Wxx J S	2004	Initial Shelf-Life Trial of Alphachloralose Mouse Bait Blocks (Containing 4% Alphachloralose) Applicant's reference number ALPHCHL 223 GLP Unpublished	Yes	Rxx Ixx pxx
III B3.7 B5 Doc IIB	Wxx J S	2004	Shelf-Life Bioassay of Acclerated Aged Alphachloralose Mouse Bait Blocks (4% Alphachloralose) at "Room" Temperature Sxx Lxx Bxx Report No. PC222 Applicant's reference number ALPHCHL 231 GLP Unpublished	Yes	Rxx Ixx pxx
III B3.7 B5	Wxx J S	2004	Shelf-Life Bioassay of Acclerated Aged Alphachloralose Mouse Bait Blocks (4% Alphachloralose) at "Lowered" Temperature Sxx Lxx Bxx Report No. PC221 Applicant's reference number ALPHCHL 232 GLP Unpublished	Yes	Rxx Ixx pxx
III B3.7	Rxx Ixx pxx	2002	SOP LM306: Test Method for the Evaluation of the Palatability and Efficacy of Rodenticidal Baits Issue 04	Yes	Rxx Ixx pxx
III B4.1-1	Jxx A	2004	Validation of analytical Methodology for the Determination of Alphachloralose in Alphachloralose 4 % Bait Blocks Cxx Sxx Lxx Study N.º PGD-144 Applicant's reference	Yes	Pxx

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			ALPHCHL 250		
III B4.1-2	D J Txx	2005	Method validation of SOP: RADAM 155, issue 2- Determination of Alphachloralose and Betachloralose in AlphaRapid by Reverse Phase HPLC according to SOP:Radam 101 part2, issue 6 Method validation Report N.º PC 287 Applicant's reference ALPHCHL 325	Yes	Rxx Ixx pxx
III B5 Doc IIB	Wxx J S	2004	Palatability and Efficacy of Alphachloralose Mouse Bait Blocks (containing 2% and 4% Alphachloralose with 80 ppm Bitrex) vs. Albino TO Mice ("Room" Temperature Sxx Lxx Bxx Report No. PC207 Applicant's reference number ALPHCHL 228 GLP Unpublished	Yes	Rxx Ixx pxx
III B5 Doc IIB	Wxx J S	2004	Palatability and Efficacy of Alphachloralose Mouse Bait Blocks (containing 4% Alphachloralose) vs. Wild-Derived Sxx Lxx Bxx Report No. PC223 Applicant's reference number ALPHCHL 229 GLP Unpublished	Yes	Rxx Ixx pxx
III B5	Rentokil Ltd	1993	Technical Committee Report N.º 93/25. A review of the literature in the public domain related to the symptoms produced by alphachloralose / Not GLP / Unpublished. (Applicant's reference number ALPHCHL 236)	No	Rentokil Initial plc
III B6.4 Key study	Fxx G	2005	Chloralose: Dermal Penetration Study Bxx Study N.º RTK102 Applicant's reference number ALPHCHL 312 GLP	Yes	Oxx (Rxx Ixx pxx)

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			Unpublished		
III B6.7.2 Doc IIC	Cxx & Sxx	2004	Study to determine potential exposure to operators during simulated use of anticoagulant rodenticide baits Sxx Lxx/Cx Exx Bxx Pxx Fxx Rxx Dxx Dxx Gxx/Study n.º SYN/1302 Applicant's reference number ALPHCHL 233 GLP Unpublished	Yes	Rxx Ixx pxx
Doc IIC	Sxx S	2004	Human Exposure Assessment Rxx Ixx pxx ALPHCHL 216 Unpublished	Yes	Rxx Ixx pxx
III B6.6.1 B7.1.1	Mxx DxxJ	2004	Risk assessment for the manufacture of Alphablock and Alphakil Block Rxx Ixx pxx ALPHCHL 219 Unpublished	Yes	Rxx Ixx pxx
III B6.6.2	Sxx P J	2003	Pilot study to determine primary sources of exposure to operators during simulated use of anticoagulant rodenticide baits Ccc Exx Fxx Ixx Cxx Exx Bxx Pxx Fxx Rxx Dxx Dxx Gxx Applicant's reference ALPHCHL 234 GLP Unpublished	Yes	Cxx Exx Fxx Ixx Cxx Exx Bxx Pxx Fxx Rxx Dxx Dxx Gxx
III B8 B9	Rentokil Initial plc	2004	Safety data sheet for Alphablock dated 05/01/2004 Issue 01 Safety data sheet for Alphakil Block dated 05/01/2004 Issue 01	No	Rentokil Initial plc
Doc IIA	WHO	2005	Chloral Hydrate in drinking water WHO/SDE/WSH/05.08/49	No	PUB

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Doc IIB	Armstrong, M.D. and Rowe, R.K.	1999	Effect of landfill operations on the quality of municipal solid waste leachate. *Proceedings Sardinia 99, Seventh International Waste Management and Landfill Symposium*. S. Margherita di Pula, Cagliari, Italy; 4-8 October 1999. © 1999 by CISA, Environmental Sanitary Engineering Centre, Cagliari, Italy.	No	PUB
Doc IIC	Robert M. Timm	1994	Prevention and Control of Wildlife Damage, Institute of Agriculture and Natural Resources, University of Nebraska; Animal and Plant Health Inspection Service, Animal Damage Control, United States Department of Agriculture; wildlife Committee, Great Plains Agricultural	No	PUB
Doc IIC	Jens Lodal, Ole Christian Hansen	2002	Human and Environmental Exposure Scenarios for Rodenticides – Focus on the Nordic Countries, Nordic Council of Ministers, Copenhagen	No	PUB
Doc IIC	DEFRA	20 Oct. 2005	Review of effectiveness, environmental impact, humaneness and feasibility of the lethal methods for badger control – a report to European Wildlife Division, London, UK	No	PUB