



Australian Pesticides &
Veterinary Medicines Authority

The Reconsideration of Approvals and Registrations Relating to Polihexanide

Polihexanide Review
Scope Document

JULY 2005

**Australian Pesticides &
Veterinary Medicines Authority**

**Canberra
Australia**

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Manager Pesticides Review
Australian Pesticides and Veterinary Medicines Authority
PO Box E240
KINGSTON ACT 2604
Australia

Telephone: 61 2 6272 3213
Facsimile: 61 2 6272 3218
Email: chemrev@apvma.gov.au
APVMA web site: <http://www.apvma.gov.au>

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SUMMARY

The Australian Pesticides and Veterinary Medicines Authority (APVMA) has initiated its reconsideration of the registrations of products containing polihexanide and the approvals of associated labels. This document defines the scope of the matters of concern to the APVMA and outlines the kinds of information the APVMA requires to conduct a comprehensive scientific assessment of polihexanide.

Polihexanide is a chemical widely used in Agricultural and Veterinary (Agvet) products as a biocide for control of micro-organisms, and algae in swimming pools and spas. It is also used as a disinfectant in veterinary products, and as a sanitiser for milk handling equipment, which are regulated by the APVMA.

Polihexanide is also used in non-agricultural/veterinary situations such as a biocide (disinfectant) in medical equipment, medical procedures, contact lens cleansers, food preparation surfaces, and industrial uses, regulated by the Therapeutic Goods Administration (TGA) and the National Industrial Chemical (Notification and Assessment) Scheme (NICNAS) within the Department of Health and Ageing.

Polihexanide is being reconsidered because of chemistry, toxicological, occupational health and safety, and residue concerns. The reconsiderations will be made after the APVMA assesses all the data and other information provided to it for this purpose – the assessment process is hereafter referred to as the ‘review’.

The APVMA will review the following aspects of product registrations and label approvals for polihexanide:

- Chemistry, including:
 - The method by which products and the constituent polihexanide are manufactured;
 - Stability of manufactured products;
 - The extent to which the constituent polihexanide contains impurities; and
 - The chemical composition of the constituent polihexanide, and results of analysis of the constituent polihexanide.
- Toxicology, including:
 - The potential for polihexanide to be a carcinogen in humans through either dermal and/or oral exposure;
 - Consideration of the need for an Acute Reference Dose (ARfD) and Acceptable Daily Intake (ADI); and
 - The Poisons Schedule status of polihexanide (currently in Schedule 5).
- Occupational health and safety, including:
 - Worker exposure during handling and application of product containing polihexanide; and
 - Determination of appropriate personal protective equipment and Safety Directions.
- Residues, including:
 - Human dietary exposure to residues of polihexanide in food following the sanitation of milking machines.

The APVMA will also consider whether product labels carry adequate instructions and warning statements.

The public is invited to make submissions to the APVMA regarding any of the matters raised in the scope document (see Section 10).

1 INTRODUCTION

Section 31 of the Agvet Codes, authorises the APVMA to reconsider:

- (a) the approval of an active constituent for a proposed or existing chemical product;
- (b) the registration of a chemical product; and
- (c) the approval of a label for containers for a chemical product.

The APVMA has decided to reconsider the registrations of products containing polihexanide and the approvals of associated labels, based on concerns over chemistry, toxicology, occupational health and safety and residues.

2 REGULATORY STATUS AND USE OF POLIHEXANIDE IN AUSTRALIA

2.1 Current use patterns

Polihexanide is a polymer of chlorhexidine that is used as a biocide for control of micro-organisms, and algae in swimming pools and spas. It is also used as a disinfectant in veterinary products, and as a sanitiser for milk handling equipment (Table 1). Polihexanide is also used in non-agricultural and veterinary situations such as a biocide (disinfectant) in medical equipment, medical procedures, contact lens cleaners, food preparation surfaces, and industrial uses. Polihexanide is currently listed in Schedule 5 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP), except when in preparations at a concentration of 5% or less polihexanide

Agvet products containing polihexanide were first registered in various States and Territories of Australia since 1977, prior to the National Registration Scheme.

Table 1: Uses of polihexanide on currently registered Agvet product labels

Situation	Pest	Rate	Critical Comments
Polihexanide 200g/L - biocide for control of micro-organisms, algae and fungi in swimming pools and spas			
Swimming pools and spas when used in conjunction with HTL Pool clear	Algae & Bacteria	60 ml/10,000L of pool capacity every week	This product is part of a Pool Chemical System and must be used in conjunction with HTL Pool Clear as directed. Not recommended for use in commercial pools or private pools where rubbish and leaves accumulate
Swimming Pools	Blackspot and Algae	1.5 – 2.8 L/ 10,000 L per month	Not to be used in commercial pools. Not to be used in pools where rubbish and leaves accumulate. This product in not compatible with chlorine
Swimming pools and spas	Algae & Bacteria	Start up rate: 240 ml/20,000 L pool volume (to give 5-10(ppm/L active)) Top up rate: 0.50L/ 20,000 L pool volume (to give 5-10(ppm active))	Not to be used in commercial pools. This product must be used in combination with Ozone Accelerator. Ensure there is no trace of chlorine present prior to using this system
Swimming pool Sanitiser	Bacteria	Start up rate: 1L per 20,000 L pool volume (to give 25-50 ppm Baquacil) Top up rate: 0.4L/ 20,000 L pool volume (to give 25-50 ppm Baquacil)	Not to be used in commercial pools. Not to be used in pools where rubbish and leaves accumulate. This product in not compatible with chlorine
Swimming pool Sanitiser	Bacteria	60ml/10,000L of pool capacity every week	
Polihexanide 0.36g/L, Benzalkonium Chloride 4.05g/L - germicidal shampoo for dogs, cats and horses			
Dogs, cats and horses	Bacteria and fungi		Wet the hair. Pour on shampoo and work up into a good lather. Leave for 10 to 15 minutes then thoroughly rinse off with clean water. Repeat every other day or as directed by the veterinarian until the skin condition has cleared

Polihexanide 0.3g/L, Benzalkonium Chloride 4.05g/L – germicidal barrier ointment for dogs, cats and horses				
Dogs, cats and horses	Bacteria, fungi and viruses		Remove all organic matter and clean the wound using an approved irrigating solution. Once a day apply a layer of ointment over the total wound site. Repeat daily or as directed by the veterinarian, taking care to repeat the cleaning procedure before each application	
Polihexanide 4g/L, Benzalkonium Chloride 54g/L – veterinary disinfectant				
All hard surfaces, equipment and airspaces	Gram positive bacteria: e.g. <i>Staphylococcus aureus</i>	1:1000 water	2 minutes	Use only as directed. Disinfection of hard surfaces and equipment. Clear away debris, clean and pre-rinse with water. Apply disinfectant in accordance with dilution table as a wash, or through a foamer or spray and leave to air dry. Disinfection of air spaces. Apply disinfectant in accordance with dilution table using an atomiser/fogger and leave to dry
	Gram negative bacteria: e.g. <i>Pseudomonas aeruginosa</i>	1:500 water	2 minutes	
	Fungi, Yeast, Moulds: e.g. <i>Candida albicans</i>	1:500 water	15 minutes	
	Fungal spores: e.g. <i>Aspergillus niger</i>	1:250 water	30 minutes	
	Viruses: e.g. Newcastle Disease Virus	1:500 water	10 minutes	
	Rabies	1:500 water	30 minutes	
	Infectious Bursal Disease	1:250 water	20 minutes	
	Parvovirus	1:125 water	30 minutes	
Milking machine detergent – containing polihexanide				
Milking machines		20ml/10L of water	Wash plant using a minimum of 7L of water per cluster	

2.2 Active Constituent and Products

Common name: Polihexanide

Chemical name: Poly(hexamethylene biguanide) hydrochloride

Trade names/synonyms: A-Breeze, Baquacil, Baquacil Ultra, Caswell No. 676, Chlorhexidine complex, Cosmoquil QC, PHMB, Polyhexanide, Vantocil 1B, Vantocil P

CAS Registry Nos: 27083-27-8
32289-58-0

The active constituent polihexanide is currently on the APVMA exempt active list (not requiring an approval holder and exempt from data requirements for new sources).

At the commencement of the review, there were 9 registered Agvet products containing polihexanide as either an active or non-active constituent (Attachment 1, Table 1). Of the 9 registered products, there are 2 aqueous concentrates, 5 liquids, 1 liquid concentrate, 1 shampoo and 1 ointment formulations. These product registrations are subject to this review. It should be noted that any active constituent approvals and product registrations that occur after the commencement of the review would be made subject to the outcomes of the review.

3 REASONS FOR REVIEW

Polihexanide was nominated for review because of concerns related to the potential for it to be a human carcinogen. These concerns were identified by the Office of Chemical Safety (OCS)

following a review of the First Aid Instructions and Safety Directions (FAISD) for polihexanide, undertaken at the request of the APVMA.

The OCS identified an increased potential hazard to human health based on reports of carcinogenic effects in laboratory animal studies in a preliminary risk assessment undertaken by the United States Environment Protection Agency (US EPA). The US risk assessment discusses concerns in relation to acute and chronic toxicity including those from certain types of industrial Occupational Health and Safety (OH&S) exposure and from possible dietary exposure from products containing polihexanide used on food preparation surfaces. It also discusses an apparent carcinogenic potential of polihexanide when administered to rats and mice at very high exposure levels. The US EPA concludes on the basis of conservative calculations that acute and chronic non-cancer dietary and OH&S risks are below the Agency's level of concern for adults but may indicate a risk of concern for children. Aggregate risk assessments including all sources of exposure indicated a possible concern for both adult's and children's exposures. In relation to cancer risks, the US EPA classified polihexanide into the category "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential".

The US EPA has chosen not to take any recall action for polihexanide products. The situation in Australia is likely to be one of lower aggregate human exposure levels than in the US based on fewer product uses in Australia.

As a result of the above, the APVMA may not be satisfied that use of the products in accordance with the instructions for use would not be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues and would not be likely to have an effect that is harmful to human beings, as a result of direct exposure to the chemicals and also dietary intake. The review will provide information to enable the APVMA to assess these concerns.

The details of the concerns that have been raised can be found in Sections 5 to 8 of this scope document.

4 SCOPE OF THE REVIEW

The scope of the review has been defined taking into consideration the reasons for the nomination of polihexanide, the information already available on this chemical and the way in which it is approved for use in Agvet products in Australia.

In light of the concerns identified, the APVMA might not be able to maintain its satisfaction that continued use of, or any other dealing with, products containing polihexanide in accordance with the approved instructions for use:

- would not be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues; and
- would not be likely to have an effect that is harmful to human beings.

It also appears that the labels for products containing polihexanide may not contain adequate instructions and warning statements.

On the basis of these concerns, it is appropriate that the registrations and label approvals of polihexanide be subject to reconsideration under Part 2, Division 4, of the Agvet Codes.

The APVMA will therefore review the following aspects of product registrations and label approvals for polihexanide:

- Chemistry, including:
 - The method by which products and the constituent polihexanide are manufactured;
 - Stability of manufactured products;
 - The extent to which the constituent polihexanide contains impurities; and
 - The chemical composition of the constituent polihexanide, and results of analysis of the constituent polihexanide.
- Toxicology, including:
 - The potential for polihexanide to be a carcinogen in humans through either dermal and/or oral exposure;
 - Consideration of the need for an ARfD and ADI; and
 - The Poisons Schedule status of polihexanide (currently Schedule 5).
- Occupational health and safety, including:
 - Worker exposure during handling and application of products containing polihexanide; and
 - Determination of appropriate personal protective equipment (PPE) and Safety Directions.
- Residues, including:
 - Human dietary exposure to residues of polihexanide in food following the sanitation of milking machines.

- The APVMA will also consider whether product labels carry adequate instructions and warning statements. Such instructions include:
 - the circumstances in which the product should be used;
 - how the product should be used;
 - the times when the product should be used;
 - the frequency of the use of the product;
 - the re-entry period after the use of the product;
 - the withholding period after the use of the product;
 - the disposal of the product and its container;
 - the safe handling of the product and first aid in the event of an accident caused by handling the product; and
 - any other matter prescribed by the regulations.

Registrants will be required to undertake certain actions aimed at securing relevant data that might address these matters. However, the public is invited to make submissions to the APVMA regarding any of the matters raised in the scope document (see Section 10).

5 CHEMISTRY ISSUES

Polihexanide and associated products were first registered in 1977. They were originally assessed and grandfathered in under transitional arrangements of the Agvet Codes. Polihexanide is currently listed as an active constituent on the APVMA exempt list (not requiring an approval holder and exempt from data requirements for new sources).

Associated with the review of polihexanide the APVMA will develop a standard for polihexanide and approve the active under s.14A of the Agvet Codes if appropriate. Registrants of products containing polihexanide with the following CAS numbers 27083-27-8 and 32289-58-0 will be required to provide data for a chemistry assessment.

If an active constituent is approved under s.14A Agvet Code it still requires that the APVMA be satisfied that the products containing these actives do not endanger people, animals or plants, the environment or Australia's International trade.

6 TOXICOLOGICAL ISSUES

The US EPA has recently undertaken a major hazard and risk assessment of polihexanide. The preliminary report of this assessment came to the attention of the OCS following a review of the FAISD for polihexanide, undertaken at the request of the APVMA.

According to the US EPA hazard and risk assessment, polihexanide can cause ocular irritation/corrosion, dermal irritation and sensitisation, systemic toxicity (including toxicity to the liver and male reproductive organs) and carcinogenicity in rats and mice (vascular system tumours) in two species of experimental animals (rats and mice) at very high exposure levels. The tumours occurred in response to both oral and dermal exposure.

The evidence of carcinogenicity in test animal species is sufficient to warrant review of products containing polihexanide. The US EPA toxicology summary concludes that polihexanide is not genotoxic and gives No Observable Effect Levels (NOELs) for carcinogenic and other effects, which may allow safe levels of exposure to be determined following further assessment of available data.

At present, there is no Australian hazard assessment of polihexanide, there are no public or occupational health exposure standards, and there is insufficient information on exposure to assess the risk of systemic toxicity (including carcinogenicity) to persons using products containing polihexanide, or exposed to the chemical in swimming pools or via the diet.

The US EPA preliminary hazard and risk assessment of polihexanide “US EPA (2004) Poly(hexamethylene biguanide) hydrochloride (PHMB): Preliminary risk assessment for the re-registration eligibility decision, PC Code 111801, Case 3122, Antimicrobials Division, US Environment Protection Agency”, is available at: <http://www.epa.gov/oppad001/index.htm> and <http://docket.epa.gov/edkpub/do/EDKStaffCollectionDetailView?objectId=0b0007d4803bb38f>

7 OCCUPATIONAL HEALTH AND SAFETY ISSUES

The US EPA preliminary risk assessment concluded that short-term aggregate risks to adults and children from all sources combined (dietary exposure and exposure from disinfectant uses, handling liquid swimming pool products and exposure from swimming) were of concern. Aggregate Margins of Exposure (MOEs) were 83 – 90 (target 100) for adults and 21 for children. The single largest contributor to the aggregate exposures was exposure via the diet from disinfectants used to clean food preparation areas. With regard to occupational exposure, the US EPA concluded that there was unacceptably high exposure for workers using polihexanide in

some industrial settings but dermal and inhalation MOEs were acceptable for commercial swimming pool operators.

It is therefore essential to obtain comprehensive information on Australian uses of Agvet products that contain polihexanide, together with information on other polihexanide-based disinfectants used in domestic or food processing and non-food related industrial settings, (i.e. the aggregate exposure for all Agvet and other uses).

The APVMA will work cooperatively with other national regulators such as the Therapeutic Goods Administration (TGA) and the National Industrial Chemical (Notification and Assessment) Scheme (NICNAS) to address the aggregate exposure for polihexanide.

8 RESIDUE ISSUES

Human dietary exposure from polihexanide residues in food (specifically milk) will be evaluated due to polihexanide being present in products used in the sanitation of milking machines.

Additionally, as an outcome of the review appropriate public health standards may require setting or amending. Under these circumstances further residue assessment may be required.

9 INTERNATIONAL REGULATORY STATUS OF POLIHEXANIDE

The US EPA hazard and risk assessment report is preliminary, and the induction of tumours in the rat and mouse studies were seen only at very high levels. The US EPA has not proposed any regulatory action at this stage.

The agency responsible for regulation of biocides in the European Union has advised the APVMA that polihexanide is scheduled for review in the EU, with submission of data due by July 2007 and review completion by July 2008.

10 SUBMISSIONS FROM THE PUBLIC INVITED

Interested parties are invited to provide information or data relevant to the issues raised in this scope document. These must reach the APVMA by no later than 2 September 2005. Submissions can be sent either by email to chemrev@apvma.gov.au or by mail to:

Manager Pesticides Review
Australian Pesticides and Veterinary Medicines Authority
PO Box E240
KINGSTON ACT 2604
Telephone: (02) 62723213
Facsimile: (02) 6272 3218

11 DATA ASSESSMENT AND POSSIBLE OUTCOMES

The APVMA will seek expert advice for toxicology, occupational health and safety, chemistry and residues in conducting the technical assessment of data submitted for the review of polihexanide. The OCS and APVMA Chemistry and Residues Program (CRP) will advise the APVMA regarding the concerns raised in Sections 5, 6, 7 and 8.

Depending on the findings of the technical assessment, a review can result in one of three broad outcomes:

- The APVMA is satisfied that products containing polihexanide continue to meet the conditions to which registration are currently subject and affirms the registration and associated label approvals; or
- The APVMA is satisfied that the conditions to which the registration is currently subject can be varied in such a way that the requirements for continued registration and associated label approvals will be complied with, and varies the conditions of registration and label approvals; or
- The APVMA is not satisfied that the conditions continue to be met and suspends or cancels the registration and associated label approvals.

The data might lead agencies that provide expert advice to the APVMA to consider setting appropriate public health and chemistry standards, which in this case might involve:

- the OCS revising the Acceptable Daily Intake (ADI);
- the NHMRC¹ revising the drinking water standard;
- the OCS revising or establishing an acute reference dose (ARfD);
- the NDPSC² revising the existing poisons schedule;
- the APVMA revising or establishing Maximum Residue Limits (MRL);
- the APVMA revoking the exemption of the active constituent; and
- the APVMA establishing a standard for the constituent polihexanide.

The APVMA will have regard to the appropriate public health and chemistry standards in its reconsideration of approvals and registrations.

12 CONSULTATION THROUGHOUT THE REVIEW PROCESS

From initiation of the review through to the implementation of the review outcomes, the APVMA will consult with relevant stakeholders and interested parties. Prior to finalisation of any report, comments from key stakeholders and the public will be sought.

The Preliminary Review Findings (PRF) including the proposed recommendations will be made available to the stakeholders and public through the APVMA website or direct communication. A period will be allowed for the stakeholders and the public to comment on the PRF report.

REFERENCES

US EPA (2004) Poly(hexamethylene biguanide) hydrochloride (PHMB): Preliminary risk assessment for the re-registration eligibility decision, PC Code 111801, Case 3122, Antimicrobials Division, US Environment Protection Agency.

¹ National Health and Medical Research Committee (NHMRC)

² National Drugs and Poisons Scheduling Committee (NDPSC)

ATTACHMENT 1

Table 1: Registered products containing polihexanide.

Product Number	Product Name	Registrant	Label Approval Numbers
48356	HTL Bio-Blu Swimming Pool & Spa Water treatment & Sanitiser	HTL Pty Ltd	48356/01
48888	Tropical 1 Pool Sanitiser Blackspot and Algae Killer	A M Ilarda T/A Morning Light Chemicals	48888/1097
49284	King Neptune's Ozone pool Sanitiser	Isacc Technologies Pty Ltd	49284/1098
50301	Purex Baquacil	Price Chemicals Pty Ltd	50301/1097
54149	F10SC Veterinary Disinfectant	Health and Hygiene (Pty) Ltd	54149/0502
54477	Delaval Low Foam Acid Milking Machine Detergent	Delaval Pty Ltd	54477/0202 54477/0703
57606	Lo-Chlor Aquacadabra Pool Sanitiser	M.I. International Pty Ltd T/A Lo-Chlor Chemicals	75606/0603
58543	F10 Germicidal Shampoo	Health and Hygiene (Pty) Ltd	58543/250ml/0904 58543/500ml/0904 58543/5L/0904
58544	F10 Germicidal Barrier Ointment	Health and Hygiene (Pty) Ltd	58544/100g/0904 58544/500g/0904