**NRA Special Review of**

# Chlorpropham

## November 1997

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**by the**
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# FOREWORD

*The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) is an independent statutory authority with responsibility for the regulation of agricultural and veterinary chemicals. One of the NRA's regulatory responsibilities is to conduct reviews of registered agricultural and veterinary chemicals to ensure that they continue to do the job that they are supposed to do and that they do not pose unacceptable risks to people, the environment or trade.*

*The Special Review Program examines urgent or specific concerns about a currently registered agricultural or veterinary chemical, which may require a rapid resolution. It addresses one or more specific aspects of a given chemical, and can be triggered, for example, by the findings of new research, the availability of new scientific data or concerns raised about the use or safety of a chemical.*

*In undertaking reviews, the NRA works in close cooperation with advisory agencies including the Department of Health and Family Services (Chemicals and Non-Prescription Drug Branch), Environment Australia (Risk Assessment Branch), Worksafe Australia (Chemical Assessment Division) and State Departments of Agriculture.*

*The NRA has a policy of encouraging openness and transparency in its activities and community involvement in decision-making. When the NRA decides that a review is to be conducted, it consults parties affected by the review (such as applicants, commodity groups, State regulatory agencies) and gives them an opportunity to respond to concerns raised and participate in the review. All participants are notified of the Board's decision and outcomes of special reviews are published in the NRA's Agricultural and Veterinary Chemicals Gazette.*

*This review report provides an overview of the review that has been conducted by the NRA and advisory agencies. The review findings are based on information collected from a variety of sources, including data packages and information submitted by registrants, information submitted by members of the public, and government organisations and literature searches.*

*The NRA also makes these reports available to the public and regulatory agencies of other countries which are part of the OECD ad hoc exchange program and as part of bilateral exchange agreements with other countries. Under the OECD ad hoc exchange program, it is propsed that countries receiving these reports will not utilise them for registration purposes unless they are also provided with the raw data from the relevant applicant.*

*The information and technical data required by the NRA to review both new and existing chemical products must be derived according to accepted scientific principles, as must the methods of assessment undertaken. Details of required data are outlined in various NRA publications.*

*Other publications explaining the NRA's requirements for registration can also be purchased or obtained by contacting the NRA. Among these are: Ag Manual: The Requirements for Agricultural Chemicals; Vet Manual: The Requirements Manual for Veterinary Chemicals and Volume II of Interim Requirements for the Registration of Agricultural and Veterinary Chemical Products.*

*The NRA welcomes comments on this review and its review program. They can be addressed to Manager, Chemical Review, National Registration Authority for Agricultural and Veterinary Chemicals, PO Box E240 Kingston ACT 2604 Australia.*

## ABBREVIATIONS AND ACRONYMS

| | | | |
|---|---|---|---|
| **d** | Day | **mL** | Millilitre |
| **h** | Hour | **mM** | Millimolar |
| **Kg** | Kilogram | **ng** | Nanogram |
| **L** | Litre | **nM** | nanomolar |
| **m** | Metre | **s** | Second |
| **mg** | Milligram | **µg** | Microgram |
| **min** | Minute | | |
| | | | |
| **GI** | Gastrointestinal | **po** | Oral |
| **iv** | Intravenous | **ppb** | parts per billion |
| **ip** | Intraperitoneal | **ppm** | parts per million |
| **im** | Intramuscular | **sc** | Subcutaneous |
| **bodywt** | Bodyweight | | |
| **mg/kg bw/d** | Mg/kg bodyweight/day | | |

| | |
|---|---|
| **AAVCC** | Australian Agricultural and Veterinary Chemicals Council |
| **ACAC** | Agricultural Chemicals Advisory Council |
| **AChE** | Acetyl Cholinesterase |
| **ACPH** | Advisory Committee on Pesticides and Health |
| **ADI** | Acceptable Daily Intake |
| **ALT** | Alanine aminotransferase (SGPT) |
| **AP** | Alkaline phosphatase |
| **AST** | Aspartate aminotransferase (SGOT) |
| **BUN** | Blood urea nitrogen |
| **CPK** | Creatinine phosphokinase |
| **DU** | Dust |
| **GGT** | Gamma-glutamyl transpeptidase |
| **Hb** | Haemoglobin |
| **Hct** | Haematocrit |
| **LD** | Liquid |
| **LDH** | Lactate dehydrogenase |
| **LOEL** | Lowest Observed Effect Level |
| **MCH** | Mean corpuscular haemoglobin |
| **MCHC** | Mean corpuscular haemoglobin concentration |
| **MCV** | Mean corpuscular volume |
| **MOE** | Margin of Exposure |
| **MRL** | Maximum Residue Limit |
| **MSDS** | Material Safety Data Sheet |
| **NDPSC** | National Drugs and Poisons Scheduling Committee |
| **NHMRC** | National Health and Medical Research Council |
| **NOEL** | No Observable Effect Level |
| **OP** | Organophosphorus Pesticide |
| **PACC** | Pesticides and Agricultural Chemicals Committee |
| **PCV** | packed cell volume |
| **POEM** | Predicted Operator Exposure Model |
| **PPE** | Personal Protective Equipment |
| **RBC** | Red blood cell/erythrocyte |
| **SUSDP** | Standard for the Uniform Scheduling of Drugs and Poisons |
| **TGAC** | Technical Grade Active Constituent |
| **WBC** | White blood cell/leucocyte |
| **WHP** | Withholding Period |

# Executive Summary

## Background

Chlorpropham (isopropyl N-(3-chlorophenyl) carbamate) is a selective systemic herbicide and plant growth regulator belonging to the N-phenylcarbamate group of pesticides. Chlorpropham is registered for the control of annual grasses and some broadleaf weeds in various food and non-food crops, and as a sprouting inhibitor in potatoes.

In 1988, the National Drugs and Poisons Scheduling Committee (NDPSC) placed chlorpropham in Appendix M[1] of the Standard for Uniform Scheduling of Drugs and Poisons (SUSDP) due to the inadequacy of supporting toxicological data.

Because of concerns relating to the adequacy of the supporting toxicology data package for chlorpropham the NRA has reconsidered under Division 4 , Part 2 , of the Agvet Code, its approval of chlorpropham, the registration of all products containing chlorpropham, and the approval of associated product labels.

At various stages prior to the Commonwealth States Agreement on Agricultural and Veterinary Chemicals coming in to effect in 1989, several States had products containing chlorpropham registered under the existing regulatory arrangements. While the NRA or its predecessors did not grant new registrations for chlorpropham after that time, some of these registrations continued after the introduction of the National Registration Scheme in 1994.

Six products are registered for use in Australia for pre-emergent and/or post-emergent weed control in ornamental bulbs, onions, garlic and turf and as a sprouting inhibitor in potatoes.

## Objective

The objective of the review was to determine whether the continued registration of chlorpropham products could be supported. Since a NOEL and ADI have not been established by the Commonwealth Authorities, due to incomplete toxicological data, the NRA special review sought primarily to address the outstanding toxicological issues relating to chlorpropham.

As a consequence, evaluations of only those toxicological studies required to address the deficiencies have been reported in full in this Report, with other studies provided in the Consolidated Toxicology Summary only.

[1] Appendix M: 'Substances for which registration under agricultural and veterinary chemicals legislation cannot be supported by scheduling until further toxicological information becomes available'.

The NRA also advised registrants, the Registration Liaison Committee (RLC) members and other interested parties of the review and called for appropriate data and comment. Several comments pointed to the lack of effective alternatives to chlorpropham, especially for potato sprout inhibition.

**Outcomes**

Based on assessment of the data (including published literature), the appropriate public and occupational health standards and maximum residue limits (MRL) have been established for chlorpropham. The review has also resulted in certain label amendments and, accordingly, variations to the conditions of registration for products containing chlorpropham.

Key outcomes of the review include:

- The National Drug and Poisons Schedule Committee (NDPSC) of the Australian Health Ministers Advisory Council (AHMAC) recommended chlorpropham be placed in schedule 5 of the Standard of the Uniform Scheduling of Drugs and Poisons SUSDP;

- The No Observable Effects Level (NOEL) for chlorpropham was established at 5 mg/kg bw/day,

- The Acceptable Daily Intake (ADI) for chlorpropham was established at 0.05 mg/kg bw/day,

- First Aid Instructions, Safety Directions and Re-entry Statements have been either established or revised, and

- The following MRLs have been recommended for chlorpropham.

| | |
|---|---|
| Potato | 30 mg/kg |
| Onions, bulb | * 0.05 mg/kg |
| Garlic | *0.05 mg/kg |

(* MRL has been set at or about the limit of analytical quantitation. )

# Part I

# Main Report

# 1. Introduction

Chlorpropham (isopropyl 3-chlorophenylcarbamate) is a selective systemic herbicide and plant growth regulator belonging to the N-phenylcarbamate group of pesticides. Chlorpropham is registered for the control of annual grasses and some broadleaf weeds in various food and non-food crops, and as a sprouting inhibitor in potatoes.

The products registered for use are of three formulation types; emulsifiable concentrates containing 600 g/L, liquid preparations containing 500 g/L and a dust preparation containing 25 g/kg.

# 2. Reasons for Review

In 1988, the National Drugs and Poisons Scheduling Committee (NDPSC) placed chlorpropham in Appendix M[2] of the Standard for Uniform Scheduling of Drugs and Poisons (SUSDP) due to the inadequacy of supporting toxicological data.

Because of concerns relating to the adequacy of the supporting toxicology data package for chlorpropham the NRA has reconsidered under Division 4 , Part 2 , of the Agvet Code, its approval of chlorpropham, the registration of all products containing chlorpropham, and the approval of associated product labels.

The aim of the review was to determine if the continued registration of chlorpropham products could be supported. In order to achieve this the NRA required the neccessary toxicological data to be submitted for assessment. The NRA also advised the Registration Liaison Committee (RLC) members and interested parties and invited them to provide comments on the review.

# 3. Scope of the Review

Since a NOEL and ADI, and TGAC approval had not been established or granted due to incomplete toxicological data, the NRA special review sought primarily to address these toxicology isssues for chlorpropham.

The review involved a consideration of all approved uses of the currently registered products, their associated labels and technical grade active constituent (TGAC) approvals.

# 4. Registration / Regulatory Status Overseas

[2] Appendix M: 'Substances for which registration under agricultural and veterinary chemicals legislation cannot be supported by scheduling until further toxicological information becomes available'.

**European Union (EU)**

As at 14 October 1996, products containing chlorpropham are registered as herbicides and plant growth regulators in all member states within the EU, including Finland, Sweden, Denmark, Ireland, United Kingdom, Netherlands, Belgium, Luxembourg, Germany, Estonia, France, Spain, Italy and Greece.

In 1994, a decision was made to investigate the EU maximum residue limit (MRL) for chlorpropham. Additional toxicological data was requested to be submitted by March 1995, with the timetabled review and recommendations to be made in March 1996. Several companies stated that they wished to support the review of chlorpropham in the EU.

Chlorpropham is an important chemical for the potato industries in the EU, as no alternative products are available. Companies which had chlorpropham registered for use in the EU were requested to submit toxicological and ecological data for evaluation in order to support continued registration (re-registration) and to enable establishement of an EU MRL. However, no outcomes of the EU review of chlorpropham are known at this stage.

**United States of America (USA)**

Chlorpropham was initially registered in the USA in 1962, for similar herbicidal and growth regulation purposes as those currently approved in Australia. The US EPA in 1987 published an evaluation of chlorpropham from existing data and this identified certain data gaps. This additional data covering product chemistry, residue chemistry, environmental fate, toxicology and ecological effects, was requested as part of chlorpropham re-registration. By 1990, the primary registrants had deleted all claims for use for chlorpropham except those covering the control of sprouting of potatoes.

## 5. Registration/Regulatory Status in Australia

Six products are registered for use in Australia by three registrants and are approved for use within the following situations and purposes:

Ornamental bulbs: pre-emergent weed control,
Onions: post emergent weed control,
Garlic: pre-emergent and post emergent weed control,
Turf: selective weed control and
Stored Potatoes: sprouting inhibition.

**Registered products**

| Registrant | Product Name (NCRIS No.) |
|---|---|
| Crop Care Australasia Pty Ltd | Agchem Allicide 600 Selective Pre-Emergent Herbicide (31622) |
| Crop Care Australasia Pty Ltd | Agchem Potato Stop-Sprout Dust (33320) |
| Crop Care Australasia Pty Ltd | Agchem Tato-Vapo Potato Stop Sprout (33322) |
| Kendon Chemical & Manufacturing Co. P/L | Kendon Chloro-IPC Fogging Solution (33325) |
| Kendon Chemical & Manufacturing Co. P/L | Kendon Chloro-IPC Herbicide (31624) |
| Serve-Ag Pty Ltd | Allicide Herbicide (42429) |

**Current Permits**

Two permits have been issued (PER429 and PER849) to allow the use of the product Agchem Tato-Vapo Potato Stop Sprout in Western Australia for sprout inhibition of stored potatoes.

The NDPSC decided in 1988 to place chlorpropham in Appendix M, although registrations for products containing chlorpropham continued in several States under regulatory arrangements at the time. Some of these registrations continued after the introduction of the national registration scheme in 1994.

Chlorpropham MRLs for all uses other than potato were withdrawn in 1989, while the MRL for potato was extended as required to support this use.

## 6. Notification of Review

All registrants of agricultural products containing chlorpropham were notified of the review, the reasons for review and the specific data required as part of the review. The NRA also notified all members of the Registration Liaison Committee (RLC) and major users of chlorpropham based products within the potato processing industry, including those holding current permits for the use of chlorpropham in Western Australia.

# 7. Consideration of Stakeholder Responses

During the review, the NRA consulted with several interested parties and registrants, as detailed below.

State Authorities provided comment as follows.

**NSW, ACT, QLD and NT**

In NSW, ACT, QLD and NT: products containing chlorpropham are not currently registered for use in these states and no concerns were raised during the review.

**Western Australia**

Western Australia (WA) indicated that the product Agchem Tato-Vapo Potato Stop Sprout was being used under permit by two potato processors. The WA State Authorities were of the view that if appropriate toxicology data being requested could not be supplied then the potato industry would be required to pursue chemical and other alternatives to chlorpropham.

**South Australia**

South Australia (SA) stated that three products were registered for use in that state, the major use being the two potato sprout suppressants within the potato processing industry.

The use as a potato sprout suppressant is essential for the storage of potatoes, as there is a need for the potato industry to supply markets all year round, with approximately 30,000 tonnes stored on an annual basis. Alternative methods, such as refrigeration, are available but the method is regarded as short term storage as suppression is for approximately only six to twelve weeks. Refigeration is not considered to be cost efficient and can have adverse effects on potatoes when later fried (ie, turn black). Therefore, storage is required for extensive periods of time, up to 8 months, whilst providing acceptable quality. Chlorpropham is the only product currently available that can offer sprout suppression for these extended periods of time. The bulb industry also see the use of chlorpropham as an important herbicide to their industry, as only two alternative products are registered. Therefore, the removal of chlorpropham would have significant impacts upon both the potato and bulb industries in SA.

**Victoria**

While not commenting specifically about the uses of chlorpropham, Victoria provided considerable background information regarding the registration status of chlorpropham products in that State. Victoria also advised of (d) Carvone, being developed as a possible alternative to chlorpropham.

**Tasmania**

Tasmania indicated that chlorpropham is an extremely important chemical for use as a sprout suppressent in the potato industry and for use as a herbicide in controlling wild radish in onion crops. No currently registered alternative exists for use by the potato industry for sprout suppression and it was therefore considered neccessary that chlorpropham remained available for use by the onion industry in controlling a significant weed.

**Potato Proccessing Industry**

The various potato processors consulted indicaded that no alternative product was currently available for sprouting inhibition in stored potatoes, a use that is deemed essential to the viability of potato proccessing industry.

**Registrants/Data Provider**

Data was provided by the Aceto Agricultural Chemicals Corporation through an Australian registrant, Crop Care Australasia Pty Ltd

## 8. Public Health Standards

The toxicological data submitted were forwarded to the TGA (Chemicals and Non-Prescription Drugs Branch) for assessment, for determination of an appropriate poisons schedule, first aid instructions and TGAC approval neccessary for the continued registration of chlorpropham products within Australia.

Following the evaluation of the data:

(i) the NDPSC recommended chlorpropham be placed in schedule 5 of the SUSDP;

(ii) Chemicals and Non-Prescription Drugs Branch - Theurapeutic Goods Administration (TGA) recommended, approval of the technical material sourced from MTM Agrochemicals Ltd,

(iii) a No Observable Effects Level (NOEL) was established at 5mg/kg bw/day,

(iv) an Acceptable Daily Intake (ADI) was established at 0.05 mg/kg bw/day, and

(v) first aid instructions, and safety directions were set.

**First Aid Instructions (all products)**

If poisoning occurs, contact a doctor or Poisons Information Centre.

For the complete TGA toxicological reports, refer to Part IV - ‘Toxicology Assessment Report’.

# 9. Safety Directions and OH&S Standards

Following the assessment of acute toxicity data and recommendation of a NOEL from TGA, Worksafe Australia recommended safety directions, including personal protective equipment (PPE) and re-entry periods into treated areas.

**Safety Directions**

Chlorpropham DU all strengths
Will irritate the eyes and skin. Avoid contact with eyes and skin. Do not inhale dust. When using the product wear cotton overalls buttoned to the neck and wrist, elbow-length PVC gloves, goggles, and disposable dust mask. If product in eyes, wash it out immediately with water. Wash hands after use. After each day's use, wash gloves, goggles and contaminated clothing

Chlorpropham EC 650 g/L or less in xylene
Poisonous if swallowed. Will irritate the eyes and skin. Avoid contact with eyes and skin. Do not inhale vapour. When preparing spray wear cotton overalls buttoned to the neck and wrist, elbow-length PVC gloves, and goggles. If product on skin, immediately wash area with soap and water. If product in eyes, wash it out immediately with water. Wash hands after use. After each day's use, wash gloves, goggles,and contaminated clothing.

Chlororopham LD all strengths
Will irritate the eyes and skin. Avoid contact with eyes and skin. Do not inhale vapour. When using the product, wear cotton overalls buttoned to the neck and wrist, elbow-length PVC gloves, goggles, and half facepiece respirator. If product on skin, immediately wash area with soap and water. If product in eyes, wash it out immediately with water. Wash hands after use. After each day's use, wash gloves, goggles,and respirator and if rubber wash with detergent and warm water and contaminated clothing

**Re-entry statements *(Dust and Vapour Formulations Only)***

Do not allow entry into treated areas for 48 hours after treatment.
When prior entry is necessary, wear all protective clothing, including respirator.
Clothing must be washed after each days use.

For the OH&S Assessment report refer to Part III - ‘Occupational Health & Safety Assessment Report’.

## 10. Maximum Residue Limits

The Chemistry and Residue Evaluation Section of the NRA conducted an assessment of the residue profile for chlorpropham. From this assessment, the following maximum residue limits (MRLs) have been recommended for chlorpropham.

| | |
|---|---|
| Potato | 30 mg/kg |
| Onions, bulb | * 0.05 mg/kg |
| Garlic | *0.05 mg/kg |

(* MRL has been set at or about the limit of analytical quantitation. )

For further details of the assessment of residues, refer to Part II - 'Residues Assessment Report'.

## 11. Review Outcomes

The continued registration of products containing chlorpropham is supported based upon the following:

- chlorpropham be placed in schedule 5 of the Standard of the Uniform Sheduling of Drugs and Poisons (SUSDP);

- the establishment an ADI for chlorpropham at 0.05 mg/kg bw/day;

- the establishment a NOEL for chlorpropham at 5 mg/kg bw/day;

- the establishment of appropriate first aid and safety directions and precautionary statements covering Re-entry Periods into areas treated with chlorpropham (see Sections 8 & 9);

- the establishment apropriate maximum residue levels (MRLs) for chlorpropham chlorpropham (see Section 10).

## 12. Data Protection Status of Submitted Data

Certain studies submitted by the registrants in response to the NRA's request for data have been designated as protected information. Several toxicology studies on chlorpropham submitted by Aceto Agricultural Corporation are in this category. The protection period applicable to the relevant studies is identified in the toxicology assessment report (Please refer to Part IV of this report).

# Part II

# Residues Assessment Report

## Introduction

The National Registration Authority (NRA) conducted an assessment of the residue profile of chlorpropham arising from its registered uses.

## Background

As at 19 May 1997, the registered products containing chlorpropham include Agchem Allicide 600 Selective Pre-emergent Herbicide (Crop Care Australasia Pty. Ltd.), Agchem Potato Stop-Sprout Dust (Crop Care Australasia Pty. Ltd), Agchem Tato-Vapo Potato Stop Sprout (Crop Care Australasia Pty. Ltd), Kendon Chloro-IPC Fogging Solution (Kendon Chemical and Manufacturing Company Pty. Ltd), Kendon Chloro-IPC Herbicide Solution (Kendon Chemical and Manufacturing Company Pty. Ltd) and Allicide Herbicide (Serve-Ag Pty. Ltd.).

Agchem Potato Stop-Sprout Dust, Agchem Tato-Vapo Potato Stop and Kendon Chloro-IPC Fogging Solution are registered for use on potatoes, whereas Agchem Allicide 600 Selective Pre-emergent Herbicide, Kendon Chloro-IPC Herbicide Solution and Allicide Herbicide are registered for use on onions, garlic and other non-food related items. In the latter three formulations, chlorpropham is used as a pre-emergence herbicide. Allicide Herbicide is also used for weed control on blackcurrant plants. The label directions call for its application to the base of the plants and warns against overall spray as damage may occur.

At present chlorpropham has a temporary MRL[1] of 50 mg/kg in potatoes.

The history behind the setting of the temporary MRL of 50 mg/kg in potatoes can be found in minutes of the Pesticide and Agricultural Chemical Committee (PACC) and Pesticide and Agricultural Chemicals Standing Committee (PACSC) [2,3,4], and the Commonwealth Department of Health, Housing and Community Services[5] files. In February 1990, PACC considered chlorpropham and noted that residues in washed, unpeeled, peeled and processed potatoes can be less than that of the raw commodity, potatoes, thus allowing lower MRLs to be recommended in the commodities. The Committee recommended the following provisional MRLs.

Chlorpropham

| | |
|---|---|
| Potato (Brushed) | P 50 mg/kg |
| Potato (Washed and unpeeled) | P 5 mg/kg |
| Potato (Peeled or processed) | P 0.5 mg/kg |

However, the provisional MRLs were conditional to the Committee obtaining additional data on residues trials under Australian conditions and toxicology studies.

At its May 1990 meeting, the committee noted that the Public Health Committee (PHC) had at the March 1990 meeting agreed to a provisional MRL for chlorpropham at 50 mg/kg in potato (brushed), pending receipt of additional residue data.

A residue profile of chlorpropham arising from the use of Tato-Vapo, Mirvale 500, Kendon CIPC and Stop-Sprout Powder was compiled in October 1992 and considered by the PACSC in November 1992. The Committee confirmed earlier finding of a reduction in residues under processing and that most of the residues appeared in the discarded peel waste. Majority of unwashed potatoes contained residues below 25 ppm with only a minor proportion containing residues below 30 ppm. Based on the data the committee considered reducing the chlorpropham MRL for potato to 25 ppm, but agreed to await the receipt and evaluation of adequate toxicology data.

In September 1996 and March 1997, the Department of Health and Family Services[6,7,8] reviewed additional toxicology studies submitted by companies in support of the continued use of chlorpropham, following which an ADI of 0.05 mg/kg/d was proposed.

## Discussion

### Residue Data

The label rates and application methods have not changed since the last review of residue data submitted by the sponsor company. Consideration of the review by the PACSC has assisted in the setting of a MRL of 30 mg/kg in potatoes.

No residue data in onions and garlic has been made available as part of the ad hoc review. However, it should be noted that an Australian MRL of at or about 0.05 mg/kg was revoked in 1980 when deficiencies in the toxicology data were noted. Since additional toxicology studies have been submitted and considered adequate by the Department of Health and Family Services, it would be acceptable to re-establish the MRL of chlorpropham of at or about 0.05 mg/kg each in onions and garlic. Its use pattern as a pre-emergent herbicide would support a view that there is negligible potential for persistence of the compound in the commodity. However, these MRLs have not been proposed by the sponsor companies and they may wish to conduct confirmatory trials.

The potential for chlorpropham residues on blackcurrants is negligible as the direction of use as given on the Allicide Herbicide calls for the application to the base of the plant and warns against overall spray as damage may occur.

## Regulatory Standards

Maximum Residue Levels

The following maximum residue levels are proposed for chlorpropham.

Potatoes 30 mg/kg
Onion, bulb * 0.05 mg/kg
Garlic * 0.05 mg/kg

Dietary Intake Risk Analyses

The setting of an Australian ADI for chlorpropham has allowed for a dietary intake risk analyses to be conducted. The adoption of the MRL of 30 mg/kg in potatoes and *0.05 mg/kg each in onion, bulb and garlic results in a TMDI and EMDI 112 % and 13 % respectively based on the current Australian ADI of 0.05 mg/kg/d (Appendix 1). Based on the TMDI and EMDI calculations, there are no objections to the continued use of chlorpropham in the products registered to date.

Withholding Period

As noted in PACSC in November 1992, no withholding period is necessary.

In Australia, approximately 64000 tonnes of raw, cooked and peel potato waste are used as stockfeed (Edgell's telephone correspondence of 12 June 1997), out of which approximately 41% are from potatoes treated with a sprout suppressant. The sponsor companies should be requested to submit ruminant feeding studies, so that the setting of appropriate MRLs for animal commodities may be considered.

## Trade Implications

There are no Codex MRLs established for residues of chlorpropham and as a result compatibility with proposed Australian MRLs cannot be made at this time.

It is recognised by the US EPA[9] that potato commodities are not considered to be significant poultry feed items and therefore tolerances for poultry commodities will not be necessary. Similar considerations are also applicable in Australia.

The US EPA have also noted that the maximum theoretical dietary burden of chlorpropham for ruminants is estimated to be 940 ppm (dry matter basis) based on a diet consisting of 75% processed potato waste consisting of 88.6% dry matter.

* MRL has been set at or about the limit of analytical quantitation.

A data requirement for a ruminant feeding study existed and this data was to be submitted to the EPA in October 1995. Subsequent to the review of the ruminant feeding study, appropriate levels for the animal commodities are to be determined. The companies should be requested to submit the ruminant feeding study for review by the NRA and at which time the NRA may wish to consider setting MRLs for animal commodities.

The MRLs for onions and garlic each at 0.1 mg/kg have been revoked in the USA because there are no current registered uses of chlorpropham on those commodities.

## Recommendations

1. MRLs are recommended for chlorpropham in potatoes, onion (bulb) and garlic and the following amendments will be made to the *MRL Standard*:

**Table 1**

| Compound | | Food | MRL (mg/kg) |
|---|---|---|---|
| **Delete** | | | |
| Chlorpropham | VR 0589 | Potato | T50 |
| **Add:** | | | |
| **Chlorpropham** | | | |
| | VR 0589 | Potato | 30 |
| | VA 0385 | Onions, bulb | *0.05 |
| | VA 0381 | Garlic | *0.05 |

2. The sponsor companies of products recommending the use of chlorpropham on potatoes should be requested to submit a ruminant feeding study in support of the establishment of MRLs in animal commodities.

3. The MRL recommended for potatoes, onions and garlic are not proposed by the sponsor companies. The agreement of the applicant to the entries proposed above should therefore be sought.

4. The sponsor companies of products recommending the use of chlorpropham on onions and garlic may wish to consider carrying out confirmatory trials of maximum residue levels in onions and garlic, although this is not deemed to be mandatory, based on the pre-emergence use-pattern of chlorpropham.

## References

1. MRL Standard (Current to 30 November 1996, NRA for Agricultural and Veterinary Chemicals.

2. Department of Health and Family Services, PACC February 1990 Report.

3. Department of Health and Family Services, PACC May 1990 Report.

4. Department of Health and Family Services, PACSC November 1992 Report.

5. Department of Health and Family Services, Residue Evaluation Report ([HADRES] REVIEWS 0417, DEW:DEW) 9 October 1992.

6. ADI List. Acceptable daily intakes for agricultural and veterinary chemicals. TGA, Commonwealth Department of Health and Family Services, April 1997, ISBN 0644 397837.

7. Chlorpropham, Toxicology Evaluation Report, Department of Health and Family Services, (S:\CO\TGA\CNPD\CPA\CSUTOX\C\CHLO2176.WPD), September 1996.

8. Chlorpropham, Toxicology Evaluation Report, Department of Health and Family Services, March 1997.

9. Reregistration Eligibility Decision (RED) Chlorpropham, US EPA, EPA 738-R-96-023, October 1996

# Appendix 1

## TMDI Calculation for Chlorpropham

ADI for Chlorpropham 0.05 mg/kg/d

| Commodity | Food Consumption Kg/person/day | MRL mg/kg | TMDI mg/person |
|---|---|---|---|
| VR 0589 Potato | 0.11[a] | 30 | 3.3 |
| | 0.099[a] | 0.5 | 0.0495 |
| VA 0385 Onion, bulb | 0.012 | *0.05 | 0.0006 |
| VA 0381 Garlic | 0.0001 | *0.05 | 0.000005 |

Total 3.350105 mg/person

0.055835 mg/kg bw**

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*At or about the limit of detection

**Equivalent to 112 % of the hypothetical ADI

aThis figure is based on the assumption that 90% of the potatoes consumed is peeled, washed and cooked and 10% of the potatoes consumed is washed and cooked without peeling.

These calculations have been made in accordance with the Guidelines for Predicting Dietary Intake of Pesticide Residues (World Health Organisation)

ADIAcceptable Daily Intake

MRLMaximum Residue Limit

TMDITheoretical Maximum Daily Intake

# EMDI Calculation for Chlorpropham

ADI for Chlorpropham 0.05 mg/kg/d

| Commodity | Food Consumption Kg/person/day | MRL mg/kg | TMDI mg/person |
|---|---|---|---|
| Potato | 0.011 | 30 | 0.33 |
| | 0.099 | 0.5 | 0.0495 |
| Onion, bulb | 0.012 | *0.05 | 0.0006 |
| Garlic | 0.0001 | *0.05 | 0.000005 |

Total 0.380105 mg/person

0.00633508 mg/kg bw**

---

*At or about the limit of detection

**Equivalent to 13 % of the hypothetical ADI

These calculations have been made in accordance with the Guidelines for Predicting Dietary Intake of Pesticide Residues (World Health Organisation)

ADIAcceptable Daily Intake

MRLMaximum Residue Limit

TMDITheoretical Maximum Daily Intake

# Part III

# Occupational Health and Safety Assessment

## Introduction

Chlorpropham is a N-phenylcarbamate which is used as a pre-emergent and early post-emergent herbicide, and as a post-harvest treatment of potatoes to prevent sprouting. There are no existing safety directions for chlorpropham. The NRA are reconsidering the registration of all products containing chlorpropham.

Chlorpropham is currently registered in Australia in the following products:

Herbicides

AGCHEM ALLICIDE 600 SELECTIVE PRE-EMERGENT HERBICIDE, No 31622, for control of a range of weeds in golf fairways and crops of garlic, onion, Bulbous iris, Cape Tulip, Gladiolus and Narcissus.

ALLICIDE HERBICIDE, No 42429, for the control of seeds of weeds in crops of onions and garlic, bulbs, blackcurrants, pyrethrums and some ornamentals.

KENDON CHLORO-ICP HERBICIDE. No 31624, for use on a variety of weeds in crops of onion, Cape Tulip and daffodil.

Potato Sprout Suppressants

AGCHEM POTATO STOP SPROUT DUST, No 33320

AGCHEM TATO-VAPO POTATO STOP SPROUT, No 33322

KENDON CHLORO-ICP FOGGING SOLUTION, No 33325

## Toxicity

Chlorpropham has low acute oral, and dermal toxicity (oral LD50 4200 mg/kgbw, dermal LD50 >2000 mg/kgbw). It is a mild eye and skin irritant in the rabbit. It is not a skin sensitiser in the guinea pig.

In an inhalation study in rats on the product Sprout Nip Ag, containing 46.8% chlorpropham in an isopropyl alcohol/propylene glycol base, the LC50, 4 hours was found to be > 1880 mg/m3 (low).

In a 21 -day dermal study in rabbits at 0, 104, 520 or 1040 mg/kg /d for 6 hours/d for 21 or 22 days, topical effects were noted at 104 mg/kg/d. Systemic effects, ie an increase in reticulocyte counts was observed from 520 mg/kg. The selected NOEL for risk assessment is 104 mg/kg/d, noting that considerations of protective equipment requirements will need to take into account the topical effects which occurred at that dose. (Note that in assessing chlorpropham the US EPA discounted the effects seen at 520 mg/kg, selecting a NOEL of 1040 mg/kg for OHS assessment).

Chlorpropham gave negative results in a mutagenicity assay and a weakly positive result in a chromosomal aberration study in Chinese hamster ovary cells.

Agchem Potato Stop Sprout Dust (33320) is expected to have low acute oral, dermal and inhalational toxicity, and to be a slight skin and moderate eye irritant

Allicide Herbicide (42429), Agchem Allicide 600 Selective Pre Emergent Herbicide (31622), and Kendon Chloro-lCP Herbicide (31624), are all expected to have low acute oral, dermal and inhalational toxicity, and to be moderate to severe eye irritants. These three products contain a high proportion of xylene.

Agchem Tato-Vapo Potato Stop Sprout (33322) and Kendon Chloro-lCP Fogging Solution (33325) are expected to have low oral, dermal and inhalational toxicity, and to be moderate skin and eye irritants.

## Use pattern

For the purpose of this assessment, the pioneer products only are described. Other products are image products with identical or closely similar use patterns.

Agchem Allicide 600 Selective Pre-Emergent Herbicide is used on onion crops at the rate of 2-4.4 L/ha. Application is by standard boom spray in 500 L of water/hectare. Total usage is 5000 litres/year. The total area to be sprayed varies between 4-8 hectares. The product will be sprayed on bulbs at the rate of 40 mLs/10 L of water/100 m2. The area sprayed was estimated to be 0.1 ha/d. In golf fairways Agchem Allicide 600 Selective Pre-Emergent Herbicide will be used at the rate of 3.0 L/500 L of water/ha, and the total area sprayed was estimated to be 5 ha/d.

Agchem Tato-Vapo Potato Stop Sprout is applied undiluted on stored table potatoes through conventional fogging equipment. Fogging is conducted from outside the storage area, or from a control area with adequate ventilation. Fogging is usually done on a weekend when there are minimal personnel in the vicinity. It is preferable that two people are present during fogging. During the fogging procedure, ventilation equipment is set at permanent re-circulation. At completion of treatment, ventilation is turned off for 24-48 hours.

After 24 hours the seals and covers are removed and entry to the workplace is permitted. The application rate of Agchem Tato-Vapo Potato Stop Sprout varies from 3-10 1itres/100 tonnes 3-4 times over a period of 6 months. No more than 12L/100 tonnes should be used in any one season.

Agchem Potato Stop Sprout Dust is used once a year 2-4 weeks after the potatoes are placed in storage to allow cuts caused by harvest to heal.

Potatoes are stored in half tonne bins. The product is sprinkled on top of the potatoes and a rubber sheet with holes is placed over the treated potatoes. The nozzle of an air hose is pushed through the holes of the rubber sheets and compressed air used to blow the dust throughout the bin.

## Risk assessment

Chlorpropham has low acute systemic and topical toxicity. The primary acute hazards associated with the chlorpropham emulsifiable concentrates and the liquid preparations are derived predominantly from the non active constituents namely xylene and methylated spirit. For short term occupational exposures, topical effects are expected to occur before any systemic effects.

### Acute toxic potential

The dermal LD50 for the EUP was >2000 mg/kgbw in rabbits. For spraying with Agchem Allicide 600 Selective Pre-Emergent Herbicide this would correspond to a dose of >120 g of product for a 60 kg human or 13.6 L of concentrated spray (4.4 L/500 L). This calculation does not include a safety factor.

### Repeat dose toxic potential

The 21 day dermal NOEL of 104 mg/kg/d was selected for assessment of repeat dose exposure. This corresponds to 10.4 mLs/day of the product Agchem Allicide 600 Selective Pre-Emergent Herbicide or 1.2 L of spray. This calculation does not include a safety factor.

Workers may be exposed to the product during mixing, application, and when cleaning up spills and equipment. The most likely routes of exposure for the fogging and dusting operations are inhalational and dermal. The most likely route of exposure for the EC applied by boom spray is the dermal route.

## Safety directions

Chlorpropham DU all strengths

| | |
|---|---|
| 161 162 164 | Will irritate the eyes and skin |
| 210 211 | Avoid contact with eyes and skin |
| 220 221 | Do not inhale dust |
| 279 283 290 292b 294 297 306 | When using the product wear cotton overalls buttoned to the neck and wrist, elbow-length PVC gloves, goggles, and disposable dust mask |
| 340 343 | If product in eyes, wash it out immediately with water |
| 351 | Wash hands after use |
| 360 361 363 366 | After each day's use, wash gloves, goggles and contaminated clothing |

Chlorpropham EC 650 g/L or less in xylene

| | |
|---|---|
| 130 133 | Poisonous if swallowed |
| 161 162 164 | Will irritate the eyes and skin |
| 210 211 | Avoid contact with eyes and skin |
| 220 222 | Do not inhale vapour |
| 279 281 290 292b 294 297 | When preparing spray wear cotton overalls buttoned to the neck and wrist, elbow-length PVC gloves, and goggles |
| 340 342 | If product on skin, immediately wash area with soap and water |
| 340 343 | If product in eyes, wash it out immediately with water |
| 351 | Wash hands after use |
| 360 361 363 366 | After each day's use, wash gloves, goggles, and contaminated clothing |

Chlororopham LD all strengths

| | |
|---|---|
| 161 162 164 | Will irritate the eyes and skin |
| 210 211 | Avoid contact with eyes and skin |
| 220 222 | Do not inhale vapour |
| 279 283 290 292b 294 297 300 | When using the product, wear cotton overalls buttoned to the neck and wrist, elbow-length PVC gloves, goggles, and half facepiece respirator |
| 340 342 | If product on skin, immediately wash area with soap and water |
| 340 343 | If product in eyes, wash it out immediately with water |
| 351 | Wash hands after use |
| 360 361 363 364 366 | After each day's use, wash gloves, goggles, and respirator and if rubber wash with detergent and warm water and contaminated clothing |

## Re-entry

The re-entry statement should appear on the labels of the following two products:

Agchem Tato-Vapo Potato Stop Sprout (33322)
Kendon Chloro-lCP Fogging Solution (33325)

Avoid entry for 48 hours. If re-entering wear all protective clothing, including respirator.

## Recommendation

Worksafe Australia supports continued registration of chlorpropham for use in Agchem Potato Stop Sprout Dust at 25g/kg, in Agchem Tato-Vapo Potato Stop Sprout at 500 g/L, in Agchem Allicide 600 Selective Pre-Emergent Herbicide at 600 g/L, and the existing image products, provided the revised safety directions are included on labels. In addition, the Agchem Tato-Vapo Potato Stop Sprout and Kendon Chloro-lCP Fogging Solution labels should include the re-entry statement.

# SAFETY DIRECTIONS

## AGCHEM POTATO STOP SPROUT DUST
## NEW ENTRY

Chlorpropham DU all strengths

| | |
|---|---|
| 161 162 164 | Will irritate the eyes and skin |
| 210 211 | Avoid contact with eyes and skin |
| 220 221 | Do not inhale dust |
| 279 283 290 292b 294 297 306 | When using the product wear cotton overalls buttoned to the neck and wrist, elbow-length PVC gloves, goggles, and disposable dust mask |
| 340 343 | If product in eyes, wash it out immediately with water |
| 351 | Wash hands after use |
| 360 361 363 366 | After each day's use, wash gloves, goggles and contaminated clothing |

## ALLICIDE HERBICIDE
## AGCHEM ALLICIDE 600 SELECTIVE PRE-EMERGENT HERBICIDE
## KENDON CHLORO-ICP HERBICIDE

Chlorpropham EC 650 g/L or less in xylene

| | |
|---|---|
| 130 133 | Poisonous if swallowed |
| 161 162 164 | Will irritate the eyes and skin |
| 210 211 | Avoid contact with eyes and skin |
| 220 222 | Do not inhale vapour |
| 279 281 290 292b 294 297 | When preparing spray wear cotton overalls buttoned to the neck and wrist, elbow-length PVC gloves, and goggles |
| 340 342 | If product on skin, immediately wash area with soap and water |

| | |
|---|---|
| 340 343 | If product in eyes, wash it out immediately with water |
| 351 | Wash hands after use |
| 360 361 363 366 | After each day's use wash gloves, goggles, contaminated clothing and respirator, and if rubber wash with detergent and warm water |

**AGCHEM TATO-VAPO POTATO STOP SPROUT**
**KENDON CHLORO-ICP FOGGING SOLUTION**

Chlororopham LD all strengths

| | |
|---|---|
| 161 162 164 | Will irritate the eyes and skin |
| 210 211 | Avoid contact with eyes and skin |
| 220 222 | Do not inhale vapour |
| 279 283 290 292b 294 297 300 | When using the product, wear cotton overalls buttoned to the neck and wrist, elbow-length PVC gloves, goggles, and half facepiece respirator |
| 340 342 | If product on skin, immediately wash area with soap and water |
| 340 343 | If product in eyes, wash it out immediately with water |
| 351 | Wash hands after use |
| 360 361 363 364 366 | After each day's use, wash gloves, goggles, contaminated clothing and respirator, and if rubber wash with detergent and warm water |

# Part IV

# Toxicology Assessment Reports

1. **Evaluation of July 1996**
2. **Evaluation of March 1997**

# 1. Evaluation of July 1996

## Introduction

Chlorpropham, an N-phenylcarbamate, is used as a pre-emergent and early post-emergent herbicide, and as a post-harvest treatment of potatoes to prevent sprouting. Aceto Agricultural Chemicals Corporation have submitted genotoxicity, carcinogenicity, metabolism, reproduction and developmental data in support of the clearance and scheduling of chlorpropham TGAC. No ADI has previously been set due to inadequate data from which to set a NOEL.

## Toxicokinetics and Metabolism

In a preliminary study in rats $^{14}$C-chlorpropham (ring labeled) was administered orally by gavage at doses of 5, 100, 300, and 500 mg/kg. Urine was the predominant excretion path in both sexes at all dose levels, with 70 to 90% of the administered dose excreted via this route within 24 hours, and 80 to 90% within 72 hours. Faecal excretion accounted for the bulk of the remaining administered radioactivity with the total recovery from urine and faeces at 72 hours between 90 and 100%. Negligible radioactivity was recovered as $CO_2$. Thirteen metabolites were identified, primarily glucuronide or sulfonic acid conjugates of various oxidation / hydroxylation or decarbanilation products of the parent compound, together comprising 88-95% of the administered dose.

In an absorption, distribution and excretion study in rats, chlorpropham was rapidly and efficiently absorbed and excreted. Almost the entire administered dose was recovered from urine and faeces 24 hours after administration, with a residue of less than 1%. Tissue residues as a percentage of administered dose, and excretion patterns, were unaffected by; sex, dose or frequency of administration (single or multiple doses of 5 mg/kg or a single dose of 200 mg/kg), or route of administration (oral or IV).

## Short-term Studies

In a range finding study designed to select doses for a teratology study, female rabbits were administered chlorpropham by intragastric tube at levels of; 200, 500, 800 and 1500 mg/kg bw/day for 12 days. Chlorpropham was acutely toxic to does at 800 and 1500 mg/kg bw/day. All animals in these groups either died or were sacrificed on humane grounds prior to dosing on days 7 and 3 respectively. At doses above 500 mg/kg bw/day marked weight loss, anorexia, chromourea, reduced faecal output, cold ears and dark eyes (at 1500 mg/kg bw/day) were observed.

## Chronic Studies

Albino mice were treated with chlorpropham in their diets for 78 weeks, at doses of 0, 100, 500, and 1000 mg/kg bw/day. Mortality was significantly increased in the high dose male group and was associated with an increased incidence of amyloidosis. A bluish tint on the skin of their extremities and distinctly darker eyes developed rapidly in all animals treated at 1000 mg/kg bw/day, and slowly in many animals treated at 500 mg/kg bw/day, with liver and spleen weights increased in males at 1000 mg/kg bw/day. An increase in reticulocytes and mean corpuscular haemoglobin, and an increased erythropoiesis in the spleen, bone marrow and liver was seen at 1000 mg/kg bw/day and in some animals treated at 500 mg/kg bw/day, together with increased haemosiderosis in the spleen. No treatment related increase in the incidence of neoplastic pathology was observed. The NOEL for this study was 100 mg/kg bw/day based on darkened eye colouration, blue skin on the extremities, altered reticulocyte counts, increased haemosiderosis in the spleen and increased amyloidosis at higher doses

Source data for a previously published (and evaluated) two year dietary study in rats were assessed. Animals were fed chlorpropham in the diet at levels of 0, 200, 2000 or 20000 ppm (approx. 10, 100 and 1000 mg/kg/day) for 2 years. Survival was low for all groups at 104 weeks. In the final 13 weeks of the study the death rate at 20000 ppm in males was greater than in controls. Bodyweight gain and food consumption were decreased slightly in males and females at 20000 ppm. Haemoglobin levels and haematocrit values were also generally depressed at this dose level. Relative liver and testes weights were increased at 20000 ppm and relative spleen weights were increased at both 2000 and 20000 ppm, although the small number of survivors at 104 weeks made meaningful comparisons difficult. A high incidence of respiratory tract infection was observed throughout all groups. Because of the inherent limitations in this study (small number of animals on test, a high incidence of respiratory infection, poor survival at termination, a lack of clinical chemistry, and a general lack of detail), it was considered inadequate to set a NOEL. The NOEL for this study was previously set at 2000 ppm from an evaluation of the published paper.

Rats were treated with chlorpropham in their diets for 104 weeks, at 30, 100, 500 and 1000 mg/kg bw/day. Males at 1000 mg/kg/day had an increased incidence of ocular opacities but this was not statistically significant. Group mean body weight gain was depressed at 500 and 1000 mg/kg bw/day. Increased urinary bilirubin was observed in males and females at 1000 mg/kg/day throughout the study and in 500 mg/kg bw/day animals at termination. Animals treated at 500 and 1000 mg/kg bw/day had dark blood with a brownish tint, a persistent decrease in RBC and haemoglobin and increased reticulocyte count, mean corpuscular haemoglobin and mean corpuscular volume. At various time points in these same groups, increased albumin, and albumin/globulin ratio, a decreased AST and an elevated blood cholesterol level were observed. T4 levels were intermittantly reduced at doses above 30 mg/kg/days but persisted only in males at 500 and 1000 mg/kg bw/day at terminal sacrifice. Absolute and relative spleen weights and relative liver weights were increased significantly at 500 and 1000 mg/kg bw/day.

Increased haematopoiesis and haemosiderosis were demonstrated histologically in the spleen of animals treated at 100 mg/kg bw/day at both the 52 and 104 weeks. In animals treated at 500 or 1000 mg/kg bw/day increased haematopoiesis was observed in bone marrow, liver and spleen, with increased haemosiderosis and congestion observed in the spleen, and pigmentation observed in the reticuloendothelial cells of the liver, at both terminal and interim sacrifice. Non neoplastic, potentially treatment related observations, consisted of: lenticular degeneration in some males at 1000 mg/kg/day; increases in mineralised deposits, cysts and pigments in the kidneys of males and females at 1000 mg/kg/day; increased alveolar macrophages and focal lymphoid infiltrate in the lungs; and chronic nephritis in the kidneys of females at 1000 mg/kg/day. A significant increase in testicular interstitial cell tumours was observed in males at 1000 mg/kg but as this is a common tumour in aged male rats, and the incidence was neither dose related nor of great magnitude, the effect cannot be ascribed to treatment despite statistical significance, and is more likely due to an abnormally low control incidence. Three gliomas were observed in the brain of animals treated at 1000 mg/kg bw/day, 2 in males and 1 in females. As this is a rare spontaneous tumour the observation is notable, but as the incidence is within the historical control range for the conducting laboratory the toxicological, and public health, significance is low. A decreased incidence of islet cell adenomas of the pancreas of males at 1000 mg/kg and of adenocarcinoma and fibroadenoma / adenocarcinoma lesions in females at this level, were observed. The NOEL for this study was 30 mg/kg bw/day based on anaemia and haemosiderosis and congestion in the spleen at the next highest dose.

**Reproduction Study**

In a two generation reproduction study, rats were treated with chlorpropham in their diets at levels of 0, 1000, 3000 and 10000 ppm (approximately equal to m/f; 70/85, 220/260, 720/850 mg/kg bw/day). Body weight gains in the premating period were reduced in F0 and F1 males and females at 10000 ppm and in F1 females at 3000 ppm, but food consumption was unaffected. During gestation, body weight gains in F0 females at 10000 ppm were reduced, but were increased during lactation. In F1 females gestational body weight gains were unaffected by treatment but lactation gains were 6 times control, although the control value was unusually low. Adult F1 animals at 10000 ppm at sacrifice had increased relative brain, heart, liver, testes, and spleen weights. Females at 3000 ppm also had marginal but significant increases in relative brain, kidney, heart and liver weights, but a marked increase in spleen and ovary weights over controls. An increased incidence of brown pigmented granules was observed in the reticuloendothelial / kupfer cells of the liver and the tubular epithelial cells of the kidneys of animals at 3000 and 10000 ppm. Marrow hypercellularity of the sternum was most prominent at 10000 ppm and albuminous degeneration of central lobular hepatocytes was slightly increased at 1000 ppm and above. Suburothelial focal mineralization was observed in treated females. F1 pup survival indices were marginally decreased at 10000 ppm between days 4 - 21 and F1 and F2 pup weights at 10000 ppm were markedly reduced by day 21 post partum. In F2 weanlings the brain weight at 10000 ppm was increased and spleen weights were decreased.

Gross post mortem of F1 pups revealed an increased incidence of dark red spleens at 3000 and 10000 ppm. The NOEL for pup development was 1000 ppm based on

altered spleen appearance at the next highest dose. The NOEL for adults was 1000 ppm (approximately 70 mg/kg bw/day) based on decreased body weight gains, increased relative brain, heart, spleen and liver weights, and altered liver and kidney histology at higher doses.

**Developmental Studies**

Rats were treated with chlorpropham as a 40.2% mixture with a carrying agent (Hi-Sil 233) at doses of 40, 400 and 2000 mg/kg bw/day (of chlorpropham) by gastric intubation for 14 days from day 6 to 19 post coitum. Clinical observations of toxicity were confined to the 400 and 2000 mg/kg/day dose groups and included matting and staining of the urogenital fur, pale extremities and ears, and red material on the facial area. At 2000 mg/kg, body weight gains were markedly reduced, relative liver weights were significantly increased, and spleen weights were increased by 270% of control. A significant increase in spleen weights was also observed at 400 mg/kg bw/day. Chlorpropham at 2000 mg/kg bw/day caused total litter loss in 10 females and reduced the mean number of viable foetuses and the mean foetal weight. The incidence of malformations at 2000 mg/kg was substantially greater than in concurrent and historical controls due to an increased incidence of bent ribs, bent limb bones (a rare abnormality), and unossified pubis. The NOEL for maternal toxicity was 40 mg/kg bw/day based on increased spleen weights and altered spleen appearance at the next highest dose. The NOEL for foetal development was 400 mg/kg bw/day based on increased early resorptions, decreased pup viability and body weight gain and an increased incidence of fetal skeletal malformations at higher doses.

Rabbits were administered chlorpropham on days 6 to 18 post coitum, by intragastric tube at levels of; 125, 250 and 500 mg/kg bw/day. No mortalities occurred. Cold ears were observed in most animals at 200 and 500 mg/kg bw/day, with anorexia and reduced faecal output observed in some animals at 500 mg/kg bw/day towards the end of the study period. A dose related decrease in body weight gains was observed across all treatment groups during the first two days of treatment but persisted beyond this only in the group treated at 500 mg/kg bw/day. Two females aborted at 500 mg/kg/day and mean litter size was smaller at both 250 and 500 mg/kg bw/day. Pre and post implantation losses were elevated at 250 mg/kg bw/day and post implantation loss at 500 mg/kg bw/day. Foetal development, as indicated by the incidence of malformation, was unaffected by chlorpropham administration. The NOEL for maternal and embryo toxicity was 125 mg/kg bw/day.

## Genotoxicity

In a chromosomal aberration study in Chinese hamster ovary cells a weakly positive result was obtained in cultures with metabolic activation, at toxic concentrations causing severe cell cycle delay (120 & 140 μg/ml). Results in replicate cultures were not consistently positive over repeated assays. At slightly higher concentrations (160 μg/ml) chlorpropham caused complete cytotoxicity.

In a cell transformation study in Syrian hamster embryo cells chlorpropham induced a stable morphologically transformed phenotype at 70 μg/ml and above in 24 hour exposure studies and at 20 μg/ml and above in 7 day exposure studies. The relative plating efficiency was reduced to below 80% in the 24 hour exposure study at 85 ug/ml and above, and in the seven day exposure study at 30 ug/ml, reflecting chlorpropham cytotoxicity.

## Discussion

The studies reported here expand the toxicology database for chlorpropham and provide the information necessary to set an ADI and to assign a poisons schedule.

The primary target for chlorpropham in these and previous studies in mice, rats and dogs is the haemopoietic system, although in dogs a depression of thyroid function was seen at doses below that initiating significant hamatological effects. Increased red cell turnover at higher chlorpropham treatment levels in the chronic studies was indicated by increased urinary bilirubin, increased reticulocyte count, decreased haemoglobin levels and evidence of increased haematopoiesis in the liver and spleen as a compensatory mechanism for low level anaemia. The bluish colouration seen in sub chronic and chronic mouse studies and the increased liver and spleen weights and dark discolouration of the spleen in mice, rats and dogs are also likely to be reflective of increased RBC turnover. Increased blood cholesterol levels in rats at 500mg/kg bw/day and above and in dogs at 360 mg/kg bw/day and above may reflect altered hepatic metabolism. Thyroid function in rats was significantly depressed only at 500mg/kg bw/day and above, and was not the determinate of the NOEL in studies on this species.

Chronic studies in rats and mice were otherwise largely unremarkable. An apparent increase in the incidence of testicular interstitial cell tumours in the rat study was more a reflection of an unusually low control incidence for this common tumour in aged rats, rather than an indication of potential carcinogenicity of chlorpropham. Non neoplastic findings in these studies were minimal. Apart from altered haematopoiesis, some evidence of kidney and lenticular pathology was observed in high dose rats. In dogs altered thyroid function was demonstrated at doses of 51 mg/kg/day and above through reduced thyroxine (T4) production following TSH stimulation, increased thyroid weights, and increased cellular activity demonstrated histologically.

Decreased T4 levels were observed in rats also at doses of 100 mg/kg bw/day and above but persisted only in males at 500 mg/kg and above. Altered thyroid function sets the overall NOEL for chlorpropham at 5 mg/kg bw/day.

Bent limb bones, observed in rat foetuses from a developmental study, is an unusual finding in rats and unlikely to be incidental. This malformation occurred at a dose that was overtly toxic to the dams however and was not observed in a developmental study in rabbits. It was considered that the foetotoxicity was unlikely to represent a primary effect of chlorpropham.

Positive results in two mammalian cell genotoxicity studies were obtained at cytotoxic concentrations. Chlorpropham is known to interfere with the cell cycle machinery, disorganising the microtubule assembly and inhibiting spindle formation. In the CHO chromosome aberration assay weak positives were only obtained at concentrations producing severe cell cycle delay. Observed cell transformations and chromosomal aberrations were considered more likely a reflection of a dose dependent cytotoxicity rather than an indication of genotoxic potential. Chlorpropham was not found to be mutagenic in the Ames test in *Salmonella typhimurium* either with or without S9 mix.

## Recommendations

1. There are no objections on toxicological grounds to the approval of chlorpropham sourced from MTM Agrochemicals Ltd, 18 Liverpool Road, Great Sankey, Warrington, Cheshire WA5 1QR England, and from MTM Agrochemicals Ltd, Hall Lane, Rookery Bridge, Moston Sandbach, Cheshire, England.

2. Chlorpropham has low acute oral and dermal toxicity, is a slight dermal and moderate eye irritant and can produce anemia following chronic exposure. Inclusion of chlorpropham in schedule 5 of the SUSDP would be consistent with the toxicity profile of this compound.

3. An ADI of 0.05 mg/kg bw/day is recommended for chlorpropham based on a 100 fold safety factor and a NOEL of 5 mg/kg bw/day in a one year dog study.

4. **First Aid Instructions**

   As chlorpropham is of low acute toxicity with an oral $LD_{50}$ of 4200 mg/kg in rats, a first aid entry of ‘a’ is appropriate. The following amendment is recommended:

   **New Entry**

   | | | |
   |---|---|---|
   | Chlorpropham | a | 420 |

5. Sponsors of chlorpropham containing products should be requested to provide formulation details and acute toxicity studies on each product in order that appropriate safety directions may be developed.

## Summary of Toxicological Hazard

| | |
|---|---|
| Date of Preparation: | July 1996 |
| Chemical name: | Chlorpropham |
| Worst oral LD50 in rats: | 4200 mg/kg. |
| Worst oral LD50 in other species: | No data |
| Worst dermal LD50: | >2000 mg/kg in rabbits. |
| Worst inhalation LC50: | No data |
| Skin irritation: | Slight irritant in rabbits. |
| Eye irritation: | Moderate irritant in rabbits. |
| Skin sensitisation: | Not a skin sensitiser in guinea pigs. |
| T-value: | 420 |
| NOEL: | 5 mg/kg bw/day in a one year dog study |

# Chlorpropham

## Introduction

Chlorpropham, an N-phenylcarbamate, is used as a pre-emergent and early post-emergent herbicide, and as a post-harvest treatment of potatoes to prevent sprouting. Aceto Agricultural Chemicals Corporation have submitted genotoxicity, carcinogenicity, metabolism, reproduction and developmental data in support of the clearance and scheduling of chlorpropham TGAC. No ADI has previously been set due to inadequate data from which to set a NOEL.

## Toxicokinetics and Metabolism

1. **Metabolism of $^{14}$C-Chlorpropham in rats: Preliminary range finding study.** D Wu. Xenobiotic Laboratories, Inc., Princeton, NJ, USA. (EPA Guidelines 85-1) GLP: 40 CFR Pt 160. Study Number XBL89071. 10 June 1991. ***Protected Information until 15 Nov 1998***

Male and female Sprague-Dawley rats (6 to 10 weeks old, 150 - 250g) in groups of two were dosed orally by gavage with $^{14}$C-chlorpropham (99% pure, ring labelled) in corn oil (5 to 7.3 ml) at 5, 100, 300, or 500 mg/kg. Faeces, urine and $CO_2$ were collected and radioactivity measured daily for three days in the low dose group, and faeces and urine were collected in the other groups.

Less than 0.02% of the dosed radioactivity was recovered as $CO_2$, indicating the radioactive label was located in a metabolically stable location. Urine was the predominant excretion path in both sexes at all dose levels with 70 to 90% of the administered dose excreted via this route within 24 hours and 80 to 90% within 72 hours. Females differed slightly from males only at the lowest and highest doses. At the low dose the percentage excreted in urine was greater in females than in males (92% versus 83%) and at the highest dose lower than males (73% versus 80%). Faecal excretion accounted for 9 to 15 % of the administered dose in males at all doses. In females the percentage excreted in faeces increased with increasing dosage (8, 5, 13, 21 %; lowest to highest dose).

2. **Metabolism of $^{14}$C-Chlorpropham in rats: Preliminary metabolite isolation and identification study.** D Liu. Xenobiotic Laboratories, Inc., Princeton, NJ, USA. (EPA Guidelines 85-1) GLP: 40 CFR Pt 160. Study Number XBL90050. 10 June 1991. ***Protected Information until 15 Nov 1998***

Urine from the high dose group of the previous study was pooled, fractionated and then analysed by HPLC and mass spectrophotometry to identify chlorpropham metabolites. Thirteen metabolites were isolated and identified. Three major metabolic pathways were proposed. The first pathway involves the hydroxylation of the phenyl ring at the 4' position with subsequent conjugation with glucuronide or sulfate. The second pathway involves the oxidation of the isopropyl side chain with subsequent conjugation. The third pathway is decarbanilation to 3-chloroaniline followed by either N-acetylation and 4'-hydroxylation and conjugation, or direct 4'-hydroxylation and conjugation.

3. **Absorption, distribution and excretion studies of chlorpropham in the rat.** S Selim. Biological Test Centre, Irvine, CA, USA. (EPA Guidelines 85-1) GLP:40 CFR Pt 160. Study Number BTC P01879. 2 May 1991. ***Protected Information until 15 Nov 1998***

Male and female Sprague-Dawley rats in groups of five were given a single oral dose of $^{14}$C-chlorpropham at 5 or 200 mg/kg, or a single IV dose of 0.5 mg/kg. An additional five males and five females were dosed orally with unlabelled chlorpropham for 14 days at 5 mg/kg then given a single dose of 5 mg/kg $^{14}$C-chlorpropham. All animals were placed in individual metabolism cages and urine and faeces collected for seven days. Following the collection period animals were sacrificed and tissue analysis performed to determine residual radioactivity levels.

Regardless of the treatment regimen no animals showed signs of toxicity and all appeared normal during the study. The amount of administered dose excreted in urine (89-97%) and faeces (4-7%) did not alter significantly with the dose, route or frequency of administration, and was not sex dependent.

The pattern of tissue residues was not affected by dose level, route, or frequency of administration, nor by sex. The highest residues were found in the blood (36% of total residues), spleen (16%), liver (12%) and carcass (14%), with negligible levels in the fat and bone (<1% of total residues). In each treatment regime the total residue in tissues and carcass was low, ranging between 0.02 and 0.7% of the administered dose. Absolute individual tissue residues were below 0.05 ppm in all low dose groups and below 2.3 ppm in the high dose groups

4. **Metabolism of $^{14}$C-chlorpropham in rats: Definitive FIFRA study, metabolite analysis and quantitation.** RA Robinson. Xenobiotic Laboratories, Inc., Industrial Research Laboratory. Plainsboro, NJ, USA. (EPA Guidelines 85-1) GLP: 40 CFR Pt 160. Study Number XBL90051. 20 August 1991. ***Protected Information until 15 Nov 1998***

The previous three studies are consolidated and summarised under this single title in the original submission. The study heading details are included here to avoid confusion and for future reference.

**Chronic Studies**

1. **18 Month oncogenicity evaluation of chlorpropham in the mouse.** JA Botta. T.P.S. Inc., Mt Vernon Indiana, USA. (EPA Guidelines 83-2). GLP:40 CFR Pt 160 Study Number 393K-002-050-89. 21 October 1992. ***Protected Information until 15 Nov*** **2002**

Male and female CD-1 albino mice (6 weeks old, males 22-32g, females 19-31g) in groups of 60 were housed in individual cages and treated with chlorpropham (96.2% pure, Batch 14065L89) in their diets for 78 weeks, at levels designed, and regularly adjusted, to achieve intakes of 0, 100 (450-780 ppm), 500 (2200-4000 ppm), 1000 (4500-8000 ppm) mg/kg bw/day. Ten animals per sex per group were designated for interim necropsy. Achieved doses were within $\pm$ 20% of target throughout the study period, after the first six weeks dosage was within $\pm$ 10% in all but seven weeks. Effects of treatment were assessed through: twice daily observations; ocular examinations at initiation and termination of the study; body weight and food consumption measurements; gross necropsy of a subset of animals (survivors of the 10 animals assigned for interim necropsy) in each group in week 52; necropsy of all surviving animals at the termination of the study; and gross pathology and histology of all animals in the control and high dose groups at termination, all premature decedents, and all gross lesions in other groups.

Within 4 weeks all animals from the high dose group exhibited a bluish tint on the skin of their extremities and distinctly darker eyes. This colouration change became apparent in a significant proportion of the mid dose group from week 34 onwards, however unlike the high dose group the two signs (dark eyes and blue skin) were not always found together. No animals in the control or low dose groups developed darkened eye colouration but a single female in each group developed bluish skin colouration. There were no other treatment related clinical observations. Ophthalmic examinations revealed no treatment related changes.

Mortality was significantly increased only in the high dose male group (22/60 versus 7/60 for control). Other than an increased incidence of amyloidosis (m/f; 3/2, 5/7, 4/8, 11/9, control to high dose), no consistent contributory cause or associated pathology was identified for the pattern of mortality.

Body weight gains and food consumption were similar to controls for all treatment groups. Relative and absolute organ weights were generally unaffected by treatment with no significant differences found in females at terminal sacrifice. In high dose males absolute liver and spleen weights were increased at 52 weeks (spleen enlargement 43%, liver 24%) which persisted at 78 weeks (spleen 89%, liver 12%).

Haematology revealed an increase in reticulocytes in both sexes at 52 weeks (m/f; 1.8/1.4, 2.1/1.9, 3.1/2.5, 3.7/4.2%, control to high dose respectively) and in males at 78 weeks (1.1, 1.3, 1.8, 4.2%, control to high dose respectively). In females an extreme outlier in the control group (13.9%) masked the increase in reticulocyte count at 78 weeks (3.3, 2.5, 2.6, 3.1%, control to high dose respectively). If the outlier is excluded the control value becomes 2.1% and a marginal dose response effect is then apparent. Mean corpuscular haemoglobin was increased to a small (<10%) but significant extent in both sexes at the high dose at 52 weeks and in males at 78 weeks.

Histopathology did not reveal any treatment related increase in the incidence of neoplastic pathology. Non neoplastic pathology included increased amyloidosis in the high dose groups and a marginal increase in low and mid dose female groups. All neoplasms observed were low in incidence and evenly distributed across all treatment groups and controls. Increased erythropoiesis was noted in the spleen, bone marrow and liver of high dose and some mid dose animals together with increased haemosiderosis in the spleen at mid and high doses (m/f incidence per group, control to high dose; 2/11, 1/15, 27/27, 35/47).

NOEL: The NOEL for this study was 100 mg/kg bw/day based on darkened eye colouration, blue skin on the extremities, altered reticulocyte counts, increased haemosiderosis in the spleen and increased amyloidosis at higher levels.

Comment. In both sexes reticulocyte counts were increased in all treatment groups at both 52 and 78 weeks (after removal of a single extreme outlier in the female control group), however the low dose values were always within the normal control range and within one standard deviation of the control mean. The NOEL was therefore set at 100 mg/kg bw/day, taking reticulocyte counts at 100 mg/kg bw/day as normal.

**2. Final report on toxicological studies on isopropyl N-(3-chlorophenyl) carbamate (CIPC) carried out at the medical college of Virginia under contract number 12-25-010-471**. 28 June 1957 ***Protected Information until 29 Jan 2003.***

This submission contains two studies which appear to be identical to those published as "Chronic toxicological studies on isopropyl N-(3-chlorophenyl) carbamate (CIPC)." (Larson et al., (1960) Toxicol Appl. Pharmacol. 2 659-673.), and previously assessed as a two year dietary study in rats and a one year dietary study in dogs, but provides additional data not available to previous evaluators, which upon analysis yields an altered NOEL for one of these studies.

a. Two year dietary study in rats.

Groups of albino rats (25/sex/dose level) were fed chlorpropham (batch and purity not stated) in the diet at levels of 0, 200 (~10mg/kg/day), 2000 (~100 mg/kg/day) or 20000 ppm (~1000 mg/kg/day) for 2 years. Animals were observed throughout the study period and weighed weekly. Haematological parameters were measured at 3 month intervals, together with urinalysis parameters. Histopathology was performed at the end of the study period.

Survival was low for all groups at 104 weeks (m/f 6/7 control and 1/3 high dose), but particularly so for high dose males in the last 13 weeks of the study where a significant decrease compared to controls was observed. Bodyweight gain and food consumption were decreased slightly in high dose males and females throughout the study. Haemoglobin levels and haematocrit values were depressed by approximately 20% and 10 to 15% respectively throughout the study at the high dose level although with an occasional normal value at some time points. Urinalysis parameters were unaffected by treatment. Organ-to-body weight ratios were unaffected by treatment up to 200 ppm. At the high dose level an increase in relative liver (m/f 46/26% above control) and testes (48% above control) weights were observed, although the small number of survivors at 104 weeks made accurate measurements difficult. Relative spleen weights were increased at both 2000 (m/f; 1.3/1.5 X control values), and 20000 ppm (m/f; 8/4 x control values).

Histopathological examination of dying animals throughout the study, and surviving animals at 104 weeks, revealed a high incidence of respiratory tract infection. There were no treatment related histopathological changes. There was no apparent increase in tumour incidence.
Because of the inherent limitations in this study a NOEL was not set.

b. One year dietary study in dogs.

No additional information is provided over that reported in the previous assessment.

Comment. The small number of animals on test in the rat study, a high incidence of respiratory infection, poor survival at termination, a lack of clinical chemistry, and a general lack of detail, renders the NOEL questionable. The NOEL for this study was previously set at 2000 ppm from an evaluation of the published paper. If a NOEL were to be set from the more complete data provided for evaluation, a NOEL of 200 ppm (approximately 24 mg/kg bw/day) would be more representative based on increased spleen weights and decreased RBC count and haematocrit at higher doses.

**3. 24 Month combined oncogenicity/toxicity evaluation of chlorpropham in rats.** JA Botta. TPS. Inc, Mt Vernon Indiana, USA. (EPA Guidelines 83-5) GLP:40 CFR Pt 160Study number 393L-103-055-89. 22 April 1993. ***Protected Information until 15 Nov* 2002**

Male and female Sprague Dawley rats (4 weeks old, males 180-240 g, females 123-195 g) in groups of 60 were housed in individual cages and treated with chlorpropham (96.2% pure, batch 14065L89) in their diets for 104 weeks, at levels designed, and adjusted, to achieve intakes of 0, 30 (270-900 ppm), 100 (920-2700ppm), 500 (4650-13600ppm) and 1000 mg/kg bw/day (9400-25000ppm). Ten animals per sex per group were designated for interim necropsy. Achieved doses were within 81 to 133% of target throughout the study period, except for weeks 13 and 14 when a transient SDA viral infection altered food consumption patterns. Effects of treatment were assessed through; twice daily observations, ocular examinations at initiation and termination of the study, body weight and food consumption measurements, urinalysis, clinical chemistry, gross necropsy of a subset of animals (survivors of the 10 animals assigned for interim necropsy) in each group in week 52, necropsy of all surviving animals at the termination of the study and gross pathology. Histology of all animals in the control and high dose groups at termination, all premature decedents, and all gross lesions in other groups, was performed.

Survival was not adversely affected by treatment, however female groups were sacrificed at 102 weeks, to ensure enough animals for meaningful analysis, due to a low survival rate across all female groups. Analysis of the major contributory causes for death in premature decedents did not indicate any treatment related trends. Some evidence of a trend to increased survival was observed in high dose animals (survivors, m/f: 22/15, 22/20, 22/14, 23/31, 30/24, control to high dose at week 100). Clinical observations revealed no treatment related signs. Although high dose males had an increased incidence of ocular opacities (15 versus 8 for control) this was not significant and was probably a chance event. Food consumption was not affected by treatment however group mean body weight gain was significantly and consistently depressed at 500 and 1000 mg/kg bw/day from approximately week 7 through to the end of the study (52 weeks m/f; 12/14, 22/25 % below control respectively).

Urinalysis revealed increased levels of bilirubin in high dose male and female animals throughout the study and in 500 mg/kg bw/day animals at termination (male, +ve/No. tested; 0/19, 0/14, 0/16, 5/15, 24/27: females, +ve/No. tested; 0/15, 1/19, 1/13, 6/29, 13/22 - Control to high dose respectively at termination). Other urinalysis parameters were not affected by treatment.

Blood samples taken from animals at the two highest doses were noted to be dark in colour with a brownish tint. Haematology revealed a persistent decrease in RBC (20 to 30% below control) and haemoglobin (10 to 20% below control) and increased reticulocyte count (3 to 9 x control), mean corpuscular haemoglobin (20%) and mean corpuscular volume (~20%), in animals of the 500 and 1000 mg/kg bw/day groups. Similar changes, but of lesser magnitude, were seen in animals of the 100 mg/kg bw/day groups at 26 and 52 weeks but did not persist thereafter.

Blood cholesterol was increased in the high dose group by 40 to 100 % and in the 500 mg/kg bw/day group by 20 to 70 % throughout the study period. Albumin, and the albumin/globulin ratio, were increased by 10 to 15% and AST decreased by up to 50% at various time points at the two highest treatment levels. T4 levels throughout the study were reduced at various time points by up to 40% at the three highest treatment levels but persisted only in males at 500 and 1000 mg/kg bw/day at terminal sacrifice. Absolute and relative (to body weight) spleen weights and relative liver weights were increased significantly (2 to 3 x control, and 1.2 to 1.6 x control respectively) at 500 and 1000 mg/kg bw/day. Other relative organ weight variations were attributable to the decreased weight gain in the 500 and 1000 mg/kg bw/day groups.

Increased haematopoiesis and haemosiderosis were demonstrated histologically in the spleen of animals treated at 100 mg/kg bw/day at both 52 and 104 weeks. In animals treated at 500 or 1000 mg/kg bw/day increased haematopoiesis was observed in bone marrow, liver and spleen, with increased haemosiderosis and congestion observed in the spleen, and pigmentation observed in the reticuloendothelial cells of the liver, at both terminal and interim sacrifice.

Non neoplastic potentially treatment related observations consisted of: lenticular degeneration in five high dose males; increases in mineralised deposits (m/f; 17/44 versus 5/33 for control), cysts (m/f 21/7 versus 7/0 for control) and pigments (m/f 36/37 versus 0/6 for control) in the kidneys of high dose male and female groups; increased alveolar macrophages and focal lymphoid infiltrate in the lungs, and chronic nephritis in the kidneys of high dose females (44 versus 33 for control).

A significant increase in testicular interstitial cell tumours (1/60, 4/60, 2/60, 4/60, 9/60, control to highest dose) was observed in high dose males. As this is a common tumour in aged male rats, no hyperplasia was found in association with the observed tumours, and the incidence was neither dose related nor of great magnitude, the effect cannot be ascribed to treatment, despite statistical significance, and is more likely due to an abnormally low control incidence. The incidence in historical controls from the same laboratory was approximately 6.3 % or an expected observation of 4/60, supporting the proposition that the observed statistically significant increase at the high dose is an anomaly and not treatment related. Three gliomas were observed in the brain of high dose animals, 2 in males and 1 in females. As this is a rare spontaneous tumour the observation is notable, but cannot be unequivocally ascribed to treatment. A decreased incidence of islet cell adenomas of the pancreas (15 versus 21 for control) of the male high dose group and of adenocarcinoma and fibroadenoma / adenocarcinoma lesions in high dose females, were observed.

The NOEL for this study was 30 mg/kg bw/day based on, anaemia and haemosiderosis in the spleen at the next highest dose.

Comment Increased red cell turnover at higher chlorpropham treatment levels is indicated by increased urinary bilirubin, increased reticulocyte count, decreased haemoglobin levels and evidence of increased haematopoiesis in the liver and spleen as a compensatory mechanism for low level anaemia. The observation of three gliomas in high dose animals is notable.

This rare spontaneous tumour has an approximate incidence of 0.5% in published studies and historical data from other laboratories, and an incidence of 16/879 (1.8%) males in the historical controls of the conducting laboratory. The probability of three gliomas occurring spontaneously in 120 high dose but in none of the 480 other animals on test is low but not sufficiently so to be able to ascribe the finding to treatment. To attain statistical significance ($p<0.05$), with no occurrences in control animals, an incidence of 5 would be needed in any one high dose group (Fischers exact test). Consequently, given the number of animals per group and the background incidence of the neoplasm, statistical analysis is of little value in this case. As no animal at lower doses was found to have a similar lesion, and the high dose groups appear to have exceeded the maximum tolerated dose, the toxicological significance of the increased incidence of gliomas is marginal. The increased incidence of interstitial cell tumours in the high dose males is statistically significant due to an abnormally low control value, but at 15% is nevertheless outside the historical control range for Charles River CD rats. (0-12%), again however the result is of questionable toxicological significance at a dose exceeding the MTD.

**Reproduction Study**

1. **A two generation reproduction study in rats with CIPC.** RE Schroeder. Bio Dynamics Inc. East Milstone, NJ, USA. GLP: 40 CFR Pt 160. Project number 81-2573. 5 July 1983. ***Protected Information until 21 Jan 2001***

Charles River CD Sprague-Dawley rats (145 days old) in groups of 30 (female) and 15 (male) were treated with chlorpropham (98.8% pure, batch 237-2778) in their diets at levels of 1000, 3000 and 10000 ppm during a premating growth period, and throughout the following mating, gestation and lactation periods for two generations. Animals (parental, F0 generation) were pretreated for 100 days then paired for mating. Females were allowed to litter and rear their offspring (F1 generation) to weaning. The F1 generation was allowed to mature for 120 days following weaning then selected animals from each group (F1 parental) were paired for mating for up to 20 days (30 females and 15 males /dose). The females were allowed to litter and rear their young (F2 generation) for 21 days after birth.

Chlorpropham Consumption mg/kg bw/day (range) during the premating growth phase.

| | | 1000 | 3000 | 10000 |
|---|---|---|---|---|
| Males | F0 | 72 (50- 120) | 219 (160 - 340) | 723 (550 - 1080) |
| | F1 | 69 (50- 130) | 210 (150 - 370) | 721 (530 - 1290) |
| Females | F0 | 86 (70 - 120) | 260 (210 - 340) | 850 (700 - 1070) |
| | F1 | 83 (60 - 130) | 257 (200 - 390) | 844 (660 - 1290) |

Evidence of toxicity was assessed using: twice daily clinical observations, general physical condition; body weight increases; food consumption; litter sizes and viability; fertility; period of gestation; brain, erythrocyte and plasma cholinesterase of 10 of each F1 adult generation groups; and histopathology of organs of a sub sample of adults and pups from each group and generation.

Adult Animals

No fatalities occured in the F0 or F1 males and no treatment related mortalities occured in F0 or F1 adult females. Clinical observations revealed no treatment related differences between groups. For the F0 generation, body weight gains in the 14 week premating period were unaffected by treatment in low and mid dose animals but reduced by 15% in females and by 7% in males of the high dose group. In the F1 generation body weight gains were reduced by 17% in high dose males and by 14% in mid and high dose females. No treatment related effects on food consumption were observed. Body weight gains in high dose F0 females during gestation were 14% below controls but during lactation were 80% above control values. In F1 females gestational body weight gains were unaffected by treatment but gains during lactation in the high dose group were 4 times control, although this was unusually low (5g for F1 controls versus 20 g for F0 controls).

Plasma and erythrocyte cholinesterase levels in F1 adults (10 animals tested in each group) at sacrifice were unaffected by treatment. Brain cholinesterase levels were elevated by 15 - 21% at all treatment levels in males but were not elevated in females (m/f 6.2/7.2, 7.5/7.4, 7.1/7.2, 7.5/7.1 uM/g/min). Brain cholinesterase levels in all female groups were similar to those found in treated males and all RBC cholinesterase levels were within 10% of all brain cholinesterase levels (m/f 7.5/7.3, 7.8/7.3, 7.8/7.7, 7.8/7.3 uM/ml/min) except for the male controls, suggesting the control level found for males was abnormally low.

Fertility indices for the F0 and F1 adults were not affected by treatment.

High dose adult F1 animals at sacrifice had increased relative brain (m/f 13/14% above control), heart (m/f 11/13% above control), liver (m/f 7/19% above control), testes (16 % above control), and spleen (m/f 1.9/2.3 times control) weights.

The mid dose female group also had marginal but significant increases in relative brain (13%) kidney (6%) heart (8%) and liver (9%) weights, but a 45% increase in spleen weights and a 21% increase in ovary weights over controls. The increased kidney and ovary weights at the mid dose were probably artifactual given the absence of a similar effect in high dose animals.

Gross post mortem examination of F1 and F0 adults revealed no treatment related anomalies in the F0 animals and a slight increase in the incidence of hair loss in the F1 females of the mid and high dose groups (3/30, 5/30, 6/30, 6/30, control to high dose respectively).

Histopathology of the testes and epididymides of F0 males revealed no treatment related anomalies. From an examination of 15 males and 15 females from each group of F1 adults, an increased incidence of brown pigmented granules was observed in the reticuloendothelial / kupfer cells of the liver (males 2/15, 1/15, 7/15 , 15/15, and females, 2/15, 0/15, 13/15, 15/15 control to high dose respectively) and the tubular epithelial cells of the kidneys (males 1/15, 3/15, 8/15, 12/15, and females 1 /15, 1/15, 6/15, 9/15, control to high dose respectively) of mid and high dose animals. Marrow hypercellularity of the sternum was most prominent in the high dose group (males 4/15, 6/15, 11/15 and 13/15, and females 4/15, 8/15, 13/15, control to high dose respectively) and albuminous degeneration of central lobular hepatocytes was slightly increased in mid and high dose groups (males 0/15, 2/15, 6/15, 6/15, females 3/15, 1/15, 4/15, 7/15). Suburothelial focal mineralization, of minimal intensity, was observed in treated females (0/15, 4/15, 3/15, 7/15, control to high dose respectively). In all but two of these animals (one low dose and one mid dose) the mineralisation was unilateral. The relationship of this finding to treatment is uncertain.

Pups

The number of live pups per litter, and pup sex ratios, for F1 and F2 litters were unaffected by treatment. Pup survival was unchanged in the F1 litters at day 4 but marginally decreased in the high dose group for days 4 - 21 (95% versus 99.7 %). In the pups of the F2 litters an unusually low survival index for the control animals (85%), due to one animal delivering 8 dead pups, resulted in a significantly increased survival index for the high dose group (97%) at day 4 but the two values were equal for days 4 - 21 (93%). Mean F1 and F2 pup weights were unaffected by treatment until day 14 when high dose groups began to show reduced weight gain becoming marked by day 21 (23% below control).

Organ weights (brain, kidneys, liver, spleen, testes/ovaries) in sacrificed F1 weanlings were unaffected by treatment. In F2 weanlings however relative brain weights in the high dose groups were increased (m/f 121/118 % of control) and relative spleen weights were decreased (m/f 71/82% of control). Gross post mortem of F1 pups, not selected for breeding, revealed an increased incidence of dark red spleens in the mid and high dose groups. No treatment related anomalies were observed in the F2 pups at necropsy. Histopathology of randomly selected pups of the F1 and F2 generations (5/sex/group taken on day 21) did not reveal any treatment related anomalies.

Reproductive efficiency of adult rats was unaffected by the doses employed in this study. The NOEL for pup development was 1000 ppm based on altered spleen appearance at the next highest dose. The overall NOEL for chlorpropham in adults was 1000 ppm (approximately 70 mg/kg bw/day) based on decreased body weight gains, increased spleen, brain, heart and liver weights, and altered liver and kidney histology at higher doses.

Comment The finding of suburothelial focal mineralization has not been considered in the determination of a NOEL for adults. This finding was of uniformly low intensity, was not bilateral in most animals, and has no obvious relationship with the normal toxicological observations with chlorpropham. The finding is considered incidental.

**Developmental Studies**

1. **A teratology study in rats with a formulation of CIPC (40.2% on Hi-Sil)**. EJ Tasker. WIL Research Laboratories Inc., Ashland, Ohio, USA. (EPA guidelines for teratology evaluations of the time of the study) GLP: 19 May 1983. ***Protected Information until 29 JAN 1999***

Mature virgin female Sprague-Dawley rats (14 weeks old and 237 - 348g) were mated and housed in individual wire mesh cages. Animals were treated with chlorpropham (purity not separately specified) as a 40.2% mixture with Hi-Sil 233, suspended in aqueous 0.5% methylcellulose, at doses of 40, 400 and 2000 mg/kg bw/day (of chlorpropham) by gastric intubation for 14 days from day 6 to 19 of gestation, in groups of 25. Two control groups were treated with either vehicle only (aqueous 0.5% methylcellulose solution) or vehicle and Hi-Sil 233 suspension (2975 mg/kg bw/day Hi-Sil 233).

The parental effects of chlorpropham administration were assessed from; twice daily clinical observation, measurement of body weight, determination of liver and spleen weights and pathological investigation at the end of the study period. On day 20 of pregnancy dams were sacrificed and the ovaries and uteri removed and examined for the number of corpora lutea, with the number and position of implantations divided into; live foetuses, early resorptions, late resorptions, and dead foetuses. The sex and weight were determined for each foetus. All foetuses were examined for external malformations, half were then fixed and examined by the Wilson sectioning technique for soft tissue abnormalities, and the remainder were examined for skeletal malformations.

Five high dose animals died between gestation days 10 and 13, 2 due to intubation errors and 3 due to cerebral haemorrhaging as a result of toxicity. Clinical observations of toxicity were confined to the mid and high dose groups and included matting and staining of the urogenital fur, pale extremities and ears and red material on the facial area.

Faeces of animals in the second control group (Hi-Sil 233 control) were white. Body weight gains in the high dose group were markedly reduced (by 41% of control) from day 6 to day 20. Spleen weights in the mid and high dose groups were increased by 85% and 270% of control. Relative liver weights were significantly increased in the high dose group (28%).

In the high dose group 10 females had total litter loss (145 early resorptions, control 11) and the mean number of viable foetuses (91 in 17 surviving gravid females, control 309 in 23 gravid females) and the mean foetal weight (2.8 versus 3.5g for control) were both reduced. Sex distribution was unaffected by treatment.

The incidence of malformations in skeletally examined foetuses of the high dose group (10/48 pups) was substantially greater than in controls (5/157 pups) due to an increased incidence of bent ribs (7/48 versus 3/157 pups), bent limb bones (2/48 versus 0/157 pups, 2/5 versus 0/23 litters), and unossified pubis (2/48 versus 0/157 pups). The authors suggest that bent ribs are not considered a malformation but rather, are a reflection of the maternal stress and toxicity. The historical control incidence at this laboratory for bent ribs was 257/34326 or 0.75% with a range of 0 to 4.2%. Bent limb bones are a rare anomaly in rats with an historical control incidence at this laboratory of 3/34326 and a range of 0 to 0.6%. Observations of increased incidences of reduced ossification of the pubis, vertebral arches and sternebrae, and an increase in sternebral malalignment in the high dose group are attibutable to the decreased foetal weights.

The NOEL for maternal toxicity was 40 mg/kg bw/day based on altered appearance and increased spleen weight at the next highest dose. The NOEL for foetal development was 400 mg/kg bw/day based on increased early resorptions, decreased pup viability and body weight and an increased incidence of foetal skeletal malformations and variations at higher doses.

Comment: Bent limb bones are a rare anomaly and the incidence in this study is considerably greater than the upper bound of the historical control range. With an incidence of only two however, differentiation between a statistical anomally (unlikely) and toxicological effect (more likely) is not possible.

**2. A study of the effects of CIPC on pregnancy of the rabbit.** P James. Huntingdon Research Centre, Huntingdon, Cambridgeshire, England. GLP: 21 CFR Pt 58 Report number PPG 5&7/8328. 8 March 1983. ***Protected Information until 29 Jan 2001***

Both a preliminary and main study are detailed in this report. In the preliminary study female New Zealand white rabbits (2.7 - 3.7 kg) in groups of six were administered chlorpropham (batch 237-2778, purity not stated) by intragastric tube (suspended in aqueous 1% methylcellulose) at levels of; 200 (13 days), 500 (13 days) 800 (7 days) and 1500 (3 days) mg/kg bw/day. The reduced dosing period at the two highest treatment levels was due to overt toxicity in these groups, necessitating humane termination.
The effects of chlorpropham administration on parental animals were assessed from: daily clinical observation, measurement of body weight gain and food consumption, and macroscopic pathological investigation at the end of the study period (day 21).

The preliminary study indicated chlorpropham was acutely toxic to does at 800 and 1500 mg/kg bw/day. All animals in these groups either died or were sacrificed on humane grounds prior to dosing on days 7 and 3 respectively. Clinical signs were limited at lower doses but at doses above 500 mg/kg bw/day marked weight loss, anorexia, chromourea, reduced faecal output, cold ears and dark eyes (at 1500 mg/kg bw/day) were observed. Food consumption in the 500 mg/kg bw/day group was slightly lower in the first 10 days of the study but body weight gain was equivalent to control. Necropsy revealed no abnormalities attributed to treatment.

In the main study female New Zealand white rabbits (2.7 - 3.7 kg) were mated and administered 25 i.u. of luteinising hormone to ensure ovulation occurred, then assigned to treatment groups of 16 animals each. Chlorpropham was administered on days 6 to 18 post coitum, by intragastric tube (suspended in aqueous 1% methylcellulose) at levels of; 0, 125, 250 and 500 mg/kg bw/day. The effects of chlorpropham administration on parental animals were assessed from: daily clinical observation, measurement of body weight, and pathological investigation at the end of the study period. On day 29 of pregnancy does were sacrificed and the ovaries and uteri removed and examined for the number of corpora lutea, with the number and position of implantations divided into; live foetuses, early resorptions, late resorptions, and dead foetuses. The sex and weight were determined for each foetus. All foetuses were examined for external malformations, skeletal malformations and visceral abnormalities.

No mortalities occurred in the main study. Five animals (2 controls and 3 high dose) were prematurely removed from the study with uterine infections. Cold ears were observed in most animals at 500 mg/kg bw/day (11/16 versus 2/14 for controls) and 6/16 at 250 mg/kg bw/day, with anorexia (6/16) and reduced faecal output (5/16) observed in some animals at 500 mg/kg bw/day towards the end of the study period.

A dose related decrease in body weight gain was observed in all treatment groups during the first two days of treatment but persisted beyond this only in the high dose group (37% and 90% of control weight gains to days 10 and 29 respectively). Treatment did not produce any macroscopically visible abnormalities in dams at terminal necropsy.

Two females aborted in the high dose group and mean litter size was smaller at both 250 (6.5 young/litter) and 500 mg/kg bw/day (6.9) compared to control (8.0). Foetal weight was unaffected by treatment. Pre and post implantation loss were elevated at 250 mg/kg bw/day (26.8% and 15% compared to 17.1 and 7.2 % for controls) and post implantation loss was elevated at 500 mg/kg bw/day.

No treatment related malformations or anomalies were observed. Three foetuses in the high dose group, derived from two litters, had scoliosis but in different vertebral regions. The mean incidence of an extra thoracolumbar rib was markedly higher in the low dose group compared with all other groups (24.3, 46.2, 26.7, 27.4% of foetuses, control to high dose respectively) and the incidence of variant sternebrae was decreased in all treatment groups (31, 25, 25, 20%, control to high dose). These variants are common and do not reflect effects of chlorpropham.

Foetal development, as indicated by the incidence of malformation, was unaffected by chlorpropham toxicity. The NOEL for maternal and embryo toxicity was 125 mg/kg bw/day.

**Genotoxicity**

Chlorpropham was genotoxic in a chromosomal aberration study in Chinese hamster ovary cells and in a cell transformation assay in Syrian hamster embryo cells. When requested to comment on the significance of these studies the applicant supplied US EPA evaluations of the studies, and chose not to qualify the results. Chlorpropham is known to interfere with the cell cycle machinery, disorganising the microtubule assembly and inhibiting spindle formation. In the CHO chromosome aberration assay weak positives were only obtained at concentrations producing severe cell cycle delay. Observed cell transformations and chromosomal aberrations may be more reflective of a dose dependent cytotoxicity than an indication of genotoxic potential.

**Summary of Genotoxicity Studies**

| Study Type | Test Object | Concentration | Result | Ref |
|---|---|---|---|---|
| Chromosomal aberration | Chinese hamster ovary cells (CHO) | 10 - 160 µg/ml ± S9 mix | +ve* | 1 |
| Cell transformation | Syrian hamster embryo cells | 5 - 100 µg/ml (- S9 mix) | +ve** | 2 |

* Weakly positive (2 to 14% cells with chromosomal aberrations versus controls of 0 to 2%) in cultures with metabolic activation (+S9 mix) at toxic concentrations causing severe cell cycle delay (120 & 140 µg/ml). Results in replicate cultures were not consistently positive over repeated assays. At slightly higher concentrations (160 µg/ml) chlorpropham caused complete cytotoxicity. Mitomycin C was used as the positive control in non activation studies (24 % of cells with aberrations) and cyclophosphamide in the activation studies (24 - 96 % cells with aberations).

** Chlorpropham induced a stable morphologically transformed phenotype at 70, 85 and 100 µg/ml in 24 hour exposure studies (0.80 to 3.6 % versus 0.3 % for the -ve control and 0.77 % for the +ve control [benzo (a) pyrene]) and at 20, 25 and 30 µg/ml (0.80 to 1.25 % versus 0.45 % for the -ve control and 1.90 % for the +ve control) in 7 day exposure studies. The relative plating efficiency was reduced to below 80% in the 24 hour exposure study at 85 ug/ml and above, and in the seven day exposure study at 30 ug/ml, reflecting chlorpropham cytotoxicity.

1. **Mutagenicity test on chlorpropham in an in vitro cytogenic assay measuring chromosomal aberration frequencies in chinese hamster ovary (CHO) cells**.H Murli. Hazelton Laboratories America Inc., Kensington, Maryland, USA. (EPA Guidelines 84-2), GLP: EPA., Study Number 12276-0-437. 3 April 1991. ***Protected Information until 15 Nov 1997***

2. **In vitro transformation assay of chlorpropham using syrian hamster cells.** JA Poiley. Hazelton Laboratories America Inc., Kensington, Maryland, USA. (EPA Guidelines 84-2), GLP: EPA., Study Number 12276-0-485R. 29 March 1991. ***Protected Information until 15 Nov 1997***

# 2. Evaluation of March 1997

## Introduction

Chlorpropham, an N-phenylcarbamate, is used as a pre-emergent and early post-emergent herbicide, and as a post-harvest treatment of potatoes to prevent sprouting. Following a special review of chlorpropham the absence of formulation details and toxicity studies for registered chlorpropham products was noted and a recommendation made that the sponsors of registered products be requested to provide this information. Crop Care Australasia Pty Ltd, on behalf of Aceto Agricultural Chemical Corporation, have submitted an acute inhalation study on the product Sprout Nip Ag, containing chlorpropham (46.8%), as additional data. Sprout Nip Ag is not registered in Australia.

Chlorpropham has an ADI of 0.05 mg/kg bw/day based on a 100 fold safety factor and a NOEL of 5 mg/kg bw/day in a one year dog study, and is included in schedule 5 of the SUSDP.

## Acute study

**Acute inhalation toxicity study in rats.** Holbert, M.S. Stillmeadow Inc. Sugar Land, Texas. Report No 8474-91. 9 December 1991

| | |
|---|---|
| Test Chemical: | Sprout Nip Ag (Lot 04SA45710, 46.8% Chlorpropham) from Platte Chemical Company |
| Test Species: | Sprague Dawley rats from Harlan Sprague Dawley Inc. Houston, Texas |

Dose ($mg/m^3$, inhalation): 1090, 1880 (5 animals/sex/dose), 4 hour exposure

| | |
|---|---|
| GLP: | 40CFR160 |
| Guidelines: | US EPA 81-3 |

Male and female Sprague Dawley rats in groups of 5 were whole body exposed to an aerosol of liquid Sprout Nip Ag for four hours at a concentration of either 1090 $mg/m^3$ or 1880 $mg/m^3$. Animals were observed for 14 days after treatment. Toxicity was assessed through; clinical observation, body weights on days 0, 7 and 14, and gross necropsy at termination. Food, water and the housing environment were controlled and monitored. Test material concentration in the air was determined hourly during exposure and temperature and humidity every 30 minutes.

### *Results*

The mass median aerodynamic diameter of aerosol particles was 2.1 - 2.2 µm, and 14% of particles were below 1.1 µm. No animals died during or subsequent to exposure. At both exposure levels males had gained weight by day 7 and weight gain was normal by day 14. Females did not gain or lose weight during the 14 day observation period. During the first 6 hours following treatment at the lower concentration clinical signs related to the stress of treatment were apparent, including; piloerection, decreased activity, ptosis, nasal discharge, salivation and polyuria. No clinical signs were apparent subsequently. Clinical signs at the higher concentration included those seen at 1090 $mg/m^3$ together with respiratory gurgle in males and females and lacrimation in females. Clinical signs were absent by day 2 after treatment. Gross pathology at termination did not reveal any treatment related abnormalities.

The $LC_{50}$ for Sprout Nip Ag is greater than 1880 $mg/m^3$.

## Discussion

The results of the study reported here are consistent with the low acute systemic and topical toxicity of chlorpropham. The primary acute hazards associated with chlorpropham products are, in most instances, derived predominently from the non active constituents rather than from the TGAC, due to its low acute toxicity.

Formulations for each of the products currently on the market were provided. The expected acute toxicity of these formulations was determined from an analysis of their individual ingredients. As this discussion contains confidential business information it has been deleted from this report.

### *Safety Directions*

Currently listed chlorpropham products fall into the three categories of; dust (DU), emulsifiable concentrate (EC), and fogging solutions (LD).

### *Dust*

The single dust preparation, Agchem Potato Stop Sprout Dust (33320), is expected to have low acute oral, dermal and inhalational toxicity, and to be a slight skin and moderate eye irritant. Based on the expected acute toxicology and use pattern of this product the following partial safety directions, based on hazard alone, are recommended;

| | |
|---|---|
| Will irritate the eyes and skin | 161 162 164 |
| Avoid contact with the eyes and skin | 210 211 |
| Do not inhale dust | 220 221 |
| If product in eyes, wash it out immediately with water | 340 343 |
| Wash hands after use | 351 |

### *Emulsifiable Concentrate*

Three emulsifiable concentrates are currently registered; Allicide Herbicide (42429), Agchem Allicide 600 Selective Pre Emergent Herbicide (31622), and Kendon Chloro-IPC Herbicide (31624). Each of these products is expected to have low acute oral, dermal and inhalational toxicity and to be moderate skin and moderate to severe eye irritants. As each of these formulations contains a high proportion of xylene however, the inclusion of the safety directions specified for that solvent is appropriate. Based on the expected acute toxicology and use pattern of these products the following safety directions are recommended;

| | |
|---|---|
| Poisonous if swallowed | 130 133 |
| Will irritate the eyes and skin | 161 162 164 |
| Avoid contact with eyes and skin | 210 211 |
| Do not inhale vapour | 220 222 |
| When preparing spray wear elbow length PVC gloves | 279 281 290 |
| and face shield or goggles | 294 299 |
| If product on skin, immediately wash area with soap and water | 340 342 |
| If product in eyes, wash it out immediately with water | 340 343 |
| Wash hands after use | 351 |
| After each days use, wash gloves and face shield or goggles | 360 361 365 |

### *Liquids*

Two liquid preparations for direct application from fogging apparatus are currently registered; Kendon Chloro-IPC Fogging Solution (33325) and Agchem Tato-Vapo Potato Stop Sprout (33322). Both of these products are expected to have low oral, dermal and inhalational toxicity, and to be moderate skin and eye irritants. Based on the expected acute toxicology and use pattern of these products the following partial safety directions, based on hazard alone, are recommended;

| | |
|---|---|
| Will irritate the eyes and skin | 161 162 164 |
| Avoid contact with the eyes and skin | 210 211 |
| Do not inhale vapour | 220 222 |
| If product on skin, immediately wash area with soap and water | 340 342 |
| If product in eyes, wash it out immediately with water | 340 343 |
| Wash hands after use | 351 |

## Recommendations

1. From a toxicological perspective the current study does not raise issues which might affect the continued registration of chlorpropham products.

2. No change to the current poisons schedule, NOEL or ADI are required.

3. No change to the current first aid directions or T value are required

4. **Safety Directions**

   In accordance with the agreed procedures, safety directions have been set in conjunction with Worksafe Australia (refer p. 26 - 27).

# Chlorpropham

## Consolidated summary (Updated March 1997)

### Introduction

Chlorpropham, an N-phenylcarbamate, is used as a pre-emergent and early post-emergent herbicide and for post-harvest treatment of potatoes to prevent sprouting. Chlorpropham is known to interfere with the cell cycle machinery, disorganising the microtubule assembly and inhibiting spindle formation resulting in cell cycle delay. Chlorpropham has an ADI of 0.05 mg/kg bw/day based on a 100 fold safety factor and a NOEL of 5 mg/kg bw/day in a one year dog study, and is included in schedule 5 of the SUSDP.

### Metabolism and Toxicokinetics

Chlorpropham was readily absorbed after oral ingestion in the rat and was followed by rapid excretion, mainly in the urine. Faecal excretion was 4% after an oral dose and negligible after an i.p. dose. Biliary excretion was 27.5% within 6 hrs of an oral dose but these metabolites appeared to be largely re-absorbed. The major urinary metabolite (81% of administered radioactivity) and major biliary metabolite was 4-OH-chlorpropham.

In a further metabolism study in rats, ring-labelled chlorpropham metabolites were excreted mainly in the urine in the first 24 hrs. Chain-labelled chlorpropham metabolites were also excreted largely in the urine, but 30-40% of radioactivity also appeared as 14-$CO_2$ in the exhaled air in the first 72 hrs. Maximum tissue levels were reached in 1-2 hrs followed by rapid decline with an average half-life of 4.3 hrs. Labelled chlorpropham was also noted to transfer readily to the foetus in pregnant animals and to the milk in nursing animals. The major urinary metabolites were hydroxylation products which, in some cases, were conjugated.

In a preliminary study in rats $^{14}$C-chlorpropham (ring labeled) was administered orally by gavage at doses of 5, 100, 300, and 500 mg/kg. Urine was the predominant excretion path in both sexes at all dose levels, with 70 to 90% of the administered dose excreted via this route within 24 hours, and 80 to 90% within 72 hours. Faecal excretion accounted for the bulk of the remaining administered radioactivity with the total recovery from urine and faeces at 72 hours between 90 and 100%. Negligible radioactivity was recovered as $CO_2$. Thirteen metabolites were identified, primarily glucuronide or sulfonic acid conjugates of various oxidation / hydroxylation or decarbanilation products of the parent compound, together comprising 88-95% of the administered dose.

In an absorption, distribution and excretion study in rats, chlorpropham was rapidly and efficiently absorbed and excreted. Almost the entire administered dose was recovered from urine and faeces 24 hours after administration, with a residue of less than 1%. Tissue residues as a percentage of administered dose, and excretion patterns, were unaffected by; sex, dose or frequency of administration (single or multiple doses of 5 mg/kg or a single dose of 200 mg/kg), or route of administration (oral or IV).

**Acute Studies**

Chlorpropham was of low acute oral toxicity in rats (LD50: 4200 mg/kg) and dermal toxicity in rabbits (LD50: >2000 mg/kg). The IP LD50 in rats was 700 mg/kg. It was moderately irritating to the eyes and slightly irritating to the skin of rabbits, but was not a skin sensitiser in guinea pigs.

In an inhalation study in rats on the product Sprout Nip Ag containing 46.8% chlorpropham in an isopropyl alcohol / propylene glycol base, no animals died after exposure to concentrations of 1090 and 1880 mg/m$^3$ for four hours. The $LC_{50}$ is greater than 1880 mg/m$^3$.

**Short-term Studies**

In a range finding study designed to select doses for a teratology study, female rabbits were administered chlorpropham by intragastric tube at levels of; 200, 500, 800 and 1500 mg/kg bw/day. Chlorpropham was acutely toxic to does at 800 and 1500 mg/kg bw/day. All animals in these groups either died or were sacrificed on humane grounds prior to dosing on days 7 and 3 respectively. At doses above 500 mg/kg bw/day marked weight loss, anorexia, chromourea, reduced faecal output, cold ears and dark eyes (at 1500 mg/kg bw/day) were observed.

In a 21-day dermal study in rabbits given doses of chlorpropham at 0, 104, 520 or 1040 mg/kg/day for 6 hours/day for 21 to 22 days, signs of skin irritation at the application site included oedema at 1040 mg/kg/day, dose-related increased incidences of erythema and scaliness from 104 mg/kg/day, and 'fine transverse cracking' from 520 mg/kg/day. Dermal pathology revealed increased incidences of acanthosis, hyperkeratosis, and focal inflammatory cell infiltration from 104 mg/kg/day. A dose-related increase in reticulocyte counts occurred from 520 mg/kg.

In a 28-day dietary range finding study in dogs (1 sex/gp) given doses of chlorpropham at 0, 5, 50 or 500 mg/kg/d for 28 days, lower bodyweights at 500 mg/kg/day were associated with reduced food consumption. Haematological and biochemical effects included dose-related increases in platelets and cholesterol in females from 50 mg/kg/day, and creatinine in males from 5 mg/kg/day, and dose-related decreases in MCH in males from 50 mg/kg/day.

Changes occurring at the highest dose included lower RBC counts and haemoglobin concentrations, and increased MCVs, in the male leukocyte and lymphocyte counts were lower, and platelet and neutrophil counts and BUN were increased, while in the female, MCH was decreased and serum creatinine was increased. Lower spleen weights occurring from 50 mg/kg/day were associated with slight lymphoid atrophy at 500 mg/kg/day. Increased thyroid activity from 50 mg/kg/day was not associated with increased thyroid weight.

**Subchronic Studies**

In a 90-day dietary study in mice given chlorpropham at 0, 110, 215, 440 or 856 mg/kg/day, high dose males exhibited a bluish discoloration of the extremities (from week 5) and a noticeable darkening of the eyes (from week 7), and there was a dose-related 'darkening of the blood' from 215 mg/kg/day in males and 440 mg/kg/day in females. The toxicological significance of these findings is not known. At the highest dose level MCH and MCHC were increased, and reticulocyte counts were increased in males. Increased spleen weights occurred from 215 mg/kg/day in males and 440 mg/kg/day in females, and there was an increase in haemopoietic activity at 856 mg/kg/day in males and an increased incidence of haemosiderosis from 440 mg/kg/day. The incidence of haemopoiesis was also increased in the liver from 440 mg/kg/day. The NOEL was 110 mg/kg/day.

In a 30-day gavage study in rats (0 or 50 mg/kg/day), there were no clinical signs of toxicity. Relative liver weight was slightly decreased while serum and liver alkaline phosphatase were increased. Histopathology was unremarkable. There was no NOEL.

In a 90-day dietary study in rats (0, 310, 1250, 5000 or 20000 ppm), body weights and liver weights were increased in all treated groups. Liver and kidney histology was normal. The study did not demonstrate a NOEL (summary only available).

In a 90-day dietary study in rats given chlorpropham at 0, 17, 70, 300 or 1200 mg/kg/day, lower bodyweights at 1200 mg/kg/day were not associated with reduced food consumption. Haematological effects included dose-related decreases in RBC counts and Hb concentrations from 300 mg/kg/day, dose-related increases in the number of target cells and crenated RBCs from 17 mg/kg/day, and at 1200 mg/kg/day there was marked anisocytosis, and increases in haematocrits, MCHCs and the number of macrocytic cells. Serum cholesterol levels were increased, serum cholinesterase in females was decreased, and serum levels of total protein and albumin and the A/G ratio were increased in males at 1200 mg/kg/day. Hepatic effects included a dose-related increase in the incidence of haematopoiesis from 70 mg/kg/day in males and 300 mg/kg/day in females, an increased incidence of pigmentation from 300 mg/kg/day, and at 1200 mg/kg/day liver weights were increased. Splenic effects included dose-related increases in spleen weights from 300 mg/kg/day, and in the degree of haematopoiesis from 300 mg/kg/day, and at 1200 mg/kg/day dark red or red/black discolorations of spleens were noted.

A dose-related increased incidence of marked cellularity in the bone marrow also occurred from 300 mg/kg/day. A NOEL was not established due to morphological changes in RBC occurring even at the lowest dose (17 mg/kg/day).

In a 19-week dietary study in pigs (0 or 3300 ppm), body weight was normal. Histopathology of liver, kidney and spleen were normal. Haemoglobin was slightly reduced. (Summary only available).

**Chronic/Carcinogenicity Studies**

In a 116-week dietary carcinogenicity study in mice (0 or 1000 ppm (approx. 300 mg/kg/day), chlorpropham or 1000 ppm urethane), there was a significant increase in lung tumour incidence in urethane-treated animals compared to controls or chlorpropham-treatment. There was no increase in tumour incidence in chlorpropham-treated animals but there were only 25/sex/group.

Albino mice were treated with chlorpropham in their diets for 78 weeks, at doses of 0, 100, 500, and 1000 mg/kg bw/day. Mortality was significantly increased in the high dose male group and was associated with an increased incidence of amyloidosis. A bluish tint on the skin of their extremities and distinctly darker eyes developed rapidly in all animals treated at 1000 mg/kg bw/day, and slowly in many animals treated at 500 mg/kg bw/day, with liver and spleen weights increased in males at 1000 mg/kg bw/day. An increase in reticulocytes and mean corpuscular haemoglobin, and an increased erythropoiesis in the spleen, bone marrow and liver was seen at 1000 mg/kg bw/day and in some animals treated at 500 mg/kg bw/day, together with increased haemosiderosis in the spleen. No treatment related increase in the incidence of neoplastic pathology was observed. The NOEL for this study was 100 mg/kg bw/day based on darkened eye colouration, blue skin on the extremities, altered reticulocyte counts, increased haemosiderosis in the spleen and increased amyloidosis at higher doses.

Source data for a previously published (and evaluated) two year dietary study in rats were assessed. Animals were fed chlorpropham in the diet at levels of 0, 200, 2000 or 20000 ppm (approx. 10, 100 and 1000 mg/kg/day) for 2 years. Survival was similarly low for all groups at 104 weeks. In the final 13 weeks of the study the death rate at 20000 ppm in males was greater than in controls. Bodyweight gain and food consumption were decreased slightly in males and females at 20000 ppm. Haemoglobin levels and haematocrit values were also generally depressed at this dose level. Relative liver and testes weights were increased at 20000 ppm and relative spleen weights were increased at both 2000 and 20000 ppm, although the small number of survivors at 104 weeks made meaningful comparisons difficult. A high incidence of respiratory tract infection was observed throughout all groups. Because of the inherent limitations in this study (small number of animals on test, a high incidence of respiratory infection, poor survival at termination, a lack of clinical chemistry, and a general lack of detail), it was considered inadequate to set a NOEL. The NOEL for this study was previously set at 2000 ppm from an evaluation of the published paper.

Rats were treated with chlorpropham in their diets for 104 weeks, at 30, 100, 500 and 1000 mg/kg bw/day. Males at 1000 mg/kg/day had an increased incidence of ocular opacities but this was not statistically significant. Group mean body weight gain was depressed at 500 and 1000 mg/kg bw/day. Increased urinary bilirubin was observed in males and females at 1000 mg/kg/day throughout the study and in 500 mg/kg bw/day

animals at termination. Animals treated at 500 and 1000 mg/kg bw/day had dark blood with a brownish tint, a persistent decrease in RBC and haemoglobin and increased reticulocyte count, mean corpuscular haemoglobin and mean corpuscular volume. At various time points in these same groups, increased albumin, and albumin/globulin ratio, a decreased AST and an elevated blood cholesterol level were observed. T4 levels were intermittantly reduced at doses above 30 mg/kg/days but persisted only in males at 500 and 1000 mg/kg bw/day at terminal sacrifice. Absolute and relative spleen weights and relative liver weights were increased significantly at 500 and 1000 mg/kg bw/day. Increased haematopoiesis and haemosiderosis were demonstrated histologically in the spleen of animals treated at 100 mg/kg bw/day at both the 52 and 104 weeks. In animals treated at 500 or 1000 mg/kg bw/day increased haematopoiesis was observed in bone marrow, liver and spleen, with increased haemosiderosis and congestion observed in the spleen, and pigmentation observed in the reticuloendothelial cells of the liver, at both terminal and interim sacrifice. Non neoplastic, potentially treatment related observations, consisted of: lenticular degeneration in some males at 1000 mg/kg/day; increases in mineralised deposits, cysts and pigments in the kidneys of males and females at 1000 mg/kg/day; increased alveolar macrophages and focal lymphoid infiltrate in the lungs; and chronic nephritis in the kidneys of females at 1000 mg/kg/day. A significant increase in testicular interstitial cell tumours was observed in males at 1000 mg/kg but as this is a common tumour in aged male rats, and the incidence was neither dose related nor of great magnitude, the effect cannot be ascribed to treatment despite statistical significance, and is more likely due to an abnormally low control incidence. Three gliomas were observed in the brain of animals treated at 1000 mg/kg bw/day, 2 in males and 1 in females. As this is a rare spontaneous tumour the observation is notable, but as the incidence is within the historical control range for the conducting laboratory the toxicological, and public health, significance is low. A decreased incidence of islet cell adenomas of the pancreas of males at 1000 mg/kg and of adenocarcinoma and fibroadenoma / adenocarcinoma lesions in females at this level, were observed. The NOEL for this study was 30 mg/kg bw/day based on anaemia and haemosiderosis and congestion in the spleen at the next highest dose.

In a 33-month dietary carcinogenicity study in hamsters (0 or 2000 ppm chlorpropham or 2000 ppm isopropyl-N-phenyl- carbamate), there was no treatment-related effect on body weight, histopathology or tumour incidence for either compound.

In a one-year dietary study in dogs (0, 200, 2000 or 20000 ppm), body weight gain was depressed at the high dose level. Hb and haematocrit were decreased (at 6 months only) and relative liver and spleen weights were increased at the high dose level. Histopathology was unremarkable apart from evidence of splenic congestion.
Clinical chemistry data was not available. There were no effects at 2000 ppm (approx. 50 mg/kg/day).

In a 60-week dietary study in dogs given chlorpropham at 0, 5, 51, 360 or 455 mg/kg/day, reductions in bodyweights from 360 mg/kg/day were associated with reduced food intake. Decreases in RBC counts, Hb and MCH concentrations, haematocrits, MCVs and platelets occurred from 360 mg/kg/day and serum cholesterol was increased from 360 mg/kg/day. Increases in T4 levels were less marked following TSH stimulation from 360 mg/kg/day in males and 51 mg/kg/day in females,

suggesting some depression of thyroid function. T3 levels were decreased from 360 mg/kg/day. Increased thyroid weights from 51 mg/kg/day (dose-related in females) were associated with increased cellular activity from 360 mg/kg/day. Increased liver weights from 360 mg/kg/day(dose-related in males) were not associated with any gross pathological or histopathological findings. The NOEL was 5 mg/kg/day.

**Reproduction**

In a two generation reproduction study, rats were treated with chlorpropham in their diets at levels of 0, 1000, 3000 and 10000 ppm (approximately equal to m/f; 70/85, 220/260, 720/850 mg/kg bw/day). Body weight gains in the premating period were reduced in F0 and F1 males and females at 10000 ppm and in F1 females at 3000 ppm, but food consumption was unaffected. During gestation, body weight gains in F0 females at 10000 ppm were reduced, but were increased during lactation. In F1 females gestational body weight gains were unaffected by treatment but lactation gains were 6 times control, although the control value was unusually low. Adult F1 animals at 10000 ppm at sacrifice had increased relative brain, heart, liver, testes, and spleen weights. Females at 3000 ppm also had marginal but significant increases in relative brain, kidney, heart and liver weights, but a marked increase in spleen and ovary weights over controls. An increased incidence of brown pigmented granules was observed in the reticuloendothelial / kupfer cells of the liver and the tubular epithelial cells of the kidneys of animals at 3000 and 10000 ppm. Marrow hypercellularity of the sternum was most prominent at 10000 ppm and albuminous degeneration of central lobular hepatocytes was slightly increased at 1000 ppm and above. Suburothelial focal mineralization was observed in treated females. F1 pup survival indices were marginally decreased at 10000 ppm between days 4 - 21 and F1 and F2 pup weights at 10000 ppm were markedly reduced by day 21 post partum. In F2 weanlings the brain weight at 10000 ppm was increased and spleen weights were decreased. Gross post mortem of F1 pups revealed an increased incidence of dark red spleens at 3000 and 10000 ppm. The NOEL for pup development was 1000 ppm based on altered spleen appearance at the next highest dose. The NOEL for adults was 1000 ppm (approximately 70 mg/kg bw/day) based on decreased body weight gains, increased relative brain, heart, spleen and liver weights, and altered liver and kidney histology at higher doses.

## Developmental Studies

Rats were treated with chlorpropham as a 40.2% mixture with a carrying agent (Hi-Sil 233) at doses of 40, 400 and 2000 mg/kg bw/day (of chlorpropham) by gastric intubation for 14 days from day 6 to 19 post coitum. Clinical observations of toxicity were confined to the 400 and 2000 mg/kg/day dose groups and included matting and staining of the urogenital fur, pale extremities and ears, and red material on the facial area. At 2000 mg/kg, body weight gains were markedly reduced, relative liver weights were significantly increased, and spleen weights were increased by 270% of control. A significant increase in spleen weights was also observed at 400 mg/kg bw/day. Chlorpropham at 2000 mg/kg bw/day caused total litter loss in 10 females and reduced the mean number of viable foetuses and the mean foetal weight. The incidence of malformations at 2000 mg/kg was substantially greater than in concurrent and historical controls due to an increased incidence of bent ribs, bent limb bones (a rare abnormality), and unossified pubis. The NOEL for maternal toxicity was 40 mg/kg bw/day based on increased spleen weights and altered spleen appearance at the next highest dose. The NOEL for foetal development was 400 mg/kg bw/day based on increased early resorptions, decreased pup viability and body weight gain and an increased incidence of foetal skeletal malformations at higher doses.

Rabbits were administered chlorpropham on days 6 to 18 post coitum, by intragastric tube at levels of; 125, 250 and 500 mg/kg bw/day. No mortalities occurred. Cold ears were observed in most animals at 200 and 500 mg/kg bw/day, with anorexia and reduced faecal output observed in some animals at 500 mg/kg bw/day towards the end of the study period. A dose related decrease in body weight gains was observed across all treatment groups during the first two days of treatment but persisted beyond this only in the group treated at 500 mg/kg bw/day. Two females aborted at 500 mg/kg/day and mean litter size was smaller at both 250 and 500 mg/kg bw/day. Pre and post implantation losses were elevated at 250 mg/kg bw/day and post implantation loss at 500 mg/kg bw/day. Foetal development, as indicated by the incidence of malformation, was unaffected by chlorpropham administration. The NOEL for maternal and embryo toxicity was 125 mg/kg bw/day.

## Genotoxicity Studies

Chlorpropham gave negative results in a mutagenicity assay in *Salmonella typhimurium* with or without S9 metabolic activation. In mouse fibroblasts, chlorpropham caused disappearance of cytoplasmic microtubules and disorientation of microfilament bundles. In human lymphocytes, chlorpropham reduced the rate of mitosis *in vitro*.

Chlorpropham was said not to induce mutations in *Salmonella typhimurium* strain TA1535, TA1537, TA1538, TA98, TA100 with or without S9 microsomal activation. This paper, however, was inadequate to fully test the mutagenicity of chlorpropham in this system.

In a chromosomal aberration study in Chinese hamster ovary cells a weakly positive result was obtained in cultures with metabolic activation, at toxic concentrations causing severe cell cycle delay (120 & 140 μg/ml). Results in replicate cultures were not consistently positive over repeated assays. At slightly higher concentrations (160 μg/ml) chlorpropham caused complete cytotoxicity.

In a cell transformation study in Syrian hamster embryo cells chlorpropham induced a stable morphologically transformed phenotype at 70 μg/ml and above in 24 hour exposure studies and at 20 μg/ml and above in 7 day exposure studies. The relative plating efficiency was reduced to below 80% in the 24 hour exposure study at 85 ug/ml and above, and in the seven day exposure study at 30 ug/ml, reflecting chlorpropham cytotoxicity.

**Other Studies**

Chlorpropham is shown to inhibit cell proliferation in animal tumour cell lines, L1210 and EL-4 at dose levels of approximately $10^{-5}$M. The inhibition was unrelated to inhibition of DNA protein synthesis.

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