NRA Special Review of

Vinclozolin

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by the

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Executive Summary

Vinclozolin is a non-systemic fungicide of the dicarboximide group, registered for both pre- and post-harvest use on fruits, vegetables and ornamental plants to control *Botrytis spp., Sclerotinia spp., Monilia fruiticola* and *Gloeosporium .5'pp.*

Two products containing vinclozolin, BASF Ronilan Fungicide and BASF Ronilan 500 FL Fungicide, the associated label approvals and the approval of the active constituent vinclozolin have been the subject of a special review by the National Registration Authority, following notification by the registrant of regulatory concerns in Germany and the evaluation of associated data by Australian authorities.

The occupational health and safety component of the review took into account the toxicological findings regarding the active constituent vinclozolin and occupational exposure information pertinent to the use of BASF Ronilan Fungicide and BASF Ronilan 500 FL Fungicide.

German authorities have determined that vinclozolin has teratogenic potential and have subsequently imposed label risk phrases to reflect these findings. United Kingdom (UK) authorities have placed restrictions on vinclozolin product labels while Finland has banned its use. Following a review of vinclozolin, New Zealand authorities propose to place all vinclozolin preparations in Schedule 3 (New Zealand *Toxic Substances Act* 1979) and impose label warning statements. The US EPA and French authorities are currently known to be conducting a review of the toxicology of vinclozolin.

In August 1995, the registrant withdrew both products containing vinclozolin from sale in Australia under a voluntary suspension of sales notice, which was monitored by the Compliance Section of the NRA. The registration of one product (BASF Ronilan Fungicide) was not renewed for the period 1 July 1996 to 30 June 1997, by non-payment of the annual renewal fee, while the second product (BASF Ronilan 500 FL Fungicide) continued to be registered.

Several batches of supplementary data were submitted by the registrant during 1992, 1993, 1994 and also in September 1995, covering toxicokinetic, acute, subchronic, chronic, developmental and reproductive toxicity and human exposure studies. The Commonwealth Department of Health and Family Services and Worksafe Australia evaluated this data and identified concerns over adverse effects in the chronic, developmental and reproductive studies and potential exposure to users. The National Drugs and Poisons Schedule Committee (NDPSC) of the Australian Health Ministers' Advisory Council (AHMAC) recommended that vinclozolin be placed in Schedule 6 of the Standard for Uniform Scheduling of Drugs and Poisons (SUSDP) and prescribed Warning Statement 46 of Appendix F. The Advisory Committee on Pesticides and Health (ACPH) recommended the withdrawal of uses of vinclozolin with the greatest potential for public exposure, specifically those involving pre-harvest treatment of produce for post-harvest fungicidal activity.

The NRA advised the registrant of these concerns in January 1996 and commenced negotiations with the company to address the various risk factors identified. At various stages throughout the review, the NRA made available the reports of toxicology and occupational health and safety assessments to enable the registrant to address concerns raised in these reports.

During the review, the registrant provided several responses that have been taken into account by the NRA and/or the agencies which provide expert advice to the NRA. Following consideration of additional information put forward by the registrant, Worksafe Australia has confirmed that the registration of currently registered vinclozolin formulations is not supported due to unacceptable predicted levels of occupational exposure. Similarly, the Department of Health and Family Services has advised that the toxicological findings previously communicated to the registrant remain valid and the requirement remains for vinclozolin product labels to carry warning Statement 46, Appendix F of SUSDP.

State regulatory authorities were notified of the formal reconsideration of vinclozolin in January 1996 and provided information on the toxicological concerns raised. Advice was obtained from the States on the implications for agricultural production in the event of a possible withdrawal of vinclozolin products. The States have advised the NRA of the existence of suitable chemical alternatives for all label uses with the exception of uses in certain vegetables (the control of *Sclerotinia* rot in carrots, cabbage and cauliflower). Most States supported the withdrawal of vinclozolin from use while none specifically opposed its withdrawal.

Following its reconsideration of vinclozolin products, the NRA has determined that the approved labels for current products containing vinclozolin no longer adequately reflect the potential risks associated with the use of these products.

Accordingly, the following recommendations have resulted from the special review of vinclozolin and relate to currently registered products containing this chemical:

- Pursuant to section 41(3) of the AgVet Code, the NRA has decided to cancel the registration of the product BASF Ronilan FL Fungicide and the approval of the associated product label, effective from 31 December 1996.

- The registration of another product containing vinclozolin, BASF Ronilan Fungicide and the approval of the associated label ended on 30 June 1996 when the registrant voluntarily did not renew the registration. The NRA has accepted and acknowledged the ending of registration of BASF Ronilan Fungicide and will no longer be prepared to renew the application for this product.

- As no products containing vinclozolin remain registered, the NRA will also take action to have all vinclozolin Maximum Residue Level entries deleted from the MRL Standard with effect from 31 March 1997, though consideration will be given to maintaining temporary MRLs, for certain commodities, to accommodate possible trade in these commodities.

PART ONE

MAIN REPORT

1. Introduction

Vinclozolin is a non-systemic fungicide of the dicarboximide group, registered for both pre- and post-harvest use on fruits, vegetables and turf to control *Botrytis spp., Sclerotinia spp., Monilia fruiticola* and *Gloeosporium spp.*

Two products containing vinclozolin, BASF Ronilan Fungicide and BASF Ronilan 500 FL Fungicide, have been the subject of a special review by the NRA, following notification by the registrant of regulatory concerns in Germany and the evaluation of the associated data by Australian authorities.

This report consists of two parts. Part One provides a record of the review, including a chronological account of the notification/consultation process and a summary of key recommendations, while Part Two, entitled "Assessment Reports", provides technical details of the assessment of toxicology and occupational health and safety, under the NRA's special review of vinclozolin.

2. Reasons for and Scope of the Review

The NRA evaluation of data on vinclozolin submitted under section 161 of the AgVet Codes raised concerns relating to teratogenicity, adverse reproductive effects and potential exposure to users. Given the toxicology and worker exposure concerns raised, the NRA was concerned that the use of the chemical might:

- be an undue hazard to the people exposed to these products during handling; or
- be likely to have an effect that is harmful to humans.

Accordingly, the NRA reconsidered under Division 4, Part 2 of the AgVet Code, its approval of vinclozolin, the registration of all products containing vinclozolin registered for use in Australia and the approval of the associated product labels.

3. Notification of Review

In September 1995, the NRA Board was informed that the registrant, BASF Australia Limited, had provided additional toxicological data on vinclozolin to the NRA for urgent assessment, following regulatory concerns in Germany. Formal notification about the special review of vinclozolin was given to the product registrant and the States in January 1996. This followed advice from the then Department of Health and Human Services and Worksafe Australia regarding the toxicology and occupational health and safety assessment, respectively, of vinclozolin.

The States were notified of the formal reconsideration of vinclozolin and provided information on the toxicological concerns raised. Advice was solicited from the States on the implications for agricultural production in the event of a possible withdrawal of vinclozolin or products containing vinclozolin.

In providing such advice to the NRA, the State authorities consulted with representatives of the user groups in their respective jurisdictions, either directly or through their regional networks. The NRA also liaised with the registrant to ensure the chemical distribution/reseller network and end-users were kept informed of the review progress.

4. Regulatory Action Overseas

German authorities have determined that vinclozolin has teratogenic potential and have subsequently imposed risk phrases to reflect these findings. Vinclozolin carries risk phrase R43 *(may cause sensitisation by skin contact).* The additional risk phrases imposed by the German authorities are:

R40: *possible risk of irreversible effects*
R62: *possible risk of impaired fertility*
R63: *possible risk of harm to unborn child*

The registrant submitted that from September 1995 only a dry formulation in water-soluble sachets was to be marketed in Germany. UK authorities have placed certain restrictions on vinclozolin product labels while Finland has banned the use of vinclozolin. Following a review of vinclozolin, New Zealand authorities have proposed to place all vinclozolin preparations in Schedule 3 (New Zealand *Toxic Substances Act 1979)* and impose the following Director General of Health warning statement on the label:

> WARNING: This product contains vinclozolin which causes birth defects in certain laboratory animals. Women of child bearing age should avoid contact with vinclozolin.

The US EPA and French authorities are currently conducting a review of the toxicology of vinclozolin.

5. Regulatory Status in Australia

The only registrant of products containing vinclozolin is BASF Australia Pty Limited which, at the time of commencement of review, had the following products registered:

BASF Ronilan 500 FL Fungicide (30519)
BASF Ronilan Fungicide (30520)

In August 1995, the registrant suspended sales of the two registered products in Australia under a voluntary suspension of sales notice. This suspension of sales was monitored by the Compliance Section of the NRA.

The registrant did not renew registration of one product (BASF Ronilan Fungicide) for the period 1 July 1996 to 30 June 1997, by non-payment of the annual renewal fee, whilst the other product BASF Ronilan 500 FL Fungicide continued to be registered.

Under section 161 of the AgVet Code, several batches of supplementary data were submitted by the registrant during 1992, 1993, 1994 and also in September 1995 covering toxicokinetic, acute, subchronic, chronic, developmental and reproductive toxicity and

human exposure studies. These studies were evaluated by the NRA and the Commonwealth Department of Health and Family Services and Worksafe Australia.

6. Evaluation of Public Submissions

In the course of the review, the NRA took into consideration any submissions received from interested members of the public or organisations. While no specific requests for submissions from the public or industry organisations were made during the review, the NRA received a submission from the Victorian Farmers Federation. This submission discussed the importance of continued availability of vinclozolin and other fungicides of the dicarboximide group. According to the submission, vinclozolin products were widely used by vegetable growers and orchardists growing pome fruit in the Goulburn Valley Region of Victoria.

7. Evaluation of Data

The Commonwealth Department of Health and Family Services and Worksafe Australia, having evaluated the supplementary data on vinclozolin, identified concerns over adverse effects in the chronic, developmental and reproductive studies and potential exposure to users. The National Drugs and Poisons Schedule Committee (NDPSC) of the Australian Health Ministers' Advisory Council (AHMAC) recommended that vinclozolin be placed in Schedule 6 of the Standard for Uniform Scheduling of Drugs and Poisons (SUSDP) and prescribed the following Warning Statement 46 of Appendix F, because of the potential of vinclozolin for teratogenicity and adverse reproductive effects.

> WARNING: This product contains vinclozolin which causes birth defects in laboratory animals. Women of child-bearing age should avoid contact with vinclozolin.

The NDPSC recommended at that time that all uses where operator exposure could not be prevented be phased out. The ACPH recommended that the acceptable daily intake for vinclozolin be reduced to 0.01 mg/kg/day based upon the no-observableeffect-level (NOEL) of 1.4 mg/kg/day observed in the two-year chronic rat study and using a 100 fold safety factor. Worksafe Australia recommended that none of the uses on the currently registered product labels were acceptable due to unacceptable predicted occupational exposure levels for these formulations when considered against the NOEL for chronic toxicity and teratogenic effects.

8. Responses from State Departments of Agriculture

The States were notified of the adverse toxicological findings resulting from the review of additional toxicological data and their advice was sought on the implications of a possible withdrawal of the currently registered vinclozolin products from their jurisdictions.

They were also notified of the voluntary suspension by the registrant of all sales of products containing vinclozolin since August 1995.

The States advised the NRA of the existence of suitable chemical alternatives for all label uses with the exception of uses in certain vegetables (the control of *Sclerotinia* rot in carrots, cabbage and cauliflower). Most States supported the withdrawal of vinclozolin products from use while none specifically opposed their withdrawal.

Queensland, Victoria and South Australia indicated that there were uses of vinclozolin for which no registered chemical alternatives exist. The control of *Sclerotinia* rot in carrots, cabbage and cauliflower were cases in point.

Victorian authorities further commented that restrictions on use in vegetables would not impact greatly on commercial production adding, however, that they anticipated a major impact on bean and lettuce production. Vinclozolin was used widely for *Botrytis* control in grapes in Southern Victoria, where its removal would affect group rotational resistance avoidance programs. Notably, on the same use, South Australia commented that in grapes resistance to the dicarboximide group of fungicides is present in many areas of that State and alternative material is being developed for release.

Tasmanian authorities advised that vinclozolin was widely used in that State; however, suitable chemical alternatives existed if it were to be removed from the market.

The Northern Territory and Western Australia advised that the agricultural production in their States would not be significantly affected by a withdrawal of vinclozolin.

NSW authorities advised that, provided a seven-day re-entry period for grapevines is not applied to other dicarboximide fungicides registered for *Botrytis* control, no implications would result for agriculture in that State.

9. Assessment of Data/Responses from Registrant

The initial toxicology assessment report in November 1995 (Attachment 1) concluded that vinclozolin was a teratogen and an anti-androgen and is able to exert chronic toxicological effects at relatively low doses. *In vitro* evidence pointed to adverse reproductive effects. The National Drugs and Poisons Schedule Committee (NDPSC) recommended that vinclozolin be placed in Schedule 6 of the Standard of Uniform Scheduling of Drugs and Poisons on the basis of chronic, developmental and reproductive adverse effects.

The data submitted by the registrant in 1995 included human exposure and percutaneous absorption studies. This information, in conjunction with exposure modelling using the UK Predictive Operator Exposure Model (POEM), was assessed by Worksafe Australia. The full report of this assessment is at Attachment II. Worksafe Australia concluded that post-harvest dip uses of vinclozolin are not supported due a lack of exposure data or models to enable a risk assessment and given the toxicology finding that vinclozolin is teratogenic. All other uses of the assessed formulations were not supported due to unacceptable margins of worker exposure (the margin between predicted exposure and NOEL in animal studies).

The registrant was notified of the adverse toxicological findings initially in October 1995 and again in January 1996. On the latter, the registrant was formally notified of the

special review of vinclozolin and provided with the toxicological assessment (Attachment 1) and Occupational Health and Safety assessment (Attachment II).

The registrant provided a response in February 1996 seeking further information and clarification on matters raised in the letter of notification and the attached toxicology and occupational exposure assessment reports. This information was provided and a subsequent meeting was held between the NRA, the advising agencies and registrant company personnel, resulting in further data and arguments being provided for assessment. The assessment of this material by the Department of Health and Family Services and Worksafe Australia resulted in the supplementary Toxicology Evaluation Report, September 1996 (Attachment III) and the Addendum to Occupational Health and Safety Assessment, August 1996 (Attachment IV), respectively.

The Toxicology Assessment Report, September 1996 (Attachment III) essentially confirmed that the previous conclusions regarding the toxicology profile of vinclozolin and no changes were recommended to the NOEL, ADI, poisons schedule or other labelling restrictions. The OH&S assessment addendum (Attachment IV) reported the evaluation of percutaneous absorption studies and the registrant's extrapolations on percutaneous absorption of vinclozolin, together with POEM calculations of operator exposure and estimations of risk. In this report, Worksafe Australia concluded that the currently registered liquid formulations of vinclozolin are unacceptable, while extrapolations using a product in water soluble packaging (not currently registered in Australia) have indicated acceptable levels of occupational exposure for use in horticulture and grapes under specified use patterns/rates, application methods and personal protective equipment.

The registrant provided a further response on 29 October 1996, raising issues of user and accidental exposure to vinclozolin and regarding the selection of time end points for dermal resorption rates. This material was considered by Worksafe Australia, which advised the NRA that their original conclusions in relation to vinclozolin reported to the registrant in January and February 1996 and subsequently in September 1996, remained applicable.

10. Collaborative Measures during Review

Throughout the review, the NRA liaised closely with the registrant to clarify issues relating to the toxicological and worker exposure concerns. There was also close cooperation with the registrant in a number of other areas:

- to ascertain the level of possible on-farm stocks and stocks held by the commercial distribution networks;
- to ensure that no sales of vinclozolin containing products were being made; and
- ensure that any industry/end-user groups using vinclozolin products were adequately informed of the need to minimise occupational exposure.

In terms of vinclozolin product stocks, the NRA obtained assurances from the registrant that industry groups and end users were kept informed of the status of vinclozolin at all times during the review. In November 1995, the registrant recalled any remaining stocks of the wettable powder formulation (BASF Ronilan Fungicide) from the market. Remaining stocks of suspension concentrate formulation (BASF Ronilan 500 FL Fungicide) were also recalled under a product buy-back arrangement. End-users with possible on-farm stocks were warned through media releases and a targeted mail campaign via the resellers, that special protective clothing was to be worn at all times when handling, mixing and using vinclozolin.

With regard to sales and supply, the NRA Compliance Section monitored the marketplace to ensure no sales of vinclozolin products were taking place.

11. Outcomes of Review/ Recommendations

Following its reconsideration of vinclozolin products the NRA has determined that the approved labels for current products containing vinclozolin no longer adequately reflect the potential risks associated with the use of these products.

As a result of the review of vinclozolin, involving its evaluation of the toxicological and worker exposure concerns, the NRA has therefore decided:

- to cancel, pursuant to section 41(3) of the AgVet Code, the registration of BASF Ronilan 500 FL Fungicide and the approval of the associated product label, effective from 31 December 1996;

- to not renew the application for BASF Ronilan Fungicide whose registration approval and associated label ended on 30 June 1996, when the registrant voluntarily did not renew the registration;

- to take action to have all vinclozolin MRL entries deleted from the MRL Standard with effect from 31 March 1997. However, consideration will be given to maintaining temporary MRLs for certain commodities to accommodate trade in these commodities; and

- to publish a notice to this effect in the December 1996 edition of the NRA Gazette.

The NRA is prepared to consider applications for certain future uses of vinclozolin, where adequate margins of occupational and public safety can be established through the use of appropriate formulations, handling and packaging technologies and product labelling.