Re-evaluation Decision RVD2018-06

Sodium Omadine and Its Associated End-use Product

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Re-evaluation Decision

Under the authority of the *Pest Control Products Act*, all registered pesticides must be regularly re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental safety standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports and other regulatory agencies. The PMRA applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

Sodium omadine is an antimicrobial active ingredient registered in Canada for use in the preservation of aqueous synthetic fibre lubricants (spin finishes); aqueous based metalworking, cutting, cooling and lubrication fluids and fluid concentrates; gypsum wallboards; and "in-can" and "dry film" preservation of latex emulsions used in adhesives, caulks, patching compounds, sealants, paints and grouts. The uses for preservation of aqueous synthetic fibre lubricants (spin finishes) and "dry film" preservation of latex emulsions are no longer supported by the registrant. Therefore, these uses were not included in the current risk assessment and will be removed from the end-use product label. The uses for "in-can" preservation of latex emulsions used in adhesives, caulks, patching compounds, sealants, paints and grouts were also not included in the current risk assessment. As noted in Re-evaluation Note REV2018-02, *Approach for the Re-Evaluation of Pesticides Used as Preservatives in Paints, Coatings and Related Uses*, the PMRA plans to assess paints, coatings and related uses of sodium omadine separately and publish a proposed re-evaluation document for these uses in the future.

There are three products containing sodium omadine currently registered in Canada under the authority of the *Pest Control Products Act*, including two technical grade active ingredient products and one commercial class end-use product. Currently registered products containing sodium omadine are listed in Appendix I.

This document presents the final regulatory decision[1] for the re-evaluation of sodium omadine, including the required risk mitigation measures to protect human health and the environment for all uses included in the current re-evaluation (uses for preservation of metalworking, cutting, cooling and lubrication fluids and fluid concentrates and gypsum wallboard). All products containing sodium omadine that are registered in Canada are subject to this re-evaluation decision. This re-evaluation decision has undergone a 90-day consultation period on the Proposed Re-evaluation Decision PRVD2016-12, *Sodium Omadine*,[2] which ended on 22 June 2016.

The PMRA received comments relating to the toxicology assessment. They are summarized in Appendix II, along with the responses by the PMRA. The comments did not result in a change to the toxicology assessment. Therefore, this decision is consistent with the proposed re-evaluation

1 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

2 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act.*

decision stated in PRVD2016-12. Comments relating to the occupational risk assessment for the paint use and value of sodium omadine to the paint industry were also received. These comments will be addressed in the proposed re-evaluation decision document for paints, coatings and related uses of sodium omadine to be published in the future. A reference list of data used as the basis for the proposed re-evaluation decision is included in PRVD2016-12. Further data used in the re-evaluation decision, including data received during the consultation period, are listed in Appendix IV.

Outcome of Science Evaluation

Sodium omadine is the only active ingredient currently registered to prevent mould and mildew growth in gypsum wallboard installed in areas of high humidity. Several active ingredients or combinations of active ingredients are registered for the preservation of metal-working fluids and latex emulsions; however, sodium omadine provides an additional option for formulators who are concerned by the use of potential skin sensitizers in the manufacture of their products.
With respect to human health, exposure from the uses for preservation of metalworking, cutting, cooling and lubrication fluids and fluid concentrates and gypsum wallboard is unlikely to affect human health when used according to the revised label directions.

Material preservative uses of sodium omadine are unlikely to result in unacceptable risk to the environment, as environmental exposure is expected to be limited. However, advisory label statements to minimize surface water contamination are required to be included on the end-use product label in order to meet current labelling standards.

Regulatory Decision for Sodium Omadine

The PMRA has completed the re-evaluation of uses of sodium omadine for preservation of metalworking, cutting, cooling and lubrication fluids and fluid concentrates and gypsum wallboard. The following regulatory decision is applicable to the uses of sodium omadine included in the current re-evaluation. Under the authority of the *Pest Control Products Act*, the PMRA has determined that continued registration of products containing sodium omadine is acceptable. An evaluation of available scientific information found that uses of sodium omadine products meet current standards for protection of human health and the environment when used according to the conditions of registration, which include required amendments to label directions. Label amendments, as summarized below and listed in Appendix III, are required for all technical and end-use products. No additional data are requested.

Risk Mitigation Measures

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health and the environment and must be followed by law.

Human Health

- Additional personal protective equipment to protect workers in industrial/manufacturing settings.

Environment

- Standard environmental hazard and advisory label statements.

Next Steps

To comply with this decision, the required mitigation measures must be implemented on all products labels sold by registrants no later than 24 months after the publication date of this decision document. Appendix I lists the products containing sodium omadine that are registered under the authority of the *Pest Control Products Act*.

Other Information

Any person may file a notice of objection[3] regarding this decision on sodium omadine within 60 days from the date of publication of this Re-evaluation Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of the Canada.ca website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

[3] As per subsection 35(1) of the *Pest Control Products Act*

Appendix I Registered Sodium Omadine Products in Canada[1]

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee (w/w)
24098	Commercial	Arch Chemicals Inc.	Sodium Omadine 40% Aqueous Solution Industrial Fungicide & Bactericide	solution	40.5%
29714	Technical	Arch Chemicals Inc.	Sodium Omadine 40% Technical	solution	40.5%
32939	Technical	Troy Chemical Corporation	Pyrithione 40 MUP	liquid	40.3%

[1] as of 8 January 2018, excluding discontinued products or products with a submission for discontinuation

Appendix II Comments and Responses

In response to the consultation document PRVD2016-12, *Sodium omadine*, the following comments were received:

1.0 Comments Related to the Health Risk Assessment

1.1 Toxicology

The PMRA received comments from one of the registrants containing a rationale and supporting documents relating to interpretation of developmental effects, a pre-publication paper concerning an oral physiological based pharmacokinetic (PBPK) model in rats and an evaluation of a developmental toxicity study. The comments and the PMRA responses are summarized based on common scientific themes.

1.1.1 Comment – Reduction of interspecies uncertainty factor based on a physiological based pharmacokinetic (PBPK) model has been developed for zinc pyrithione (ZnPT) and validated with human data.

The registrant submitted a pre-publication scientific paper describing an oral PBPK model for ZnPT. The published version of the paper was independently accessed by the PMRA. It is the registrant's position that the ZnPT PBPK model results suggest that the exposure scenarios represented in the human studies would result in an internal dose well below the internal dose no observed adverse effects level (NOAEL) estimated in the rat. Pyrithione is the active component of the pyrithione moiety; thus, the data for ZnPT is a suitable surrogate for sodium pyrithione (NaPT, or sodium omadine) and may be used to fill some of the gaps that existed at the time of the PMRA's original review. The metabolism of pyrithione salts have been studied in multiple species including rat, rabbit, monkey, dog and swine, and shown to produce the same metabolites. The pyrithione metabolite is more slowly cleared, becoming the primary plasma metabolite observed 16 to 24 h following dosing. This metabolite, 2-methylsulfonylpyridine or 2-MSP, is cleared more slowly because it is not readily metabolized further and lipophilic. 2-MSP accounts for a minor portion of the dose administered. Its presence is proportional to exposure. Infusion studies demonstrated that when 2-MSP was administered for 10 days at doses sufficient to maintain serum levels in excess of those that would have occurred with repeated oral administration of ZnPT, treated rats failed to develop hind limb paralysis, or any other signs of significant toxicity.

It is the registrant's position that there is no evidence that metabolites formed following oral administration of pyrithione salts, such as, ZnPT or NaPT, are responsible for the toxicological effects, supporting the fact that the pyrithione moiety is responsible for any observed toxicity. Therefore, based on the PBPK data for the pyrithiones as well as additional data from different salts/chelates of pyrithione, the interspecies uncertainty factor of 10 could and should be removed.

PMRA Response

The oral PBPK model for ZnPT in rats presents a select summary of data along with supplementary data including model equations; however, the full dataset, including individual animal data, supporting the model were not submitted to the PMRA for examination. Additionally, an available dermal PBPK model noted was also not submitted.

While the PBPK approach has some merit in considering a potential reduction of the 10-fold interspecies uncertainty factor, the submitted study, by itself, is not sufficient to support a reduction of this factor as it does not include all the relevant information that would be required for regulatory decision making purposes. For example, while the study cites older metabolism data, thereby suggesting a potential for a common metabolic pathway for all pyrithiones in a number of species, including humans, the underlying data to support this information was not included with the response. The published study also provides no discussion of allometric scaling to humans.

Notwithstanding the above, the authors of the article also acknowledge that the model is not yet ready for use in reducing or addressing interspecies extrapolation factors given that such refinement requires an in depth understanding of the pharmacokinetics in both species. This includes interspecies differences in physiology, pharmacokinetics including absorption, distribution, and elimination, as well as pharmacodynamics, as these are all parameters that may yield different internal dose response relationships in the two species.

In summary, while such models can serve as an important first step in constructing a framework that could ultimately be used for interspecies dosimetry extrapolation to support refinements in human risk assessment, the information provided to the PMRA was determined as not being sufficient to reduce the 10-fold interspecies extrapolation factor.

On the basis of the above, the 10-fold interspecies extrapolation factor applied in the original PMRA risk assessment will be maintained.

1.1.2 Comment - Short- to long-term dermal endpoint for which the dermal developmental toxicity study was selected for risk assessment

1.1.3 Comment – Study selection

1.1.4 Comment – Reduce the retained *Pest Control Products Act* factor from 3× to 1×

The registrant requested revision of the study selected for short- to long-term dermal risk assessment. The registrant stated that the dermal developmental toxicity study in rats was not an appropriate choice of study for this endpoint, because the maximum tolerated dose was exceeded, and the collars used to prevent animals from eating the dermally applied doses were inappropriately used. The comments indicated that because of these limitations, this study should not be used in the risk assessment. Further, the registrant requested that the PMRA reduce the *Pest Control Products Act* factor to 1-fold.

PMRA Response

As noted in PRVD2016-12, serious effects (malformations) were noted in fetuses in the presence of significant maternal toxicity (20% maternal mortality in addition to other effects) in the rat dermal developmental toxicity study. As such, a *Pest Control Products Act* factor of 3-fold was retained for scenarios in which the endpoint from this study was used to establish the point of departure.

In this dermal developmental toxicity study, maternal toxicity, comprising of mortality (5 out of 25 animals) and decreased body weight (27% compared to control), was observed in the high dose of 7 mg/kg bw/day. Fetal effects, such as rib and limb malformation (bending) and variations in ossification of skeletal elements (primary sternum and skull) were also observed in the high dose of 7 mg/kg bw/day. While excessive maternal toxicity was noted in the high dose group, the number of fetuses produced in this dose group was similar to those of the other groups. A developmental and maternal no observed effects level (NOEL) of 3 mg/kg bw/day was established for this study.

The registrant also discussed the results of a dermal developmental toxicity study conducted with ZnPT where no malformations were noted as supportive evidence to exclude the dermal developmental toxicity study from the sodium omadine risk assessment. However, the ZnPT study report was not submitted to the PMRA with the comments for evaluation and, thus, cannot be considered at this time.

A recently submitted gavage developmental toxicity study in rats established a developmental NOAEL of 1 mg/kg bw/day. The developmental lowest observed adverse effects level (LOAEL) was set at 2 mg/kg bw/day based on increased number of smaller pups and a decrease in mean litter weight. A maternal LOAEL of 2 mg/kg bw/day, based on decreased body weight gain was established. The maternal NOAEL was set at 1 mg/kg bw/day. The results of this study were considered supportive of the dermal rat developmental study currently used for risk assessment.

With respect to the dermal exposure scenarios, the new study does not alter the selection of the dermal developmental toxicity study for risk assessment. Although the maternal and developmental NOAEL values determined in the new orally dosed developmental toxicity study (1 mg/kg bw/day), appear to be lower than the currently selected NOAEL identified in the dermally dosed developmental toxicity study (3 mg/kg bw/day), after consideration of dermal absorption, the same NOAEL value is established. These studies can be considered co-critical for this exposure scenario, however, the dermally dosed study is route specific and is therefore the more appropriate study for risk assessment.

The PMRA does not agree that the use of collars generated significant limitation in the interpretation of the study findings because all study groups, control and exposed, wore the collars. Therefore, all animals are expected to have been similarly affected.

In summary, while limitations were noted in the rat dermal developmental toxicity study, no revision to the short- to long-term dermal endpoint selection or the *Pest Control Products Act* factor, was considered necessary. The developmental toxicity study summary with ZnPT submitted with the comments to the PRVD was not sufficient for evaluation and therefore did not affect the current endpoint selection.

Appendix III Label Amendments for the End-Use Product Containing Sodium Omadine

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the label statements provided below.

I) The following uses of sodium omadine are no longer supported by the registrant, and must be removed from the end-use product label:

aqueous synthetic fibre lubricants (spin finishes)

"dry film" preservation of latex emulsions used in paints, adhesives, caulks, grouts, patching compounds, and sealants

II) The following statement must be included in a section entitled **PRECAUTIONS**:

Wear chemical-resistant coveralls over a long-sleeved shirt and long pants, socks and chemical-resistant shoes, protective eyewear (goggles or a face shield), and chemical-resistant gloves during mixing/loading/application via open pour, clean up, maintenance, and repair. Chemical-resistant coveralls are not required for workers applying the product via a closed mixing/loading system.

III) The following statements must be included in a section entitled **DIRECTIONS FOR USE**:

DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

DO NOT discharge effluents containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans, and other waters unless the effluent has been detoxified by suitable means.

IV) The following statements must be included in a section entitled **ENVIRONMENTAL HAZARDS**:

TOXIC to aquatic organisms.

Appendix IV References considered following the publication of PRVD2016-12, *Sodium omadine*

A. Studies/Information Submitted by Registrant

Human and Animal Health

PMRA Document Number	Reference
1231771	Teratology study in rats (397-017), DACO: 4.5.2
2802833	2016. PMRA Sodium Omadine Risk Assessment: Lonza Response, DACO: 0.8.24
2772555	2005. Percutaneous Developmental Toxicity Study of Zinc Pyridinethione (ZPT) in Rats, DACO: 4.5.2
2344322	2002. Natrium Pyrion - Oral Prenatal Developmental Toxicity Study in Rats, DACO: 4.5.2
2802832	2016. Diamond, G., Skoulis, N.P., Jeffcoat, A.R., Nash, J.F. Physiological-based pharmacokinetic model for the broad spectrum antimicrobial zinc pyrithione: I. Development and verification. Journal of Toxicology and Environmental Health A. Accepted Manuscript. DACO: 4.5.2
2802831	2007. Carney, E. W. & Kimmel, C. A. Interpretation of skeletal variations for human risk assessment: Delayed ossification and wavy ribs. Birth Defects Research Part B - Developmental and Reproductive Toxicology, 80, 473-496. DACO: 4.5.3
2802830	1984. Rodwell, D.E., Johnson, D.E., Wedgig, J.H. Teratogenic Evaluation of Sodium Omadine Administered Topically to Rats. Paper No. 337. Society of Toxicology. Atlanta, GA. DACO: 4.5.2

B. Additional Information Considered

i) Published Information

Human and Animal Health

PMRA Document Number	Reference
2832011	2017. Diamond, Gary L. et al. A physiologically based pharmacokinetic model for the broad-spectrum antimicrobial zinc pyrithione:I. Development and verification - Journal of Toxicology and Environmental Health, Part A, Volume 80, Number 2, Pages 69 to 90, DACO: 4.8
2832035	2017. Online supplementary data. Diamond, G., Skoulis, N.P., Jeffcoat A.R., Nash, J.F. A physiological-based pharmacokinetic model for the broadspectrum antimicrobial zinc pyrithione: I. Development and verification. Journal of Toxicology and Environmental Health A. 80:2, pgs 69-90. DACO: 4.8
2831996	2014. European Commission. Scientific Committee on Consumer Safety. Opinion on zinc pyrithione. COLIPA number P81, adopted at its 2nd plenary meeting of June 18, 2013. SCCS/1512/13 Revision of 18 June 2014. DACO: 4.8