Re-evaluation Decision RVD2012-03

Nabam

(publié aussi en français)

20 April 2012

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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Canada

ISSN: 1925-1017 (print)
1925-1025 (online)

Catalogue number: H113-28/2012-3E (print version)
H113-28/2012-3E-PDF (PDF version)

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Re-evaluation Decision for Nabam

After a re-evaluation of the biocide nabam, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is granting continued registration of products containing nabam for sale and use in Canada.

An evaluation of available scientific information found that under the revised conditions of use, products containing nabam have value and do not present unacceptable risks to human health or to the environment. As a condition of continued registration of nabam, new risk reduction measures must be included on the labels of all nabam products and additional data are required under section 12 of the *Pest Control Products Act*.

The re-evaluation of nabam was first presented in the Proposed Re-evaluation Decision PRVD2011-03, *Nabam*, a consultation document.[1] This Re-evaluation Decision[2] describes this stage of the PMRA's regulatory process for the re-evaluation of nabam and as well, summarizes the Agency's decision and the reasons for it.

Since publication of the Proposed Re-evaluation Decision, the use of nabam as a preservative for hydrocarbon fuels and lubricants to prevent microbial growth has been discontinued at the request of the registrant. Comments received during the consultation process were taken into consideration. These comments, however, did not result in substantial changes to the proposed regulatory decision as described in the Proposed Re-evaluation Decision. Appendix I summarizes the comments received and provides the PMRA's response.

This decision is consistent with the proposed re-evaluation decision stated in PRVD2011-03. To comply with this decision, registrants of products containing nabam will be informed of the specific requirements affecting their product registrations.

What Does Health Canada Consider When Making a Re-evaluation Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[3] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration. The Act also requires that products have value[4] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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

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

3 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

4 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact".

To reach its decisions, the PMRA applies hazard and risk assessment methods as well as policies that are rigorous and modern. These methods consider the unique characteristics of sensitive subpopulations in both humans (for example, children) and organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What is Nabam?

Nabam (disodium ethylenebis(dithiocarbamate)) is a broad spectrum biocide based on dithiocarbamate. It is registered to control a wide range of slime-forming microorganisms such as bacteria and fungi that cause problems in the process fluids in a number of industries. Nabam is generally applied either continuously or as a slug dose into a part of the process waters where there is uniform mixing. It is specifically registered as a slime-control agent for use in air washers, cooling towers, evaporative condensers, pulp and paper mills, and in oil field operations where it is used in drilling fluids, and secondary and tertiary petroleum recovery. The use of nabam as a preservative for hydrocarbon fuels and lubricants to prevent microbial growth has now been discontinued at the request of the registrant.

Health Considerations

Can Approved Uses of Nabam Affect Human Health?

Additional risk reduction measures are required on nabam labels. Nabam is unlikely to affect human health when used according to the revised label directions.

Potential exposure to nabam may occur through handling during use in an industrial setting. When assessing health risks, two key factors are considered: the levels at which no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when products are used according to the label directions.

Nabam was of low acute oral and inhalation toxicity in rats and of low dermal toxicity in rabbits. It was non-irritating to the eyes and skin of rabbits and was not a skin sensitizer in guinea pigs.

Overall, study results indicate that thyroid toxicity and developmental effects are the primary toxicological endpoints of concern following exposure to nabam. When nabam was administered to pregnant rabbits, an increase in the incidence of head malformations was observed at a dose not toxic to the mothers. When exposed via the dermal route, decreased serum thyroxine was observed at a very high dose in female rats. Due to the nature of these endpoints and their potential implications on the health of the fetus, additional uncertainty factors were applied during the risk assessment to further reduce the allowable level of worker exposure to nabam. Ethylene thiourea (ETU) is a metabolite of nabam. ETU has been shown to cause thyroid cancer in both mice and rats and liver cancer in female mice. The mutagenic test data on nabam yielded both positive and negative results, therefore, nabam's genotoxic potential is considered equivocal.

The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Occupational Risks from Handling Nabam

Nabam is unlikely to affect human health when used according to the revised label directions, primarily the use of modern, enclosed systems for handling the product, and use of personal protective equipment for handlers and other workers in industrial facilities.

Workers can be exposed to nabam and its ETU metabolite/degradate through mixing, loading or applying the pesticide in industrial settings. Postapplication exposure also might occur from handling treated process fluid or material. Exposure would occur primarily through the dermal route although it is also possible through inhalation.

Exposure estimates for mixer/loaders and applicators do not reach the target margin of exposure (MOE) for occupational scenarios. However, there is a degree of uncertainty with the exposure estimates due to limitations in the study on which they are based. Exposure is expected to be very low when using modern, enclosed systems for handling products containing nabam. The registrant is required to submit a study to characterize potential exposure using modern, enclosed systems, and confirm the assumption of low exposure.

For postapplication workers, no data are currently available to characterize and quantify potential exposure to nabam and ETU from its use in industrial settings (pulp and paper mills, industrial recirculating water, air washers with effective mist eliminators, drilling fluids, secondary and tertiary petroleum recovery). This is considered to be a data gap and additional data is required from the registrant to assess this exposure potential. Label directions for use of personal protective equipment are required until adequate data are available to conduct a quantitative risk assessment for postapplication workers.

Potential exposure for postapplication workers, as well as consumers, may also occur from handling paper or paperboard containing nabam. The concentration of nabam and ETU in paper and paperboard is expected to be low, thus exposure is expected to be negligible. However, in the absence of adequate data to demonstrate that exposure is negligible, both postapplication workers and consumers handling treated paper products have potential for exposure to nabam and ETU. Data are required to characterize exposure potential.

The potential for bystander exposure is considered to be negligible during use in industrial process fluids (for example, pulp and paper mills, cooling towers, etc.) as these uses are limited to industrial settings.

The registrant will be required to conduct new occupational studies to fully characterize and quantify potential exposure to nabam and ETU from its use in all industrial settings as noted above. In the meantime, users of nabam products will be required to wear additional personal protective equipment (PPE) and use closed mixing and loading systems to minimize exposure.

Environmental Considerations

What Happens When Nabam Is Introduced into the Environment?

Nabam is unlikely to affect non-target organisms when used according to the revised label directions.

Nabam is used as an antimicrobial in industrial process fluids, therefore, the potential for nabam to enter the environment is limited. Laboratory studies indicate that nabam will transform very rapidly in aquatic systems primarily due to hydrolysis, aerobic and anaerobic aquatic biotransformation. The transformation products are also generally not persistent in the aquatic environment. Although nabam is very soluble in water, it hydrolyzes quickly, so leaching to groundwater is not a concern. It is unlikely that nabam will volatilize from soil or water surfaces.

Ethylene thiourea (ETU) is a transformation product of nabam and could be a risk to terrestrial mammals. However, due to the currently registered use pattern of nabam, ETU will not be a concern in the environment.

Laboratory data on toxicity of nabam and ETU to bees, birds, mammals and aquatic organisms were evaluated. However, a risk assessment was not necessary because environmental exposure is expected to be negligible based on the current use pattern.

Value Considerations

What Is the Value of Nabam?

Nabam contributes to the control of slime formation in a variety of industrial process fluids.

Nabam is an antimicrobial active ingredient that acts to reduce the number of viable microorganisms within industrial process fluids. It is used in a wide range of industrial applications including airwashers, cooling towers, paper mills, oil field waterflooding and drilling fluids. It is important that these industrial process fluid sites have a number of different active ingredients available, as occasionally changing the biocide regime plays an important role in preventing the development of resistant biofilm.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk reduction measures to protect human and environmental health. These directions must be followed by law. As a result of the re-evaluation of nabam, the following additional risk reduction measures are required (See also Appendix V).

Human Health

- To protect mixer/loader/applicators using commercial products: additional personal protective equipment and closed mixing and loading systems for all solutions (dry coupling) are required.
- To protect postapplication workers in industrial settings: additional personal protective equipment are required.

Environment

- As nabam is toxic to some aquatic species, precautionary label statements are required.

What Additional Scientific Information is Being Requested?

Data are required as a condition of continued registration under Section 12 of the *Pest Control Products Act*. The registrants of this active ingredient must provide these data (See Appendix IV) or an acceptable scientific rationale to the PMRA within the timeline specified in the decision letter.

Other Information

The relevant test data on which the decision is based are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

Any person may file a notice of objection5 regarding this decision on nabam 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 Health Canada's website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

5 As per subsection 35(1) of the *Pest Control Products Act.*

Appendix I Comments and Responses

1.0 Comment related to Nabam being a Potential Skin Sensitizer

The registrant disagrees with the PMRA conclusion that nabam is a potential skin sensitizer. The registrant noted that according to the submitted 1986 GLP study, *Dermal Sensitization Study in Guinea Pigs*, nabam was not considered to be a skin sensitizer in guinea pigs. The PMRA conclusion was based on the US EPA RED and is proposing a statement, "Potential skin sensitizer", on product labels, whereas, the EPA did not require any such label statement.

PMRA Response

The study in question is a 1986 sensitization study. Although the study showed negative results, the PMRA classified nabam as a skin sensitizer based on the EPA RED (1996). The EPA based their label comments on open literature and human case reports. However, since EPA did not ultimately require this statement on the labels, it is no longer required by the PMRA.

2.0 Comment related to Exposure from Food

The registrant questioned the PMRA recommendation that nabam product labels include specific prohibition against the use of nabam-treated materials for food packaging.

PMRA Response

The registrant has since provided the clearance for "food contact" use from the Food Directorate of Health Canada. The Food Directorate found nabam technical product to be acceptable, from a food safety standpoint, for use in specified food packaging applications. Therefore, the PMRA does not require the label statement that prohibits the use of nabam-treated products for food packaging.

3.0 Comments on Additional Data Requirements

3.1 Comment

The technical registrant commented on the PMRA's requirement of further use description (DACO 5.2) and additional occupational exposure data (DACO 5.4/5.5 and DACO 5.6/5.7/5.9) for industrial scenarios.

The registrant stated that they do not have access to the information on activities associated with industrial processes of their customers and suggested that this information should be requested directly from the industry.

PMRA Response

As specified under Section 19 of the *Pest Control Products Act*, the burden is on the registrant to provide this information. Registrants can submit the information directly or can arrange and ensure that studies are generated and provided to PMRA in coordination with industry. Furthermore, the data required are consistent with internationally accepted protocols and guidelines required for the evaluation and risk assessment of pest control products. As such, under Section 12 of the *Pest Control Products Act*, additional information is being requested to allow continued registration of nabam.

The required studies must be representative of the scenario in which the pest control product is used, and do not necessarily need to be conducted under actual use conditions. Additionally, as noted in the PRVD2011-03, the PMRA would consider alternative data that would address these requirements, such as migration data proposed by the registrant. The registrant is encouraged to consult the PMRA on possible ways to address the data requirements (see also response to Comment 3.2).

3.2 Comment

The technical registrant stated that studies being conducted by the *American Chemistry Council Biocides Panel's Antimicrobial Exposure Assessment Task Force II (AEATF II)* should be sufficient to satisfy Canadian risk assessment needs.

The registrant indicated that a study entitled: *Exposure and Risk Assessment for Applicators of Nabam Containing Microbiocides* was submitted to the PMRA for consideration but it was not included in the list of studies that were considered during the re-evaluation. The registrant suggested that this study should be reviewed.

PMRA Response

The AEATF II is proposing to conduct a study to assess mixer/loader/applicator exposure from the use of liquid formulations of antimicrobials in typical treatment facilities. When completed, this study would address the requirements for a study under DACO 5.4/5.5. The PMRA is not aware of any other studies that the AEATF II is conducting that would address the other data requirements. If the registrant is aware of such studies, they should cite them directly and provide appropriate documentation from the Task Force as a commitment to conduct these studies. The other data requirements are still outstanding and must be submitted by the registrant.

The study entitled *Exposure and Risk Assessment for Applicators of Nabam Containing Microbiocides* was not included in the list of studies that were considered during the re-evaluation because it was submitted after the assessments of nabam were completed and the Proposed Re-evaluation Decision was prepared. The PMRA has now reviewed this study and due to significant limitations, it cannot be used in the assessment of nabam. This study is not appropriate to assess mixer/loader/applicator exposure to nabam. As mentioned above, the study being conducted by the AEATF II would address this data requirement (DACO 5.4/5.5).

3.3 Comment

The registrant indicated that they could provide the PMRA with a residue study which shows that residues of both the dithiocarbamate active ingredient and ethylenethiourea (ETU) in samples of water (including effluent waters from a commercial paper mill and a water cooling tower), paper, pulp, sugar and molasses at various stages of processing were below the detection limits of < 0.1 ppm. The registrant commented that since the residue of both nabam and ETU was below the detection limit of 0.1 ppm, the need for additional exposure data is unnecessary.

PMRA Response

Data under DACO 5.6/5.7/5.9 were requested to characterize the exposure potential from handling treated paper and paperboard. The PMRA recognizes that the concentrations of nabam and ETU in paper and paperboard are low, and thus, potential exposure to consumer and postapplication worker is expected to be low. However, in the absence of data to demonstrate that exposure is negligible, both post-application workers and consumers handling treated paper products have the potential for exposure to nabam and ETU. Therefore, data are required to characterize exposure potential.

As a result of the registrant's comment above, the PMRA requested and reviewed the cited residue study, *Residue Studies of Dithiocarbamates from a Slimicide Used in the Manufacture of Paper and Sugar and in Water-Cooling Towers*, to potentially assess the exposure to workers and consumers handling paper and paperboard containing nabam and ETU. This study has significant limitations and does not meet current standards for use in exposure and risk assessments.

As such, data as stated in the Proposed Re-evaluation Decision (i.e., DACO 5.6/5.7/5.9 and DACO 5.14) are still required. Potential data that the registrant could submit include migration data, transferable residue data, chemistry data, biological monitoring data, passive dosimetry data or a scientifically based rationale for a data waiver. The registrant is encouraged to consult the PMRA on possible ways to address the data requirements.

Appendix II Products containing Nabam Registered in Canada as of 24 January 2012[a]

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
15934	Commercial	Ashland Canada Corp.	Amerstat 272	Solution	15%
18775			Biosperse 280 Liquid For Control Of Bacteria & Fungi	Solution	15%
18211		Akzo Nobel Surface Chemistry LLC	Aquatreat DNM-30 Industrial Microbiocide	Solution	15%
18211.12		Emerald Foam Control LLC.	KCIDE 800	Solution	15%
20127		Buckman Labs Of Canada Ltd.	Busan 1035 Liquid Microbicide	Solution	15%
18211.15		Kemira Chemicals, Inc.	Fennosan 131-C	Solution	15%
18211.16		Commercial Chemtreat Inc.	Chemical Treatment CL-216	Solution	15%
23182		Dubois Chemicals Canada, Inc.	X-Cell 419 Papermill Slimicide	Solution	15%
23501		Nalco Canada Co.	Nalcon 7614 Pulp & Paper Slimicide	Solution	15%
18960	Technical	Akzo Nobel Surface Chemistry LLC	Aquatreat DNM-30 Manufacturing Concentrate	Solution	30%
18962	Manufacturing Concentrate		Aquatreat DNM-360 Manufacturing Concentrate	Solution	17%

a Excluding discontinued or suspended products, or products with a submission for discontinuation

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Appendix III Uses of Commercial class Products of Nabam Registered in Canada as of 24 January 2012[a]

Site(s)	Pest(s)	Formulation Type	Application Methods and Equipment	Maximum Application Rate (kg a.i./10 000 L fluid)		Application Timing	Minimum Interval Between Applications (days)	Registrant Supported Use?
				Single	Cumulative			
Air washers with effective mist eliminators	Slime-forming organisms	Solution	Pre-clean; dose to any location with good distribution	0.212	Unable to calculate	Once, twice or three times weekly or as required	Not stated	Yes
Cooling towers and evaporative condensers		Solution	Apply to cleaned system					
Paper mills			Continuous feed; dosage will vary depending on conditions	0.15 kg/tonne of paper		As early as possible in the system		
Secondary and tertiary petroleum recovery	Fungi and sulfate-reducing bacteria	Solution	Into the produced water, fresh or salt water or commingled water or the secondary or tertiary oil recovery waterflood systems	0.0551		Not available		
	Heterotropic bacteria			0.794				
Drilling fluids	Fungi and bacteria		To mud hopper or pump suction	2.20				

a Excluding discontinued uses of commercial products of nabam.

Appendix IV Additional Data Requirements for Nabam

The following data are required as a condition of continued registration under Section 12 of the *Pest Control Products Act*. The registrant(s) of technical nabam is required to provide these data or an acceptable scientific rationale within the timelines specified in the decision letter that will be sent by the PMRA.

DACO 5.2 Use Description/Scenario – This includes information which fully describes the use of the product and human activity associated with its use. Specifically, information on the amount of active handled per day, number of days a typical worker is exposed per year, average working lifetime of industrial workers, the typical and maximum volume of material produced at a facility per day (i.e. paper), type of PPE typically worn, and facility engineering controls. Furthermore, information on activities associated with the handling of the treated process fluid or material in industrial settings is required.

DACO 5.4/5.5 Mixer/Loader/Applicator - Passive dosimetry or biological monitoring for workers mixing and transferring products containing nabam in an industrial facility (both open and closed systems). Prior to conducting these studies, it is highly recommended that the registrant confirm the amount of ETU in the formulation and the amount of ETU formed in processing waters of industrial uses (see DACO 5.14). Generic passive dosimetry studies are acceptable. If biological studies are conducted, both nabam and ETU must be measured. The toxicokinetics of the compounds must be well-understood prior to conducting the biological monitoring studies.

DACO 5.6/5.7/5.9 Postapplication - Data are required to characterize exposure potential for consumers and workers handling paper and paperboard containing nabam and ETU. This may include migration data, transferable residue data, chemistry data or a scientifically acceptable rationale.

Postapplication - Data are required to characterize exposure potential for postapplication workers in all industrial sites (for example, pulp and paper mills, industrial recirculating water, air washers with effective mist eliminators, drilling fluids, secondary and tertiary petroleum recovery, etc.). This may include passive dosimetry data or a scientifically acceptable rationale.

DACO 5.14 Other Studies/Data/Reports - A study that quantifies the amount of ETU in nabam formulations and industrial process fluids.

Appendix V Revised Label Amendments for Commercial Class Products Containing Nabam

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. Additional information on labels of currently registered products should not be removed unless it contradicts the label statements below.

The Canadian commercial end-use product labels must be amended to include the following statements to further protect workers and the environment.

I) The following statement must be included on the **PRIMARY PANEL** of the label.

For use with closed loading and transfer systems only (i.e. dry coupling).

II) 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 effluent containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans or other waters.

Wear protective eyewear (goggles or face shield), chemical-resistant coveralls over long-sleeved shirt, long pants, and chemical-resistant gloves and footwear when handling the concentrate and contacting treated process fluids.

III) The following statement must be included in a section entitled **ENVIRONMENTAL HAZARDS**.

TOXIC to aquatic organisms.

Additional References[6]

Studies/Information Provided by the Applicant/Registrant

Studies Considered in the Health Assessment-Exposure

PMRA Document Number: 2066580
References:1988, Exposure and Risk Assessment for Applicators of Nabam-Containing Microbiocides, DACO: 5.1

PMRA Document Number: 2074169References:
Residue Studies of Dithiocarbamates from a Slimicide Used in the Manufacture of Paper and Sugar and in Water-Cooling Towers, DACO: 5.14

[6] These references are in addition to the ones listed in the Proposed Re-evaluation Decision PRVD2011-03, *Nabam*.