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Proposed Re-evaluation Decision PRVD2011-03

Nabam

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Overview

Proposed 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 and Regulations, is proposing continued registration of products containing nabam for sale and use in Canada.

An evaluation of available scientific information found that under the proposed 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 are proposed for the labels of nabam products and additional data are required.

The PMRA's pesticide re-evaluation program considers potential risks as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, *PMRA Re-evaluation Program*, presents the details of the re-evaluation activities and program structure. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information available.

This proposal affects all end-use products containing nabam registered in Canada. Once the final re-evaluation decision is made, registrants will be instructed on how to address any new requirements.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for nabam and presents the reasons for the proposed re-evaluation decision. It also proposes additional risk-reduction measures to further protect human health and the environment.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessment of nabam.

The PMRA will accept written comments on this proposal up to 60 days from the date of publication of this document. Please forward all comments to Publications (see contact information on the cover page of this document).

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

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[2] 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[3] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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 (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.

Before making a final re-evaluation decision on nabam, the PMRA will consider all comments received from the public in response to this consultation document.[4] The PMRA will then publish a Re-evaluation Decision[5] on nabam, which will include the decision, the reasons for it, a summary of comments received on the proposed re-evaluation decision and the PMRA's response to these comments.

For more details on the information presented in this overview, please refer to the Science Evaluation of this consultation document.

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

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

3 "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".

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

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

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. Nabam is also registered as a preservative for hydrocarbon fuels and lubricants to prevent microbial growth.

Health Considerations

Can Approved Uses of Nabam Affect Human Health?

There may be risk concerns due to exposure of nabam and its degradation product and metabolite, ethylenethiourea (ETU) from occupational exposure in industrial uses.

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. 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. When exposed via the dermal route, decreased serum thyroxine was observed at a very high dose in female rats.

A cancer concern exists for nabam based on ethylene thiourea (ETU), a contaminant, metabolite and degradate 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.

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. In the case of nabam, human health risks are of concern and require mitigation.

Occupational Risks from Handling Nabam

Occupational risks are of concern when used according to current label directions.

Exposure estimates 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. The registrant will be required to conduct a new occupational study to fully characterize and quantify this exposure potential. In the interim, users of nabam products will be required to wear additional personal protective equipment (PPE) and use closed mixing and loading systems to minimize exposure.

Additional data is required to characterize potential occupational postapplication exposure risks.

There are no data currently available to characterize postapplication worker exposure to nabam and ETU from its use in pulp and paper mills, industrial cooling water systems, air washers with effective mist eliminators, drilling fluids, secondary and tertiary petroleum recovery, and hydrocarbon fluids. In addition, there is no data to assess exposure to nabam and ETU to postapplication workers handling treated paper products. Additional data is required to assess this exposure potential.

Additional data is required to assess potential exposure to consumers from handling treated paper products.

There is no data available to assess potential exposure to consumers from handling treated paper products. Due to the absence of data demonstrating that this exposure is negligible, additional data is required to assess this exposure potential.

Environmental Considerations

What Happens When Nabam Is Introduced into the Environment?

Environmental exposure to nabam will be limited due to its use pattern. Therefore, nabam does not pose a potential risk to terrestrial and aquatic organisms or the environment.

Nabam is used as an antimicrobial in industrial process fluids and material preservatives, 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 in addition to the preservation of hydrocarbon fuels and lubricants.

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 changing the biocide regime occasionally plays an important role in preventing the development of resistant biofilm. Nabam is also used as a preservative in hydrocarbon fuels, lubricants and hydraulic fluids. While there are many alternative active ingredients registered for use as slimicides, the options for fuel and hydrocarbon fluid preservatives are more restrictive.

Measures to Minimize Risk

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

Risk-reduction measures are being proposed to address potential risks identified in this assessment. These measures, in addition to those already identified on existing nabam product labels, are designed to further protect human health and the environment.

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)
- To protect postapplication workers in industrial settings: additional personal protective equipment
- Prohibit the use of nabam-treated materials for food packaging

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 or an acceptable scientific rationale to the PMRA within the timeline specified in the decision letter.

DACO 5.2	Use Description/Scenario
DACO 5.4/5.5	Mixer/Loader/Applicator - Passive dosimetry or biological monitoring data
DACO 5.6/5.7/5.9	Postapplication - Data to characterize postapplication worker exposure and exposure potential from handling treated paper and paperboard (consumers and workers)
DACO 5.14	Other Studies/Data/Reports - A study that quantifies the amount of ETU in nabam formulations and industrial process fluids

Next Steps

Before making a re-evaluation decision on nabam, Health Canada's Pest Management Regulatory Agency will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision, which will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

Other Information

At the time that the re-evaluation decision is made, the PMRA will publish an Evaluation Report on nabam in the context of this re-evaluation decision (based on the Science Evaluation section of this consultation document). In addition, the test data on which the decision is based will also be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa, Ontario, Canada).

Science Evaluation

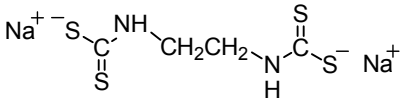
1.0 Introduction

Nabam (disodium ethylenebis(dithiocarbamate)) is a broad spectrum antimicrobial that is based on dithiocarbamate.

Following the re-evaluation announcement for nabam, the registrant of the technical grade active ingredient and primary data provider in Canada, indicated that it intended to provide continued support for all uses included on the label of Commercial Class end-use products. There are no Domestic Class end-use products containing nabam registered in Canada.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active

Common name	nabam
Function	fungicide with protective action, and algicide
Chemical Family	ethylenedithiocarbamate
Chemical name	
1 International Union of Pure and Applied Chemistry (IUPAC)	disodium ethylenebis(dithiocarbamate)
2 Chemical Abstracts Service (CAS)	disodium 1,2-ethanediylbis(carbamodithioate)
CAS Registry Number	142-59-6
Molecular Formula	$C_4H_6N_2Na_2S_4$
Structural Formula	
Molecular Weight	256.3
Purity of the Technical Grade Active Ingredient	30% minimum
Registration Number	18960

Identity of relevant impurities of human health and environmental concern:

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the *Canada Gazette*, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the product.

2.2 Physical and Chemical Properties of the Technical Active Ingredient

Property	Result
Vapour pressure	Negligible
Ultraviolet (UV)/visible spectrum	Not expected to absorb at λ >300 nm
Solubility in water `	200 g/L

Property	Result
n-Octanol–water partition coefficient (Log K_{ow})	Not applicable - Product insoluble in organic solvents
Dissociation constant	Not applicable - No dissociable groups present

2.3 Description of Registered Nabam Uses

Appendix I lists all Nabam products that are registered under the authority of the *Pest Control Products Act*, including one technical grade active ingredient, one manufacturing concentrate and nine Commercial Class end-use products.

Appendix II lists all of the uses for which nabam is presently registered. All uses were supported by the registrant at the time of re-evaluation initiation and were therefore considered in the health and environmental risk assessments of nabam.

Uses of nabam belong to the following use-site categories: industrial process fluids and material preservatives.

3.0 Impact on Human Health and Animal Health

Toxicology studies in laboratory animals describe potential health effects resulting from various levels of exposure to a chemical and identify dose levels at which no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species.

3.1 Toxicological Summary

Nabam is a broad spectrum fungicide of the ethylene bisdithiocarbamate (EBDC) group of pesticides (nabam, maneb, mancozeb, metiram and zineb). Ethylene thiourea (ETU) is a metabolite, degradate and contaminant of the EBDCs. Nabam and other EBDC fungicides are all metabolized to ETU in the body and all degrade to ETU in the environment. The majority of the studies in the nabam database were conducted with an end-use product containing 30% active ingredient, with the remainder being water. The nabam database currently lacks studies characterizing chronic toxicity and oncogenicity, rat reproductive and rat developmental toxicity. Published studies were also available. Overall, study results indicate that thyroid toxicity and developmental effects (hydrocephaly and cleft palate in the rabbit) are the primary toxicological endpoints of concern following exposure to nabam.

Nabam was rapidly absorbed and excreted in rats following oral dosing. Total recovery was 77-84% in urine and 15-26% in feces. The highest levels were in the thyroid, with the primary metabolite being ETU. Although the amount of radioactivity in the thyroid was only

0.001-0.008% of total administered dose, the concentrations in this organ were 10-31 times higher than relative carcass values.

For the purposes of risk assessment, the extent of in vivo metabolic conversion of parent EBDC pesticide to ETU was determined to be 7.5% on a weight basis [USEPA 1989]. This value represents an average value for all EBDC pesticides (mancozeb, metiram, maneb, zineb, nabam). Based on urinary and biliary excretion of ETU in rat metabolism studies, about 20% of an administered EBDC dose is converted to ETU on a molar basis. In order to express the in vivo dose of ETU on a mg/kg basis, a molecular weight correction factor was applied. The molecular weight correction factor, 0.38, was calculated as the ratio of the ETU molecular weight (102 g/mole) and the average of all parent EBDC molecular weights (270 g/mole). Therefore, a 100 mg dose of an EBDC given to a rat would yield an *in vivo* ETU dose of 7.5 mg.

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.

Short-term dermal toxicity in rats identified decreased thyroxine (T4) levels in females at the highest dose tested. In a published drinking water study, dose-related decreases in triiodothyronine (T3) and T4 levels were observed, with no effect on thyroid stimulating hormone (TSH) levels. In a combined short-term oral toxicity and neurotoxicity study, rats exhibited increased absolute and relative thyroid weight, decreased T4 levels, increased TSH levels (males only) and mild hypertrophy of thyroid follicular epithelium (males only). No neurotoxicity was observed.

Two in vivo cytogenetic assays, an Ames assay and an in vitro cell transformation assay were negative. However other in vitro tests, including an unscheduled DNA synthesis assay, a Hypoxanthine-Guanine Phosphoribosyl Transferase (HPRT assay, with activation) and two sister chromatid exchange studies (with and without activation) were positive. Therefore, nabam's genotoxic potential was deemed equivocal.

Chronic and oncogenicity studies were not submitted for nabam. However, since ETU is a common metabolite/contaminant for all EBDCs, longer term studies with ETU were deemed appropriate for use in nabam cancer and non-cancer risk assessments. The National Toxicology Program (NTP) conducted reproductive/chronic/oncogenicity studies in the mouse and rat, combining both perinatal and adult exposures to ETU. Similar to the short-term studies, the thyroid, liver and pituitary were primary targets after exposure to ETU. Although the weight-of-evidence suggested that ETU was weakly genotoxic, thyroid tumours in both the mouse and rat had a clear mode and mechanism of action. ETU inhibits thyroid peroxidase, leading to chronic thyroid hormone deficiency (decreased T_4). This in turn stimulates the hypothalamus and pituitary, causing the production of more thyroid stimulating hormone (TSH). This hormonal imbalance leads to thyroid growth, hyperplasia and subsequent follicular cell neoplasia. Frequently, pituitary gland neoplasia also occurs, which was evident with ETU exposure in the mouse. Similar to the short-term studies, the mouse was more sensitive to liver effects than the rat in long-term studies. In the NTP study, mice exhibited an increase in liver adenomas and carcinomas, showing a clear dose-response in females. These adenomas/carcinomas occurred at comparable or lower doses than the thyroid and pituitary tumours. Since there is no current

evidence supporting a threshold for induction of liver tumours, a cancer unit risk (Q_1^*) of 0.0601 (mg/kg bw/day)$^{-1}$ based on liver tumours was generated for the cancer risk assessment of ETU and all EBDCs. With respect to non-neoplastic effects, 90-day and 1-year dog studies with ETU, resulted in body weight and blood effects, indicative of hemolytic anemia, which occurred at lower or at the same dose levels causing thyroid toxicity (JMPR, 1993; CalDPR, 2005; EPA, 1996).

Two rabbit developmental toxicity studies with nabam demonstrated pre-natal toxicity and sensitivity of the young. In both studies, hydrocephaly was observed at the lowest dose tested, in the absence of maternal toxicity. In one of the developmental toxicity studies, a dose-related increase in the incidence of soft spot and/or domed cranium was observed in the absence of maternal toxicity, and late resorptions and abortion were observed in the presence of maternal weight loss. In the other rabbit study, increased incidences of cleft palate were observed in the mid- and high-dose groups with decreased weight gain and increased thyroid weight observed in the dams at the high dose only. Thus, in these two studies there is increased concern related to sensitivity of the young, as well as seriousness of the effects, as evidenced by hydrocephaly, domed cranium and cleft palate. Cleft palate in the rabbit is a rare malformation. Since pup malformations occurred at the lowest dose tested, a developmental No Observed Adverse Effect Level (NOAEL) could not be established.

Reproductive and developmental toxicity studies in rats were not available for nabam. However, given the severity of effects observed in the rabbit developmental toxicity studies and the low doses at which these effects occurred, submission of these additional studies would not appreciably impact the risk assessment.

Epidemiology

The registrant did not submit any epidemiological studies for nabam. In addition, a search of published literature did not yield any studies. However, the EBDC maneb (no-longer registered in Canada), is potentially associated with Parkinson's Disease (PD), also referred to as Parkinson's-like Disease or Parkinsonism. Maneb is nabam plus elemental manganese. The neurological effects noted with maneb may also be related to the manganese content. Manganese causes 'manganism', a disease similar to PD. In animal studies, co-administration of maneb and paraquat increased neurological effects in rats (Thiruchelvam et al. 2000, 2002, 2003, 2005; Barlow et al, 2003, Cicchetti et al, 2005, Cory-Slechta et al., 2004, 2005). Costello et al (2009) conducted a case-control study to examine the relationship between PD and residential exposure to paraquat and maneb in California, USA. Combined exposure to maneb and paraquat between 1974 and 1999 was associated with an increased risk of PD (OR=1.75, 95% CI: 1.13, 2.73). However, this increase was mainly attributable to exposures between 1974 and 1989 (OR=2.14, 95% CI: 1.24, 3.68) as exposures between 1990 and1999 were not associated with an increased risk of PD (OR=0.93, 95% CI: 0.45, 1.94). Exposure to paraquat alone was not associated with an increased risk of PD and too few cases were exposed to only maneb to conduct a meaningful analysis. When stratified by age, PD risk was greatest among subjects with disease onset before 60 years of age. The reported findings suggest that combined exposure to paraquat and maneb may increase the risk of PD; however, this combination of exposures is no longer expected as maneb has been withdrawn by the registrant for use in Canada. Currently, epidemiological

evidence does not establish a clear cause and effect relationship between a particular pesticide exposure and PD.

Hazard Identification

3.1.1 PCPA Hazard Consideration

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects. This factor should take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, as well as potential pre- and post-natal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

Since there are only industrial uses for nabam, the PCPA factor is not applicable. It should be noted that the PCPA factor may be applicable in the future, if it is determined that there is exposure to consumers from treated paper. This scenario was not assessed in the current assessment because there is no data to characterize this exposure potential.

3.2 Occupational and Non-Occupational Risk Assessment

Occupational and non-occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects. However, MOEs less than the target MOE require measures to mitigate (reduce) risk.

3.2.1 Toxicology Endpoint Selection for Occupational and Bystander Risk Assessment

3.2.1.1 Dermal and Inhalation Exposure

Nabam (intermediate- to-long-term duration of exposure)
For intermediate-to-long-term dermal and inhalation exposures, a Lowest Observed Adverse Affect Level (LOAEL) of 0.33 mg/kg bw/day from a rabbit developmental toxicity study was selected. At this dose level and greater, an increase in the fetal incidence of hydrocephaly was observed, and occurred in the absence of maternal toxicity. Since worker populations could include pregnant or lactating women, it was necessary to ensure an adequate level of protection for this sub-population. The available 21-day dermal study in rats did not assess the relevant endpoints of concern.
The target margin of exposure (MOE) for these scenarios was 3000, which included uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, 3-fold for use of a LOAEL and 10-fold to account for serious endpoints (cleft palate and hydrocephaly) occurring in the absence of maternal toxicity.

ETU (intermediate- to long-term duration of exposure)

For intermediate-to-long-term dermal and inhalation exposures, a one-year oral dog study was selected. At 1.79 mg/kg bw/day, decreased body weight and increased thyroid weight, hypertrophy and colloid retention were observed. A NOAEL of 0.18 mg/kg bw/day was established. The target MOE is 300. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. An additional 3-fold factor was applied for database deficiencies. The NOAEL established in this one-year dog study is several fold lower than the NOAEL for serious developmental effects observed in the rat after ETU administration and thus, provides inherent protection for worker populations that could include pregnant or lactating women.

3.2.1.2 Cancer Assessment

As discussed above, a Q_1^* of 0.0601 $(mg/kg\ bw/day)^{-1}$ for liver adenomas/carcinomas in a National Toxicology Program study for ETU, was deemed appropriate for assessing nabam's cancer risk.

3.2.1.3 Dermal Absorption

Based on chemical-specific in vivo dermal absorption studies, a dermal absorption factor of 16% and 45% was determined for risk assessment purposes for nabam and ETU, respectively.

3.2.2 Occupational Exposure and Risk Assessment

Workers can be exposed to nabam and ETU through mixing, loading or applying the pesticide in industrial settings. Postapplication exposure might occur from handling treated process fluid or material.

3.2.2.1 Mixer, Loader and Applicator Exposure and Risk Assessment

Exposure to nabam and ETU from its use in industrial settings is expected to be intermittent (a few minutes daily or once a week) over an intermediate to long-term duration (i.e. >30 days to several months), predominately via the dermal route.

There are potential exposures to mixers, loaders, and applicators.

Exposure estimates were based on the American Chemical Manufacturer's Association (CMA), Antimicrobial Exposure Assessment Study. Even though there are a number of limitations associated with the study, it is currently the only occupational study available to assess potential exposure from antimicrobial uses. The study monitored 46 replicates for 6 active ingredients used in 4 different settings for 4 different application methods. Each replicate was representative of the time spent performing the antimicrobial-related task in one day; therefore the data was not normalized. Since application of biocides in industrial processes is similar regardless of the use site (for example, cooling towers, pulp and paper, etc.), it was considered appropriate to combine replicates based on the application method. Due to limitations in the exposure study (low and variable laboratory and field recoveries), the 90^{th} percentiles generated from the input CMA data

were used to estimate potential exposure to operators handling industrial products containing nabam.

The following scenarios were assessed:

- Mixing/transfer of liquids, open pour
- Mixing/transfer of liquids, pump method (i.e. closed mixing and loading)

3.2.2.1.1 Occupational Exposure Non-Cancer Risk Estimates

Occupational risk estimates associated with mixing and transferring products containing nabam in industrial settings is summarized in the following table.

Table 3.2.2.1.1a Occupational Risk Assessment for Industrial Products Containing Nabam

Application Method	Dermal Unit Exposure (mg/kg bw/day)	Dermal Exposure[1] (mg/kg bw/day)	Inhalation Unit Exposure (mg/kg bw/day)	Total Exposure (mg/kg bw/day)	Margin of Exposure[2]
Liquid, Pour	0.1034	0.0165	0.001	0.0175	**19**
Liquid, Pump	0.0268	0.0043	0.0032	0.0075	**44**

Shaded cells indicate that the MOE is less than the target MOE

[1] Calculated using a dermal absorption factor of 16%

[2] Calculated using the oral developmental rabbit LOAEL of 0.33 mg/kg bw/day, target MOE of 3000

There is potential for exposure to ETU from the use of nabam since ETU is present as a contaminant in nabam formulations, and can be formed in the body from the metabolism of nabam. It was assumed that nabam formulations contain 0.5% ETU (US EPA, 1996). To estimate ETU exposure from using nabam formulations, exposure estimates from the CMA study were multiplied by 0.5%. To estimate the amount of ETU that is formed *in vivo* from the metabolism of nabam, a value of 7.5% was used as described in Section 3.1. The amount of ETU formed internally was quantified by multiplying total internal dose of nabam by 7.5%. Total exposure to ETU was calculated by summing all routes of ETU exposure. Occupational risk estimates for ETU are summarized in the table below.

Table 3.2.2.1.1b Occupational Risk Assessment for Industrial Products Containing Nabam: Exposure to ETU

Application Method	Exposure to ETU from Nabam Metabolism (mg/kg bw/day)[1]	Dermal Exposure to ETU (mg/kg bw/day)[2]	Inhalation Exposure to ETU (mg/kg bw/day)[3]	Total Exposure to ETU (mg/kg bw/day)[4]	Margin of Exposure[5]
Liquid, Pour	1.31×10^{-3}	2.33×10^{-4}	5.00×10^{-6}	1.55×10^{-3}	116
Liquid, Pump	5.63×10^{-4}	6.03×10^{-5}	1.60×10^{-5}	6.39×10^{-4}	282

Shaded cells indicate that the MOE is less than the target MOE

1 Calculated using the total exposure values in Table 3.2.2.1.1a and the ETU *in vivo* conversion factor of 7.5%

2 Dermal exposure value from the CMA Antimicrobial Exposure Assessment Study (90th percentile), multiplied by 0.5% to account for the amount of ETU present in nabam products and a dermal absorption factor of 45%

3 Inhalation exposure value from the CMA Antimicrobial Exposure Assessment Study (90th percentile), multiplied by 0.5% to account for the amount of ETU present in nabam products

4 Calculated by summing exposure to ETU from metabolism of nabam, dermal exposure to ETU and inhalation exposure to ETU from its presence as a contaminant in nabam formulations

5 Calculated using the NOAEL of 0.18 mg/kg bw/day from the oral 1-year dog, target MOE of 300

3.2.2.1.2 Occupational Exposure Cancer Risk Estimates

The cancer risk for ETU for occupational workers was determined by calculating the lifetime average daily dose (LADD) from dermal and inhalation exposure. The LADD was then compared to the Q_1^* to obtain cancer risk estimates. Occupational cancer risk is calculated assuming 36 years of exposure (i.e. a career in industrial settings) over a 75-year lifetime. Occupational workers were considered to be exposed from 52 to 156 days per year based on the maximum number of weekly applications being made (1 to 3 times weekly times 52 weeks per year). The product of the expected exposure (LADD) and the cancer potency factor (Q_1^*) estimates the lifetime cancer risk as a probability. A lifetime cancer risk in the range of 1 in 10^{-5} to 1 in 10^{-6} in worker population is generally considered acceptable.

Lifetime cancer risk estimates for ETU associated with mixing/loading and applying nabam is presented in the following table.

Table 3.2.2.1.2 Cancer Exposure and Risk Estimates for ETU from Occupational Exposure to Industrial Products Containing Nabam

Application Method	Absorbed Daily Dose (mg/kg bw/day)[1]	Treatment Frequency (# of Days per Year)	Lifetime Average Daily Dose (mg/kg bw/day)[2]	Cancer Risk[3]
Liquid, Pour	1.55×10^{-3}	52	1.06×10^{-4}	6×10^{-6}
		156	3.18×10^{-4}	2×10^{-5}
Liquid, Pump	6.39×10^{-4}	52	4.37×10^{-5}	2×10^{-6}
		156	1.31×10^{-4}	8×10^{-6}

Shaded cells indicate a cancer risk of greater than 1×10^{-5}

[1] Total exposure to ETU as specified in Table 3.2.2.1.1b

[2] Calculated using the following formula: Lifetime Average Daily Dose (mg/kg bw/day)= (Absorbed Daily Dose (mg/kg bw/day) × Treatment Frequency (days/yr) × Working Duration (36 yrs)) / (365 days/yr × Life Expectancy (75 yrs))

[3] Calculated using a Q* value of 0.0601 $(mg/kg\ bw/day)^{-1}$

Lifetime cancer risk estimates for ETU from mixing and loading nabam using a closed mixing and loading system for liquids are not of concern. Calculated cancer risks are greater than 1×10^{-5} for open mixing and loading of liquids.

Exposure frequency for nabam LADD estimates were based on the maximum number of weekly applications being made each week, every year for 36 years. This is expected to result in a upper bound estimate of exposure. The cancer risk assessment could be refined if additional information on the typical frequency of application was provided.

3.2.2.2 Postapplication Worker Exposure and Risk Assessment

There are no data to characterize potential for postapplication worker exposure and risk from nabam and ETU from its use in pulp and paper mills, industrial cooling water systems, air washers with effective mist eliminators, drilling fluids, secondary and tertiary petroleum recovery, and hydrocarbon fluids. Due to the absence of data to quantify potential exposure, additional data is being requested.

3.2.3.2.2 Bystander and Consumer Exposure

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 concentration of nabam and ETU in paper and paperboard is low, and thus, potential consumer exposure is expected to be low. However, in the absence of data to demonstrate that exposure is negligible, consumers handling treated paper products are considered to have potential for exposure to nabam and ETU. Data are required to characterize exposure potential.

3.4 Exposure From Food and Drinking Water

3.4.1 Concentrations in Drinking Water

Because nabam is only used in industrial process fluids and in material preservatives, the potential environmental exposure will be limited and contamination of water is not expected.

3.4.2 Exposure from Food

The PMRA recommends that nabam product labels include specific prohibition against the use of nabam treated products for food packaging. The proposed label amendments are listed in Appendix VI.

3.5 Incident Reports Related to Human Health

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Incidents are classified into six major categories including effects on humans, effects on domestic animals and packaging failure. Incidents are further classified by severity, in the case of humans for instance, from minor effects such as skin rash, headache, etc., to major effects such as reproductive or developmental effects, life-threatening conditions or death.

The PMRA will examine incident reports and, where there are reasonable grounds to suggest that the health and environmental risks of the pesticide are no longer acceptable, appropriate measures will be taken, ranging from minor label changes to discontinuation of the product.

There were no incident reports available for nabam as of June 25, 2009.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Nabam is very soluble in water. Given the low vapour pressure and as indicated by the Henry's Law Constant, nabam is not likely to volatilize (Table 1, Appendix V). Bioaccumulation is not a concern based on the log octanol water partition coefficient.

When nabam enters the environment it will undergo rapid hydrolysis (complete loss occurs in less than one hour), therefore, hydrolysis is the major abiotic transformation process. The first major hydrolysis product is ethylene bisisocyanate sulfide (EBIS). As EBIS is being formed it also transforms via hydrolysis and photolysis. EBIS is a photolabile species with estimated half-lives in irradiated solutions ranging from 16 to 38 hours at environmentally relevant pHs. Ethylenethiourea (ETU) can form via EBIS and other processes. In general, the formation of ETU increases as a function of time, regardless of the pH of the medium, but the amount formed is higher at pH 9. Both the aerobic and anaerobic aquatic biotransformation studies showed rapid loss of nabam with less than 37 percent of applied radioactivity associated with parent nabam remaining at day 0. This was likely due to hydrolysis. ETU, EBIS and ethyleneurea (EU) are

common transformation products in both the aerobic and anaerobic aquatic transformation studies. There is some indication that loss of ETU is more rapid in aerobic aquatic conditions than anaerobic aquatic conditions. Carbon dioxide is also formed in the aerobic and anaerobic studies.

There were no studies available for biotransformation in soil, leaching or adsorption/desorption or terrestrial dissipation and accumulation studies. Considering its use patterns, these studies are not required by the PMRA. However, if a use expansion is requested in the future these studies may be requested. Environmental fate data for Nabam are summarized in Table 1 of Appendix V.

4.2 Effects on Non-target Organisms

Environmental risk of nabam and ETU is not expected to be a concern. Based on the particular use pattern (industrial process fluids and material preservatives), exposure from nabam and ETU to the environment will be negligible. An assessment of the environmental risk of nabam and ETU to non-target organisms was not considered necessary, in view of the limited exposure.

4.2.1 Effects on Terrestrial Organisms

A summary of the available toxicity data for nabam is presented in Table 2 (Appendix V). The information includes acute toxicity of nabam to honey bees, bobwhite quail and rats. Data on acute dietary toxicity to mallard ducks, bobwhite quail and rats and developmental toxicity in rabbits are also shown in Table 2.

In view of the particular use pattern (industrial process fluids and material preservatives) and the subsequent negligible environmental exposure that is expected, an assessment of the potential risk to terrestrial organisms was not conducted.

4.2.2 Effects on Aquatic Organisms

Available acute toxicity data were evaluated for freshwater invertebrates and fish, estuarine/marine invertebrates and estuarine/marine fish and chronic toxicity to freshwater invertebrates. When frog embryos were exposed to nabam, mortality of frog embryos was not different from the controls, however, structural changes were observed in various tissues and there was no recovery from the effects. A summary of the toxicity data for nabam is presented in Table 2 (Appendix V).

In view of the particular use pattern (industrial process fluids and material preservatives) and the subsequent negligible environmental exposure that is expected, an assessment of the potential risk to aquatic organisms was not conducted.

4.2.3 Incident Reports Related to the Environment

There were no incident reports available for nabam.

4.3 Water Monitoring Data

Nabam was not detected in Canadian or United States of America aquatic systems.

5.0 Value

5.1 Commercial Class Products

Appendix III lists the registered chemical alternatives for the uses of nabam. The PMRA cannot comment on the availability and extent of use of these alternatives.

The PMRA welcomes feedback on the availability and extent of use of the chemical alternatives to nabam listed in Appendix III and further information regarding the availability, effectiveness and extent of use of non-chemical pest management practices for any of the registered uses of nabam. This information will allow the PMRA to refine sustainable pest management options for the listed site-pest combinations.

5.2 Domestic Class Products

There are no registered Domestic Class products containing nabam.

5.3 Value of Nabam

Nabam, when used in accordance with label directions, contributes to the management of slime formation on the surface of pipes and conduits of a number of industries that rely on aqueous-based processing fluids. Slime formation may cause a number of problems including inefficient heat transfer within cooling towers and an increased risk of paper breaks within paper mills. While there are currently several active ingredients already registered for this use, nabam provides an additional alternative biocide chemistry to these industries, in which the intermittent rotation of biocide active ingredients with different modes of action is important in mitigating the formation of resistance to biocides. As a preservative of hydrocarbon fuel, hydraulic fluid, and lubricating oil, nabam is one of a limited number of biocides available in Canada.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*.

During the review process, nabam and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[6] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusion:

- Nabam does not meet Track 1 criteria, and is not considered a Track 1 substance. See Table 6.1 for comparison with Track 1 criteria

- Nabam does not form any transformation products that meet all Track 1 criteria

Table 6.1 Toxic Substances Management Policy Considerations-Comparison to Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Nabam
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	No information
	Water	Half-life ≥ 182 days	No: $t_{1/2}$ <1 hour
	Sediment	Half-life ≥ 365 days	Rapid loss due to hydrolysis
	Air	Half-life ≥ 2 days or evidence of long range transport	Volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (9.45 x10^{-13} mm Hg) and Henry's Law Constant (1.60 x 10^{-18} atm/m^3/mol)
Bioaccumulation[4]	Log K_{ow} ≥ 5		No: -4.24
	BCF ≥5000		not available
	BAF ≥5000		not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

1 All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).

2 The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

3 If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

4 The log K_{ow} and/or BCF and/or BAF are preferred over log K_{ow}.

6 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

6.2 Formulants and Contaminants of Health or Environmental Concern

The use of formulants in registered pest control products identified in the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern maintained in the *Canada Gazette*[7] is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02[8].

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the list in the Canada Gazette. The list is used as described in the PMRA Notice of Intent NOI2005-01[9] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02, and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade nabam does not contain any contaminants of health or environmental concern identified in the Canada Gazette.

7.0 Summary

7.1 Human Health and Safety

While several required studies were absent from the toxicity database for nabam, data from the ETU risk assessment have been used to support the nabam risk assessment. The combined database is considered adequate to define the majority of toxic effects that may result from exposure to nabam. The toxicology database identified the thyroid and developing young as the primary targets of toxicity. A low incidence of hydrocephaly, cleft palate, and cranial anomalies of the fetus were observed following exposure of the pregnant animal to nabam. The chronic and carcinogenic risk for nabam was addressed through its metabolite, ETU (liver tumours in female mice).

Although the toxicology database for nabam was missing chronic/oncogenicity toxicity studies in the mouse and rat, and rat reproduction and developmental toxicity studies, the submission of these studies would not likely better characterize the Lowest Observed Adverse Effect Level (LOAEL) that was established at the lowest dose tested in both rabbit developmental studies

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[7] *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette,* Part II, Volume 142, Number 13, pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

[8] DIR2006-02, PMRA Formulants Policy.

[9] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act*.

(LOAEL of 0.33 mg/kg bw/day), nor would they decrease the total uncertainty factors used in the assessment.

7.1.1 Occupational Risk

Risk estimates associated with applying, mixing, and loading activities for industrial label uses are of concern. Although exposure estimates do not reach the target MOE for occupational scenarios, there is a degree of uncertainty with the exposure estimates due to limitations in the study on which they are based.

There is currently no data available to assess potential postapplication risks; therefore, additional data is required to characterize this exposure potential.

7.1.2 Consumer Risk

There is no data available to assess risk to consumer handling treated paper. Additional data is required to characterize this exposure potential.

7.2 Environmental Risk

The potential for nabam to enter the environment is extremely limited because nabam is only used in locations that will have limited to no environmental exposure. If nabam does enter the environment, it is unlikely that it will volatilize from soil or water surfaces, will not bioaccumulate in organisms and will not leach into groundwater. ETU a transformation product of concern, will also not be of concern given the registered uses of nabam, as the potential for it to enter the environment is extremely limited.

7.3 Value

From a value perspective, nabam is acceptable for continued registration provided the identified risk concerns have been addressed.

8.0 Proposed Regulatory Decision

The PMRA is proposing that nabam is acceptable for continued registration with the implementation of the proposed risk-reduction measures. These measures are required to further protect human health and environment. As a condition of the continued registration, new risk-reduction measures must be included on the labels of nabam products and additional data are required.

The proposed label amendments are listed in Appendix VI.

8.1 Proposed Regulatory Actions

8.1.1 Proposed Regulatory Actions Related to Human Health

Human health risks are of concern and therefore require mitigation. There are concerns associated with applying, mixing and loading activities and there are insufficient data to asses postaplication risks. Therefore, the PMRA is requiring additional risk-reduction measures on nabam labels and additional data to characterize exposure risks.

8.1.1.1 Toxicological Information

The following warning statements should appear on the label of the product: "Potential Skin Sensitizer."

8.1.1.2 Proposed Measures to Protect Mixers/Loaders/Applicators and Workers Re entering Treated Areas

Engineering Controls and Personal Protective Equipment
Statements must be amended (or added) to include the following directions to the appropriate labels in order to mitigate the risk of exposure to nabam:

"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."

In addition, all solutions must be used in a closed mix/load system. A closed mix/load system is defined as a procedure for removing a pesticide from its original container, rinsing the emptied container and transferring the pesticide and rinse solution through connecting hoses, pipes and coupling that are sufficiently tight to prevent exposure of any person to the pesticide or rinse solution. Furthermore, the closed mix/load system must be equipped with a dry coupling system that is designed to drip less than 2 mL per coupling.

The 'closed system' must have the following attributes:

- Remove the pesticide from the original container;
- Rinse the container;
- Transfer the pesticide to the industrial system;
- Be made of materials appropriate for use with pesticides and a pressurized system;
- Have gauges protected against breakage;
- Adequately measure the pesticide used;
- Have shut-off valves to prevent chemical from spilling when the hose is disconnected;
- Drip less than 2 mL per coupling (dry coupling).

The following label language must appear on all labels containing nabam formulated as a solution:

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

8.1.2 Proposed Regulatory Action Related to Environment

To avoid any potential exposure to the aquatic environment, precautionary label statements are required. Environmental mitigation statements are listed in Appendix VI.

8.1.3 Proposed Regulatory Action Related to Value

No regulatory actions are proposed from the standpoint of value.

8.2 Additional Data Requirements

The following studies are required under section 12 of the *Pest Control Products Act*:

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 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 or workers handling paper and paperboard containing nabam and ETU. This may include migration data, transferable residue data, chemistry data or a scientifically acceptable rationale.

DACO 5.6/5.7/5.9	Postapplication - Data are required to characterize exposure potential for postapplication workers in all industrial sites (e.g. pulp and paper mills, industrial recirculating water, air washers with effective mist eliminators, drilling fluids, secondary and tertiary petroleum recovery, hydrocarbon fluids, 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 is required.

List of Abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
AHAS	acetohydroxyacid synthase
ALS	acetolactate synthase
AR	applied radioactivity
ARfD	acute reference dose
ASAE	American Society of Agricultural Engineers
atm	atmospheres
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
bw	body weight
CEPA	Canadian Environmental Protection Act
CFIA	Canadian Food Inspection Agency
cm	centimetre(s)
d	day(s)
DEEM®	Dietary Exposure Evaluation Model
DER	Data Evaluation Report
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
DT_{50}	dissipation time to 50% (the dose required to observe a 50% decline in the test population)
DWLOC	drinking water level of comparison
EBDC	ethylenebisdithiocarbamate
EC_{25}	exposure concentration to 25% (a concentration causing 25% adverse effects in the test population
EC_{50}	exposure concentration to 50% (a concentration causing 50% adverse effects in the test population
EChE	erythrocyte cholinesterase
EDE	estimated daily exposure
EEC	expected environmental concentration
EP	end use product
ETU	ethylene thiourea
EPA	Environmental Protection Agency (US)
EXAMS	Exposure Analysis Modeling System
F_0	parental animals
F_1	first filial generation
g	gram(s)
GAP	good agricultural practice
GC-FPD	Gas Chromatography-Flame Photometric Detector
GC-MSD	Gas Chromatography-Mass Selective detector
GC-NPD	Gas Chromatography-Nitrogen Phosphorous Detector
h	hour(s)
ha	hectare(s)
Hg	mercury
IRED	Interim Reregistration Eligibility Decision (USEPA Document)

K_d	adsorption coefficient
kg	kilogram(s)
K_{oc}	organic carbon partition coefficient
K_{ow}	*n*-octanol−water partition coefficient
L	litre(s)
LC_{50}	lethal concentration 50%
LD	lethal dose 50%
LOEC	lowest observed effect concentration
mg	milligram
NOEC	no observable effective concentration
NOEL	no observed effective concentration
PMRA	Pest Management Regulatory Agency
TSMP	Toxic Substances Management Policy
EU	ethyleneurea
EBIS	ethylenebis(isothiocyanate)sulphide
USEPA	United States Environmental Protection Agency
VP	vapour pressure

Appendix I Products containing nabam registered in Canada as of July 22, 2010[1]

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%
16391		BASF Canada Inc.	Irgacide Pt 934	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%
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%

[1] Excluding discontinued or suspended products, or products with a submission for discontinuation.

Appendix II Uses of Commercial class products of nabam registered in Canada as of July 22, 2010[1]

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				
Hydrocarbon fluids	Fungi and bacteria	Solution	None listed	0.0388				

[1] Excluding discontinued or suspended products, or products with a submission for discontinuation.

Appendix III Commercial Class Alternatives to Nabam

Site	Pest	Alternative Registered Active Ingredients[1,2]	Use of Nabam supported by registrant?
Air washers	Slime-forming organisms	BCD, BRN, DDH, DDM, GLT, ISL, IST, POD	Yes
Cooling towers		AAD, BCD, BND, BRN, DCD, DDH, DDM, DUW, ISL, IST, KDD, KMC, MBC, POD, PVK, QAC, QDO, SBR, SDD, TCM, TUC	
Paper mills		AAD, BCD, BIS, BND, BRN, BRS, DCD, DDH, DDM, GLT, ISL, IST, KDD, KMC, MBC, PVK, QAC, QAL, QDM, SBR, SCH, SDD, TCM	
Secondary and tertiary petroleum recovery	Fungi, heterotropic bacteria and sulfate-reducing bacteria	AAD, DCD, GLT, KMC, TUC	
Drilling fluids	Fungi and bacteria	AAB, AAD, GLT, ISL, IST, KDD	
Hydrocarbon fluids		BIO, BND, ISL, IST, MGR, SDD	

[1] List of active ingredients: AAB = n-alkyl-1,3 propanediamine monobenzoate; AAD = n-alkyl-1,3 propanediamine acetate; AAM = 1-alkyl-1,3-aminopropane; BCD = 1-bromo-3-chloro-5,5-dimethylhydantoin; BIO = 2,2-oxybis(4,4,6-trimethyl-1,3,2-dioxaborinane); BIS = 1,4-bis(bromoacetoxy)-2-butene; BND = 2-bromo-2-nitropropane-1,3-diol; BRN = 2,2-dibromo-3-nitrilopropionamide; BRS = b-bromo-b-nitrostyrene; DCD = disodium cyanodithioimidocarbonate; DDH = 1,3-dichloro-5,5-dimethylhydantoin; DDM = 1,3-dichloro-5-ethyl-5 methylhydantoin; DUW = dodecylguanidine hydrochloride; GLT = 1,3-propanedialdehyde; ISL = 2-methyl-4-isothiazolin-3-one; IST = 5-chloro-2-methyl-4-isothiazolin-3-one; KDD = potassium dimethyldithiocarbamate; KMC = potassium n-methyldithiocarbamate; MBC = methylene bis(thiocyanate); MGR = 2,2'-(1-methyltrimethylenedioxy)bis-(4-methyl-1,3,2-dioxaborinane); POD = poly[oxyethylene(dimethyliminio) ethylene (dimethyliminio)ethylene dichloride]; PVK = 4-chloro-3-methylphenol (sodium salt); QAC = n-alkyl (40% C12, 50% C14, 10% C16) dimethyl benzyl ammonium chloride; QAL = n-alkyl (5% C12, 60% C14, 30% C16, 5% C18) dimethyl benzyl ammonium chloride; QDM = dialkyl (5% C12, 60% C14, 30% C16, 5% C18) methyl benzyl ammonium chloride; QDO = oxydiethylene bis(alkyl dimethyl ammonium chloride); SBR = sodium bromide; SCH = sodium chlorite; SDD = sodium dimethyldithiocarbamate; TCM = 2-(thiocyanomethylthio) benzothiazole; TUC = 2-(hydroxymethyl)-2-nitro-1,3-propanediol

[2] This is a list of registered options only as of February 05, 2009. Health Canada does not endorse any of the options listed. The registration status of active ingredients under re-evaluation may change pending the final regulatory decision. For additional information consult the PMRA publication websites at: http://www.hc-sc.gc.ca/cps-spc/pest/part/consultations/index-eng.php or http://www.hc-sc.gc.ca/cps-spc/pest/part/consultations/index-fra.php.

Appendix IV Toxicology Assessment for Nabam

Table 1 Toxicology Endpoints for Health Risk Assessment for Nabam

EXPOSURE SCENARIO	ENDPOINT	STUDY	DOSE (mg/kg bw/day)	MOE[1]
Occupational M/L/A[2] Intermediate- and Long-Term Dermal[3] and Inhalation [4] **Nabam**	Fetal malformations	Rabbit developmental toxicity	0.33 LOAEL	3000
Occupational M/L/A Long Term Dermal and Inhalation **ETU**	Bodyweight and thyroid effects	One-year dog toxicity	0.18 NOAEL	300
Cancer Risk	Q_1* of 0.0601 $(mg/kg\ bw/day)^{-1}$	Based on incidences of liver tumors in a combined chronic/carcinogenicity/reproduction study		

1 MOE refers to target MOE for occupational assessments
2 M/L/A refers to mixer/loader/applicator
3 Since an oral NOAEL was selected, a dermal absorption factor of 16% and 45% was used in a route-to-route extrapolation for nabam and ETU, respectively.
4 Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation for both nabam and ETU.

Table 2 Toxicology Profile for Nabam

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise specified.

Study/Species #/group	Dose Levels/Purity	NOAEL (mg/kg bw/d)	Effects / Results
METABOLISM / TOXICOKINETICS - Nabam			
Metabolism study-Rat (males and females) PMRA # 1580918	- A single iv dose of 4.5 mg of [^{14}C]-labelled nabam -A single oral dose of 4.5 mg or 100 mg of [^{14}C]-labelled nabam - 4.5 mg unlabelled nabam/kg/day for 2 weeks, and 4.5 mg labelled nabam/kg on day 15. Purity: 97%		Rapidly absorbed and excreted, via oral and iv administration. iv dose: 80% recovered in urine within 4 hours, most fecal recovery occurred at 12-24 hours. Total recovery was 91-92% in urine and 6-7% in feces. single oral low dose: total recovery in urine (at 7 days) was 77% for males and 84% for females. Recovery in feces was 26% for males and 15% for females. 2-wk unlabelled low dose, followed by labelled dose: total recovery in urine 71-75%, in feces 21 and 16%, male and female respectively. Single oral high dose: recovery in urine was 57-66% and in feces 53% (males) and 44% (females). Considerably more variation than seen in other treatment groups. Although the amount of radioactivity in thyroid was only 0.001% to 0.008% of the total administered dose, the concentrations were high (10 - 31 times) relative to carcass values.

Study/Species #/group	Dose Levels/Purity	NOAEL (mg/kg bw/d)	Effects / Results
		Ethylene thiuorea (ETU), was present in urine (11.7 to 36.6% of total ^{14}C present in urine, with the highest percentage occurring at the 100 mg/kg dose level). No ETU was detected in the faeces of iv dose group; but 65.3% of the ^{14}C in the faeces of 100 mg/kg oral dose was ETU in ♂ and 47.5% in ♀.	
Published Study (in vitro) on the mechanism of nabam and zineb-induced inhibition of the hepatic microsomal monooxygenases in the male rat. (1985) PMRA # 1791827	Nabam 2.5 x10(-3) M without NADPH 2.5 x 10(-4) M with 0.5 mM of NADPH Zineb 2.5 x10(-3) M without NADPH 2.5 x 10(-4) M with 0.5 mM of NADPH	In the absence and presence of NADPH, nabam decreased aniline hydroxylase, aminopyrine N-demethylase, cytochrome P-450 and increased cytochrome P-420. Zineb also decreased aniline hydroxylase and aminopyrine N-demthylase, but to a lesser extent than nabam. Zineb also increased cytochrome P-420 to a lesser extent and had no effect on cytochrome P-450. The study also examined what the effect of reduced glutathione, cysteine and dithiothreitol had on nabam and zineb and similarly, nabam affected the enzymes to a greater extent than zineb.	
ACUTE TOXICITY - 30% Nabam in aqueous solution			
Oral toxicity- Rat Sprague Dawley PMRA # 1580886	0, 1617, 2310, 3300 mg/kg bw Purity: 30% a.i 70% water	LD_{50} = 1.4 g/kg bw Low toxicity	
Dermal toxicity - Rabbit albino PMRA # 1580884	2000 mg/kg bw Purity: 30% a.i 70% water	LD_{50} > 2000 mg/kg bw Low toxicity	
Inhalation toxicity- Rat Sprague Dawley PMRA # 1744701	nominal concentration of 3.26 mg/L actual 2.19/L Purity: 30%	LC_{50} > 2.0 g/kg bw Low Inhalation Toxicity Supplemental	
Dermal irritation - Rabbit NZW PMRA # 1744701	0.5 mL Purity: 30% a.i 70% water	Non-irritating	
Eye irritation - Rabbit NZW PMRA # 1580911	0.1 mL Purity: 30% a.i 70% water	Non-irritating	
Dermal sensitization-	Purity: 30% a.i		

Study/Species #/group	Dose Levels/Purity	NOAEL (mg/kg bw/d)	Effects / Results
Human PMRA # 1744701	70% water	Potential skin sensitizer	
SHORT-TERM TOXICITY - Aquatreat DN-30			
21-day dermal (5 day/week)- SD rat; 5 sex/dose PMRA # 1580919	0, 46, 457, 1523, 3050 mg/kg [0, 15, 150, 500, 1000 mg ai/kg/day] Purity: 30% a.i 70% water	Systemic NOAEL ♀: 500 mg/kg bw/d ♂: 1000 mg/kg bw/d NOAEL for Dermal Effects 15 mg/kg bw/d	≥150 mg/kg bw/d: Slight to moderate erythrema at treatment sites @ 1000 mg/kg bw/d:↓ serum T4 (♀)
Combined sub-chronic neurotoxicity study and 90-day oral study- SD rat 10/sex/dose gavage PMRA # 1580879	0, 0.08, 0.8, 80, 260 mg/kg bw/d 0, 0.025, 0.25, 2.49, 24.9, 80.86mg ai/kg bw/d Purity: 31.1% a.i 69% water	Sub-chronic neurotoxicity NOAEL 80.86 mg/kg bw/d Sub-chronic oral NOAEL 2.49 mg/kg bw/d	Sub-chronic neurotoxicity study No changes in FOB or locomotor evaluations, brain weights or peripheral/central nervous system tissues were observed Sub-chronic toxicity study ≥ 24.9 mg/kg bw/d: ↑abs and rel thyroid wt (♀); ↓ T4 @ 80.86 mg/kg bw/d: ↑abs and rel thyroid wt; ↓ T_4; ↑ TSH (♂); thyroid enlargement (♂); mild hypertrophy of thyroid follicular epithelium in 3/10 ♂.
28 day Rat, Wistar (♂) 6/dose drinking water Published Study PMRA # 1791824	ETU: 0, 11, 18, 23 mg/kg bw/d Nabam: 8.4 - 30.5 mg/kg bw/d Purity: 98%	Testing for thyroid gland toxicity and function only, potential Nabam LOAEL of 8.4 mg/kg bw/d	ETU: In a dose-related manner: ↓ T_4 and T_3, ↑ TSH, ultrastructural changes of the thyroid were observed (↑ myelin bodies, dilation of rough endoplasmic reticulum, vacuolization in the epithelial cells). Nabam: dose-related ↓ T_4 and T_3, no effect on basal TSH.

Study/Species #/group	Dose Levels/Purity	NOAEL (mg/kg bw/d)	Effects / Results
28 day Rat, Wistar (♂) 6/dose drinking water Published Study PMRA # 1791825	ETU: 0, 11, 18, 23 mg/kg bw/d Nabam: 0, 50, 100 or 200 mg/L. Purity: 98%	testing for kidney effects only, Nabam had no effect on kidney (NOAEL of 200 mg/L, HDT)	Nabam had no effect on the kidney. Comparatively, the kidney, unlike the thyroid, is not highly sensitive to ETU. @ 23 mg/kg bw/d: ETU: ↑ clear ultrastructural changes in epithelium of renal proximal tubule, # lysosomes and myelin figures, as well as vacuolization and edema in epithelial cells of proximal tubules.
90-day Dog study, oral gelatin capsule 4/sex/dose Aquatreat DN-30 PMRA # 1580913	0, 0.3, 0.6, 1.2 mg/kg bw/d (5 days a week) 0, 0.09, 0.18, 0.36 mg ai/kg bw/d] Purity 30% 70% water vehicle: distilled water	Potential NOAEL of 0.36 mg/kg bw/day Supplemental	≥0.09 mg/kg bw/d: all treated females had increase in mean % monocytes. ≥0.18 mg/kg bw/d: decreased bwg wk 2-12 - males [control gained 2.5 kg, low dose 2.75 kg, mid-dose 0.80 kg and high dose 0.43 kg]. However, the mean starting wts of the animals varied greatly with the control and low dose group mean of 8 kg and a mid and high dose group mean of 9.75 and 10.15 kg, respectively. No effect on terminal bw in either sex, suggesting that the control and low-dose groups caught up with the treated groups. Male terminal wts, control-high dose: 10.5, 10.75, 10.55, 10.58 kg. Statistics were not calculated.
CHRONIC TOXICITY/ONCOGENICITY-no chronic toxicity and carcinogenicity studies exist for nabam			
Note: Chronic and carcinogenicity studies exist for ethylene thiourea (ETU), a metabolite of nabam. ETU is currently classified by the EPA as a B2 carcinogen, with a Q_1*= 0.0601 $(mg/kg/day)^{-1}$ with low dose extrapolation for human risk assessment based on liver tumours in female mice.			
ETU 2 yr Mouse feeding study, with repro dosing (explained in results). B6C3F1 (variable #/sex/dose, n = 60, 10/sex/dose sacrificed at 9	Perinatal: 0, 33, 110 and 330 ppm Adult: 0, 330, 1000 ppm for 2 yrs, one group received 100 ppm for 2 yrs Standard adult conversions	F0:F1 ppm treatments were as follows: 0:0, 0:330, 0:1000, 330:0, 330:330, 330:1000, 33:100, 110:330 9 months All adult exposed mice had centrilobular hepatocellular cytomegaly, ↑ hepatocellular adenomas. @1000 ppm ♀: eosinophilic foci. ↑ abs and rel liver wts in groups receiving adult concentrations, regardless of perinatal exp.↑ abs thyroid wts, T_3 and TSH (♂).	

Study/Species #/group	Dose Levels/Purity	NOAEL (mg/kg bw/d)	Effects / Results
months) PMRA # 1580909, 1791829	100, 330 and 1000 ppm = 15, 50 and 150 mg/kg bw/d. Purity: 99% Study combined a perinatal exp (in utero and throughout suckling) with traditional NTP chronic bioassay. Female mice (F) generation) were fed a diet of 0, 33, 110 or 330 ppm ETU for 1 wk before breeding. After mating all females were kept on the ETU diet. On post-partum day 7 the litters (F1) were standardized to 8, weaned on day 28 and separated by sex. Exposure continued and at 8 weeks the pups were divided into 60/sex at concentrations of 0, 330 and 1000 ppm. 10/sex were sacrificed at 9 months and 50/sex were sacrificed after 2 years.		<u>2-years</u> Except for perinatal-only exp, all doses had ↓ bw. Perinatal-only Exp: no effects noted. Adult-only Exp (330 and 1000 ppm): <u>Thyroid:</u> diffuse cytoplasmic vacuolization, focal hyperplasia, and neoplasia. @ 1000 ppm: follicular cell adenomas or carcinomas with multiple or bilateral neoplasms (70%). ♀ more susceptible. <u>Liver</u>: diffuse centrilobular hepatocellular cytomegaly, marked ↑ in hepatocellular adenomas/carcinomas (♀). @1000 ppm: ↑ hepatocellular carcinomas (♂). Multiple hepatocelluar neoplasms, with carcinomas metastasizing to the lung. Rare hepatoblastomas also occurred, particularly in ♂. <u>Pituitary</u>: @1000 ppm: ↑ focal hyperplasia or adenoma of pars distalis (♂) and ♀: ↑ adenoma (but not hyperplasia). Combined Perinatal-Adult Exp: <u>Thyroid, Liver, Pituitary:</u> 330-330 ppm: marginal ↑ of non-neoplastic and neoplastic lesions in all 3 organs compared to adult exposure, but this marginal ↑ not seen at the 330-1000 ppm dose. ♂: all had a marginal↑ in follicular cell hyperplasia compared to adult-only exposure.

Study/Species #/group	Dose Levels/Purity	NOAEL (mg/kg bw/d)	Effects / Results
2 yr Rat feeding study, with repro dosing. F344 (variable #/sex/dose, n = 60, 10/sex/dose sacrificed at 9 months) This study is part of the onco mouse study reported above.	Perinatal: 0, 9, 30, 90 ppm Adult: 0, 25, 83 and 250 ppm for 2 yrs. Standard conversions would be 1.25, 4.15 and 12.5 mg/kg bw/d Purity: 99% Female rats were fed a diet containing 0, 9, 30 or 90 ppm ETU for 1 wk before breeding. After breeding, dosing continued and on PND 4 litters were standardized to 8 and weaned on day 28. Pup exposure continued for 8 wks and then divided into grps of 50/sex and exposed to adult concentrations of 0, 25, 83, and 250 ppm. *This study, combined with the Schmid study above, fulfills the chronic/onco rat data requirement.	F0:F1 ppm treatments were as follows: 0:0, 0:83, 0:250, 90:0, 90:83, 9:250, 30:83 and 9:25 ppm <u>9 months</u> 0-83, 0-250, 90-83 and 90-250 ppm: ↑ abs and rel liver wt (♂), 0-250 and 90-250 ppm: ↑ thyroid wt. 0-83, 0-250, 30-83, 90-83 and 90-250 ppm: ↑ thyroid follicular cell hyperplasia 90-250 ppm: ↑ thyroid follicular cell adenomas. Except for 90-0 ppm, all dose groups had ↓ T_4 and ↑ TSH. <u>2-yr</u> Perinatal-only Exp: <u>Thyroid:</u> ↑follicular cell hyperplasia (dosed animals 18-64%, conrol: 0-9%) Adult-only Exp: <u>Thyroid:</u> 0:83 ppm:↑ follicular cell hyperplasia (58% vs 2% in control ♂, ♀: 16% vs 4% in control) , adenomas 0-250 ppm: follicular cell carcinomas, ♂ appear more sensitive. Some carcinomas invaded the adjacent parenchyma and/or esophagus and trachea, and two metastasized to the lungs. Thyroid tumour incidence in adult-only exposure was (1/49, 12/46, 37/50 for males and 3/50, 7/44, 30/49 at 0, 83 and 250 ppm, resp) Combined Perinatal-Adult Exp: <u>Thyroid:</u> 90-83 and 90-250 ppm: ↑ follicular cell hyperplasia (♂), this was greater than that observed at 0-83 ppm, indicating some type of perinatal action. There was a similar effect with follicular adenomas/carcinomas. For males, tumour incidence was as follows: 3/46, 14/47, 13/50 and 48/50 for 9:25, 30:83, 90:83 and 90:250 ppm exposures, resp. <u>Other Organs:</u> 90-83 and 90-250 ppm: ↑ neoplasms of the Zymbal's gland and mononuclear cell leukaemia.	
DEVELOPMENTAL TOXICITY - Aquatreat DN-30 (30% a.i in aqueous solution)			
Developmental study - NZW rabbit; 18 pregnant♀/dose	0, 10, 100, 200 mg DN-30/kg bw/d from days 7 through 19 of	<u>Maternal</u> 3 mg/kg bw/d <u>Developmental</u>	<u>Maternal toxicity</u>: ≥30 mg/kg bw/d: Weight loss during days 7-13 of gestation

Study/Species #/group	Dose Levels/Purity	NOAEL (mg/kg bw/d)	Effects / Results
PMRA # 1580917	gestation 0, 3, 30 and 60 mg ai/kg bw/d Purity: 30% a.i 70% water	NOAEL not set LOAEL= 3 mg/kg/d Sensitivity	Developmental toxicity: ≥3 mg/kg bw/d: ↑ incidences of hydrocephaly (0/98, 3/102 (2/16 litters), 8/95 (4/16 litters) and 10/55 (5/8 litters) fetuses at 0, 3, 30 and 60 mg/kg, respectively); dose-related trend for soft spot and/or domed cranium (0/98, 2/102, 4/95, 6/55 fetal incidences) ≥60 mg/kg bw/d: ↑ late resorptions or abortions (seven litters did not reach term)
Developmental study - Rabbit; 20 inseminated ♀/dose PMRA # 1580881	0, 0.33, 2.4, and 30 mg ai/kg bw/d from days 7 through 19 of gestation Purity: 30% a.i 70% water	Maternal 2.4 mg/kg bw/d Developmental LOAEL: 0.3 mg/kg bw/d Sensitivity	Maternal toxicity: @30 mg/kg bw/d: ↓ weight gain during first 6 days of dosing, ↑ thyroid wt Developmental toxicity: ≥0.3 mg/kg bw/d: ↑ fetal incidence of hydrocephaly (0/98, 1/117, 3/134 (1 litter), 3/114 (3 litters) at 0, 0.33, 2.4 and 30 mg/kg/d respectively) @2.4 mg/kg bw/d: 1 hydrocephalic fetus had cleft palate @30 mg/kg bw/d: 2 hydrocephalic fetuses had cleft palate Cleft palate was outside historical control for both the mid and high dose groups. Historical control values for hydrocephaly were 0-1.6% and 0-8.3% for the fetus and litter, respectively.
Developmental study- Rat			Not available

Study/Species #/group	Dose Levels/Purity	NOAEL (mg/kg bw/d)	Effects / Results
REPRODUCTIVE TOXICITY- not available			
NEUROTOXICITY STUDIES			
Acute neurotoxicity screening study - Rat			Not available
Sub-chronic neurotoxicity- Rat			Available (see short-term toxicity section)- no neurotoxic effects
GENOTOXICITY STUDIES - 30% a.i aqueous solution			
Gene mutation in Ames S.typhimuriu TA1535, 1537, 1538, 100 and 98 PMRA # 1580915	111 - 100,000 µg/mL	Negative	
Chinese Hamster Ovary/hprt assay PMRA # 1744701	0-20 µg nabam /mL 0-30 µg nabam/mL + mouse S9 or up to 300 µg nabam + rat S9	Positive: in the presence of rat S9 at 300 µg/mL	
Unscheduled DNA synthesis (UDS)- rat primary hepatocytes PMRA # 1582846	0-20 µg/mL (not certain if the values are DN-30 or nebam concentrations)	Positive: at 1, 5 and 10 µg/mL	
Sister Chromatid Exchange- Chinese Hamster Ovary cells- 2 separate studies PMRA # 1582845	Study 1: 0.5 - 5010 µg/mL Study 2: 1.67 - 50.1 µg/mL	Both studies positive (dose-dependent): with and without S9 activation	
Cell transformation assays BALB/C-3T3- 2 separate studies PMRA # 1580900	0.70 - 11,500 µg/mL	Negative	
In vivo cytogenetic assay- F-344 rat;	Five doses of 0 or 400 mg Aquatreat DN-30	Negative	

Study/Species #/group	Dose Levels/Purity	NOAEL (mg/kg bw/d)	Effects / Results
10 males/dose PMRA # 1744701	for 5 consecutive days and sacrificed 6 hrs after the final dose Purity: 30% a.i		
In vivo cytogenetic assay- SD rat PMRA # 1580905	Single oral dose of up to 1200 mg DN-30 (approx 30% nebam) and sacrificed 6, 18 and 30 hrs following dosing	Negative	

Appendix V Environmental Fate and Toxicity

Table 1 Fate and Behaviour in the Environment

Property	Test substance	Value	Transformation products	Comments	PMRA#
Abiotic transformation					
Hydrolysis	nabam	Total loss in <1 hour	EBIS, ETU, hydantoin, EU		1744701 1227895
Phototransformation Soil	No information, data not required				
Phototransformation in water	Due to rapid hydrolysis cannot determine, data not required				
Phototransformation in air	No Information, data not required				
Biotransformation					
Biotransformation in soil (aerobic and anaerobic)	No Information, data not required				
Biotransformation in aerobic water systems	Nabam	Nabam DT_{50} could not be determined ETU Apparent DT_{50}= 21 d	ETU: 89% (day 5) to 36.4% AR (day 29) EBIS: 18.5% (day 1) to <3.3% (day 8) EU: 16% (day 8) to 4.9% (day 29)	Rapid hydrolysis, non-persistent	1580892
Biotransformation in anaerobic water systems	Nabam	Nabam DT_{50} could not be determined ETU Apparent DT_{50} = 499 d	ETU: 95.8% (day 240) to 70-80% AR (day 365) EBIS: 26.6% (day 0) to 0.9% (day 8) EU: 4.2% (day 0) to 15.7% (day 121)	Rapid hydrolysis, non-persistent	1580894
Mobility					
Adsorption / desorption in soil	Not persistent enough to conduct studies, not required				
Soil leaching	Not persistent enough to conduct studies, not required				
Volatilization	No studies	VP = 9.45×10^{-13} mmHg Henry's Law Constant (1.60×10^{-18} $atm/m^3/mol$)		Will not volatilize	
Field studies					
Terrestrial and Aquatic Field dissipation	No Studies, not required				

Table 2 Toxicity to Non-Target Species

Study	Species	Endpoint	Value (units)	Degree of Toxicity
Terrestrial Biota				
Acute toxicity - invertebrates	Honey bee	contact LD_{50}	12.09 µg ai/bee	Relatively non-toxic*
Avian Acute Oral	Northern bobwhite quail (*Colinus virginianus*)	LD_{50} NOEL	>2250 mg a.i./kg bw 292 mg a.i./kg bw	Practically non-toxic*
	Mallard duck (*Anas platyrhynchos*)	No study available		
Avian Acute Dietary	Northern bobwhite quail (*Colinus virginianus)*	LC_{50} NOEC	>5620 mg a.i./kg diet 1780 mg a.i./kg diet	Practically non-toxic*
	Mallard duck (*Anas platyrhynchos*)	LC_{50} NOEC	>5620 mg a.i./kg diet 562 mg a.i./.kg diet	Practically non-toxic*
Avian (Reproduction)	No study available and not required			
Mammals (Acute Oral)	Rat	LD50	1.4 g/kg bw	Low Toxicity*
Mammals (inhalation)	Rat	LC50	>2.19 g/kg bw	Low Toxicity*
Mammal (short term dietary)	Rat Dog	NOAEL NOAEL NOAEL NOAEL	2.49 mg/kg bw/d <8.4 mg/kg bw/d 200 mg/L 0.36 mg/kg bw/d	-
Mammal (Developmental)	Rabbit Maternal Developmental Rat	 NOAEL LOAEL 	 2.4 , 3.0 mg/kg bw/d 0.3, 3.0 mg/kg bw/d Not Available	-
Mammal (Repro)	Not available, not required			
Plants	No study available and not required			
Aquatic Biota				
Invertebrates (Acute)	*Daphnia magna*	EC_{50} (30%) NOEC (30%)	5.6 mg a.i./L 1.0 mg a.i./L	moderately toxic[1]
Invertebrates (Chronic)	*Daphnia magna*	NOEC (#young/adult, length) LOEC	0.018 mg a.i./L 0.035 mg a.i./L	
Fish (Acute)	Rainbow trout (*Oncorhynchus mykiss)*	LC_{50} (30%) NOEC (30%)	3.3 mg a.i./L <0.36 mg a.i./L	Moderately toxic[2]
	Bluegill sunfish (*Lepomis macrochirus)*	LC_{50} (30%) NOEC (30%)	8.4 mg a.i./L <6.0 mg a.i./L	Moderately toxic[2]
Fish (Chronic)	No study available			
Amphibians	No study available			
Freshwater plants and algae (Acute)	No study available			
Estuarine/marine invertebrates (Acute)	Eastern oyster (*Crassostrea virginica*)	LC_{50} (30.8%) NOEC shell growth	>0.96 mg a.i./L 0.12 mg a.i./L	highly toxic[1]
	Mysid (*Americamysis bahia*)	LC_{50} (30.2%)	0.17 mg a.i./L	highly toxic
Estuarine/marine invertebrates (Chronic)	No study available			
Estuarine/Marine fish (Acute)	sheepshead minnow (*Cyprinodon variegatus*)	LC_{50} (30.8%) NOEC	>1,100 mg a.i./L >1,100 mg a.i./L	practically non-toxic[2]

Study	Species	Endpoint	Value (units)	Degree of Toxicity
		LC_{50} (15% nabam + 15% SDD)	0.14 mg a.i./L	highly toxic
Estuarine/Marine fish (Chronic)	No study available			
Estuarine/Marine Diatom	No study available			

* according to various United States Environmental Protection Agency classifications
[1] According to the USEPA (1985c) classification scheme
[2] According to the USEPA (1985d) classification scheme

Appendix VI Label Amendments for Commercial Class Products Containing Nabam

The label amendments presented below do not include all label requirements for individual endues 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.

A submission to request label revisions will be required within 90 days of finalization of the re-evaluation decision.

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

I) Add to the **PRIMARY PANEL**:

- "Potential Skin Sensitizer"
- "For use with closed loading and transfer systems only (i.e. dry coupling)"

II) Add to **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."
- For product labels involving a pulp and paper treatment process with finished products that may have direct or indirect food contact, the statement "DO NOT use to treat paper or paperboard which will contact food" if there is no Food Directorate of Health Canada clearance for "food contact" uses.

III) Because the acute lethal concentration resulting in 50% mortality for estuarine/marine invertebrates and fish is less than or equal to 1 milligram per litre (highly to very highly toxic according to the EPA aquatic acute hazard classification scheme), the following label statement must be included in the **ENVIRONMENTAL HAZARDS** section:

- **Toxic to aquatic organisms**

References

A. Studies/Information Provided by the Applicant/Registrant-Unpublished

Studies Considered in the Chemistry Assessment

PMRA Document Number	Reference
1457769	Technical Chemistry file - Aquatreat DN-30, DACO: 2.1,2.10,2.11,2.12,2.13,2.14,2.2,2.3,2.4,2.5,2.6,2.7,2.8,2.9 CBI
1448769	DACO: 0.1.6003 CBI
1303344	PRODUCT CHEMISTRY, DACO: 0.8,2.99 CBI
1457767	Technical Chemistry file - various correspondence., DACO: 0.8 CBI

Studies Considered in the Health Assessment- Toxicology

PMRA Document Number	Reference
1580886	1978, Acute Oral Toxicity - Female Rats, Data Numbering Code: 4.2.1
1580900	1985, Evaluation Of Nabam In The C3h-10t 1/2 Cell System For Transformation And Promotion Activities, Data Numbering Code: 4.5.8
1580915	1985, Salmonella Typhimurium/mammalian Microsome Plate Incorporation Assay With Compound Nabam, Data Numbering Code: 4.5.8
1582846	1985, Unscheduled DNA Synthesis Rat Heptocyte Assay With Nabam, Data Numbering Code: 4.5.8
1580884	1986, Acute Dermal Toxicity Study In Rabbits - Method, Summary, Pathology, Data Numbering Code: 4.2.2
1582845	1986, Clastogenic Evaluation Of Nabam, 30% Water Solution, Alco/vinings/uniroyal Lot #28177dp In An *In vitro* Cytogenic Assay Measuring Sister Chromatid Exchange In Chinese Hamster Ovary (cho) Cells, Data Numbering Code: 4.5.6
1582844	1986, Dermal Sensitization Study In Guinea Pigs (closed Patch Technique) - Method Summary Results, Data Numbering Code: 4.2.6
1580911	1986, Primary Eye Irritation Study In Rabbits - Methods, Summary, Data Numbering Code: 4.2.4
1580913	1986, Report On 90-day Subchronic Oral Toxicity In Dog Aquatreat Dn-30, Data Numbering Code: 4.3.2
1580918	1986, The Metabolism Of Nabam In Rats, Data Numbering Code: 4.5.9
1580917	1988, Teratogenicity Study In Rabbits Of Mrd-87-072 (aquatreat Dn-30, Approximately 30% Nabam), Data Numbering Code: 4.5.3
1580905	1989, Mutagenicity Test On Aquatreat Dn-30 (30% Nabam In Water) In The Rat Bone Marrow Cytogenic Assasy, Data Numbering Code: 4.5.7

1580909	1989, NTP Technical Report Of The Perinatal Toxicity And Carcinogenicity Studies Of Ethylene Thiourea (casno 96-45-7) In F/344 Rats And B6c3f1 Mice (feed Studies), Data Numbering Code: 4.8
1580881	1992, A Development Toxicity Of Aquatreat DN-30 In Rabbits, Data Numbering Code: 4.5.3
1580919	1993, Twenty-one Day Sub-chronic Dermal Toxicity Study With Aquatreat DN-30 (approximately 30%nabam In Water) In Rats, Data Numbering Code: 4.3.5
1580879	2007, A Combined (13 Week) Toxicity And Neurotoxicity Of Aquatreat DN-30 In Rats, Data Numbering Code: 4.3.8, 4.5.13

Studies Considered in the Health Assessment- Exposure

PMRA Document Number	Reference
1580897	1986. Dermal Absorption of 14C-Nabam in Male Rats, Hazleton Laboratories, Inc., Madison, Wisconsin, Study No. 6185-100. Unpublished.
1611915	1987. Dermal Absorption of 14C-Nabam in Male Rats after 10 Hours Exposure, Hazleton Laboratories, Inc., Madison, Wisconsin, HLA 6185-102. Unpublished.

Studies Considered in the Environmental Assessment

PMRA Document Number	Reference
1227895	1986. Photodegradation and hydrolysis of nabam in water. Hazelton Laboratories America Inc. Study No. 6015-280. Unpublished.
1227906	1986. Nabam: An acute toxicity study with the bobwhite. Wildlife International Ltd. Project No. 21-103. Unpublished.
1227919	1985. Acute Toxicity of nabam to *Daphnia magna*. Analytical Bio-chemistry Laboratories Inc. Study # 33918. Unpublished.
1227913	1985. Acute Toxicity of nabam to Rainbow Trout *Salmo gairneri*. Analytical Bio-chemistry Laboratories Inc. Study # 33917. Unpublished
1227912	1985. Acute Toxicity of nabam to bluegill subfish *Lepomis macrochirus*. Analytical Bio-chemistry Laboratories Inc. Study # 33916. Unpublished.
1457769	ALCO Chemical Corporation. Aquatreat DN-30. Product Chemistry. Unpublished.
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