Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Proposed Regulatory Decision Document PRDD2004-05

Formic Acid/NOD Formic Acid Pad and Mite-Away II™ Formic Acid Pad

The technical grade active ingredient (TGAI) formic acid and associated end-use products (EPs), NOD Formic Acid Pad and Mite-Away II™ Formic Acid Pad, for treatment of varroa mites and tracheal mites in/on honeybees are proposed for registration under Section 13 of the Pest Control Products (PCP) Regulations.

This Proposed Regulatory Decision Document provides a summary of data reviewed and the rationale for the proposed full registration of these products. The Pest Management Regulatory Agency (PMRA) will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to the Publications Coordinator at the address below.

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Foreword

The active ingredient formic acid and associated EPs, NOD Formic Acid Pad and Mite-Away II™ Formic Acid Pad containing 47.65% formic acid, are proposed for registration under Section 13 of the PCP Regulations for the control of varroa and tracheal mites in honeybee colonies.

The PMRA has carried out an assessment of available information in accordance with Section 9 of the PCP Regulations and has found it sufficient pursuant to Section 18(*b*) to allow a determination of the safety, merit and value of the active ingredient formic acid and the EPs NOD Formic Acid Pad and Mite-Away II™ Formic Acid Pad. The Agency has concluded that the use of the active ingredient formic acid and the EPs NOD Formic Acid Pad and Mite-Away II™ Formic Acid Pad in accordance with the label has merit and value consistent with section 18(*c*) of the PCP Regulations and does not entail an unacceptable risk of harm pursuant to Section 18(*d*). Therefore, based on the considerations outlined above, the use of the active ingredient formic acid and the EPs NOD Formic Acid Pad and Mite-Away II™ Formic Acid Pad is proposed for full registration, pursuant to Section 13 of the PCP Regulations.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

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1.0 The active substance, its properties and uses

1.1 Identity of the active substance and impurities

TGAI Identification

Active substance	Formic acid
Function	Acaricide
Chemical names	
IUPAC	Methanoic acid
CAS	Hydrogencarboxylic acid
CAS number	64-18-6
Molecular formula	CH_2O_2
Molecular weight	46.03
Structural formula	HCOOH
Nominal purity of active	65.0%
Identity of relevant impurities of toxicological, environmental or other significance	The TGAI does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances

1.2 Physical and chemical properties of the active substance and EPs

Technical product: formic acid

Property	Result
Colour and physical state	Colourless or yellowish
Odour	Pungent, penetrating odour, similar to vinegar
Melting point or range	Not applicable
Boiling point or range	106°C
Specific gravity at 20°C	1.19
Vapour pressure at 20°C	4.67 kPa

Property	Result
Ultraviolet (UV)–visible spectrum	Not expected to absorb at $\lambda > 300$ nm
Solubility in water	Miscible in all proportions
Solubility (g/L) in organic solvents	Miscible in all proportions in alcohol and diethyl ether
n-octanol–water partition coefficient (K_{ow})	log K_{ow} = -1.55
Dissociation constant (pK_a)	2.74
Stability (temperature, metal)	Chemically stable; acid reacts with most metals to form hydrogen gas. Product will not undergo hazardous polymerization.

EPs: NOD Formic Acid Pad and Mite-Away II™ Formic Acid Pad

Property	Result
Colour	Not provided
Odour	Pungent, penetrating odour, similar to vinegar
Physical state	Liquid
Formulation type	Slow release generator
Guarantee	47.65% nominal
Formulants	The products do not contain any List 1 formulants or formulants known to be Toxic Substances Management Policy (TSMP) Track 1 substances.
Container material and description	High density polyethylene (HDPE) pail
Specific gravity	1.02
pH of 1% dispersion in water	2.2 for formic acid
Oxidizing or reducing action	Chemically incompatible with oxidizing agents
Storage stability	Expected to be stable
Explodability	Auto-ignition point: 500°C

1.3 Details of uses and further information *(OECD 2.1.3)*

The two proposed EPs, Mite-Away II™ Formic Acid Pad and NOD Formic Acid Pad, are the same product except that the first is proposed for registration as a domestic class product, whereas the second is for registration as a commercial class product. The Mite-Away II™/NOD Formic Acid Pad is a fibre board, soaked in 250 mL of 65% formic acid, placed inside a thin, perforated plastic pouch.

Mite-Away II™/NOD Formic Acid Pad is proposed for control of varroa and tracheal mites in honeybee colonies. Application of one pad per colony for 21 days is proposed in the spring and/or early fall for single and double brood-chamber colonies, and late fall/winter for single brood-chamber colonies only. Application during summer or honeyflow is not proposed.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

An analytical method for the determination of the active was not provided. A high-performance liquid chromatography (HPLC) method with UV or with post-column pH buffered electrolytic conductivity detection for the analysis of formic acid is available on the Internet and was proposed for the analysis of the EPs. The same method may be used for the analysis of formic acid in the technical product.

2.2 Method for formulation analysis

An HPLC method with UV or with post-column pH buffered electrolytic conductivity detection for the analysis of formic acid was proposed for the analysis of the EPs. The description of the method is available on the Internet and was found to be acceptable for use as an enforcement analytical method.

2.3 Analytical methods for residue analysis

The analytical method for the determination of formic acid in honey is well established in the scientific literature. The method used to measure formic acid in honey is commercially available in a coupled enzyme reaction kit. The basis of the analysis is a UV test for the determination of formic acid in foodstuffs. The method is quick and specific for formic acid based on the following reaction:

$$\text{formic acid} + \text{NAD} + H_2O \rightarrow \text{bicarbonate} + \text{NADH} + H^+$$

This reaction occurs in the presence of the enzyme formic acid dehydrogenase (FDH). Acetic acid, propionic acid, oxalic acid and L-ascorbic acid do not influence the determination. The method is based on the measurement of the increase in light

absorbance of the coenzyme NADH at 340 nm. The amount of NADH formed is stoichiometric to the amount of formic acid present. The limit of detection (LOD) is 0.2 mg/L. This method has been recognized by the following international standardization and regulation authority:

- The Cental European Brewing Committee for Analysis (enzymatic analysis of formic acid); and
- German Food Law (Article 35).

This enzymatic method for food analysis has been accepted for formic acid in canned tomatoes and tomato ketchup. However, the analytical method cannot differentiate between endogenous and exogenous levels of formic acid in honey.

3.0 Impact on human and animal health

3.1 Effects having relevance to human and animal health arising from exposure to the active substance or to impurities in the active substances or to their transformation products

Formic acid is a colourless, fuming liquid with a highly pungent, penetrating odour. It is severely irritating and corrosive to the eyes, skin and mucous membranes and may cause permanent damage. Exposure to the vapour or mist can cause tearing of the eyes, runny nose, coughing, sore throat, bronchitis and shortness of breath; the severity of which will vary depending upon the airborne concentration. Exposure to high concentrations of formic acid may cause pulmonary edema.

The American Conference of Government and Industrial Hygienists has set the Threshold Limit Value (TLV) for formic acid at 5 ppm (9.4 mg/m^3) for an 8-hour time-weighted average (TWA) concentration. A short-term exposure limit (STEL) of 10 ppm (19 mg/m^3) was also established for periods not exceeding 15 minutes. These limits are based on the risk of severe irritation to the eyes, skin and respiratory tract.

Both human experience and animal studies indicate that exposure to vapours of formic acid result in damage to the respiratory tract consistent with the corrosive nature of the acid. However, vapours of formic acid are easily detectable at low levels, thus allowing users to avoid prolonged exposure. There are no other reported toxicological endpoints of concern associated with acute or short-term exposure to formic acid (the exposure period that is relevant for this use pattern).

The United States Food and Drug Administration has affirmed the “generally regarded as safe” status for formic acid as a direct and indirect human food ingredient.

3.2 Toxicology endpoint selection for occupational and bystander risk assessment

For beekeepers that apply NOD formic acid pads exposure is expected to be short-term in duration because application would take from one to two days for a domestic beekeeper and from one to three weeks for a commercial beekeeper. The primary endpoint of concern for formic acid is its corrosiveness. It is severely irritating and corrosive to the eyes, skin and mucous membranes and may cause permanent damage. However, since the vapours of formic acid are easily detectable at low levels, users are able to avoid prolonged exposure to the chemical.

3.3 Occupational exposure and risk

The use of formic acid was assessed and documented in the Note to CAPCO C94-05, *Proposed Scheduling of 65 Percent Formic Acid for the Detection and Control of Honey Bee Mites* (30 March 1994). The major conclusion was that formic acid may be used safely for the control of mites of honeybees, provided that appropriate safety precautions are taken. The proposed products are different in that the formic acid is impregnated in the pad.

3.3.1 Handler exposure and risk

Exposure is expected to be less than or equal to liquid formic acid that is open poured into the hive or mixed by hand with homemade pads before application for the following reasons:

- NOD and Mite-Away II™ pads are designed to release formic acid slowly over time by trapping it inside a pad; and
- the pads eliminate any need to ope, pour or mix formic acid.

When applying pads, dermal exposure would be low since applicators will be wearing chemical-resistant gloves, goggles and cotton coveralls. Inhalation exposure would also be low for the following reasons:

- the pads are only used outdoors;
- the vapours are easily detectable at low levels so they can be avoided before serious effects can occur; and
- the pads are designed to have lower volatility vs. liquid formulation.

3.3.2 Post-application exposure and risk

Post-application exposure is expected to be very low as the pads are only removed after 21 days when all the formic acid has evaporated. No other post-application activities usually occur between application and removal of the pads.

3.4 Residential exposure and risk

3.4.1 Handler exposure and risk

Exposure is expected to be less than or equal to liquid formic acid that is open poured into the hive or mixed by hand with homemade pads before application for the following reasons:

- NOD and Mite-Away II™ pads are designed to release formic acid slowly over time by trapping it inside a pad; and
- the pads eliminate any need to open, pour or mix formic acid.

When applying pads, dermal exposure would be low since applicators will be wearing chemical-resistant gloves, goggles and cotton coveralls. Inhalation exposure would also be low for the following reasons:

- the pads are only used outdoors;
- the vapours are easily detectable at low levels so they can be avoided before serious effects can occur; and
- the pads are designed to have lower volatility vs. liquid formulation.

3.4.2 Post-application exposure and risk

Post-application exposure is expected to be very low as the pads are only removed after 21 days when all the formic acid has evaporated. No other post-application activities usually occur between application and removal of the pads.

3.4.3 Bystander exposure and risk

Bystander exposure is not expected to occur since the formic acid is released inside honeybee colonies and bystanders are not exposed to the inside of honeybee colonies. The amount released into the air would be very low.

4.0 Residues

4.1 Residue summary

The metabolism of formic acid in animals has been extensively documented in the literature. Formic acid is an intermediate in normal metabolism. It takes part in the metabolism of one-carbon compounds and its carbon may appear in methyl groups undergoing transmethylation. It is eventually oxidized to carbon dioxide. There is a species difference in the extent of formic acid metabolism: in rabbits no administered formic acid is excreted, whereas in dogs about half the administered formic acid is excreted unchanged in the urine. No cumulative toxic effects are known (WHO/Food Add./24.65, FAO Nutrition Meetings, Report Series No. 38A). Honey is not considered a feed item. In this case the bees are being treated, and therefore this may be

considered analogous to a dip treatment for sheep. The treated honey is not being consumed by any livestock; therefore, traditional animal metabolism studies are not required.

In total, 20 samples of honey were collected from hives in British Columbia that were treated with formic acid (not treated during honeyflow). Samples contained 55–469 ppm formic acid (the mean was 110 ± 95 ppm formic acid). This high standard deviation was also seen in the control samples (81 ± 40 ppm formic acid). Based on the data submitted, the levels of formic acid in treated honey did not show a substantial increase from untreated samples. The range of formic acid found in the treated hives was within the range of levels of naturally occurring formic acid reported in the scientific literature (41–1178 ppm). As formic acid has a high vapour pressure (3.6 kPa), it is expected that it will dissipate before the replacement of the honey supers. The label indicates that the pad is not to be applied during honeyflow (the honey supers are not in place during treatment).

Processing studies were not required as honey is not a processed commodity. Also, honey is not normally fed to livestock and therefore no feeding studies are required.

Dietary risk assessment—The PMRA has not established an acceptable daily intake. It is anticipated that the proposed domestic use of formic acid in beehives will not pose a risk to any segment of the population, including infants, children, adults and seniors, when humans consume honey.

5.0 Fate and behaviour in the environment

The applicant provided physical-chemistry data of formic acid, which had been reviewed by the Commercial Chemicals Branch of Environment Canada. The data has since been reviewed by the PMRA and are presented in Section 1.1 and Table 5.1.

Formic acid, a member of the carboxylic/alkanoic acid chemical family, is freely soluble in water and is considered to be a moderately strong acid (pK_a = 3.76) (Table 5.1). The vapour pressure of 4.67 kPa indicates that formic acid is very highly volatile. The *n*-octanol–water partitioning coefficient of formic acid (log K_{ow}) is -1.55, indicating that bioconcentration is unlikely to occur. Carbon monoxide is the major transformation product. As a result, all major reviews of data on environmental chemistry and fate have been waived for the proposed use pattern.

Table 5.1 Physical and chemical properties of the active ingredient relevant to the environment

Property	Value	Comments
Water solubility	N/A	Miscible in all proportions
Vapour pressure	4.67 kPa	Very highly volatile
log K_{ow}	-1.55	Bioconcentration unlikely to occur
pK_a	3.76	Moderately strong acid
UV-visible absorption	Not expected to absorb at > 300 nm	Minimal/no phototransformation expected

6.0 Effects on non-target species

The proposed use of a 65% solution of formic acid for the control of mites in bee colonies is unlikely to result in significant contamination of the general environment. Therefore, all major reviews of data on the environmental toxicology of formic acid have been waived for the proposed use pattern.

Data provided by the applicant indicate a greater amount of formic acid remaining in the pouches at the end of the three-week exposure period in late summer/early fall and late fall applications as opposed to the spring applications. As such, there are concerns with regards to potential leaching of formic acid into groundwater/aquatic systems from landfill disposal and the subsequent risk to aquatic organisms. The applicant, however, had suggested a ventilation period of two weeks prior to disposal. During this two-week interval, the product pouches are to be opened on-site, protected from precipitation and allowed to ventilate.

7.0 Efficacy

7.1 Intended use

Mite-Away II™/NOD Formic Acid Pad is proposed for the reduction of varroa and tracheal mites in honeybee colonies. Application of one pad per colony for 21 days is proposed in spring and/or early fall for single and double brood-chamber colonies, and late fall/winter for single brood-chamber colonies only. Application during summer or honeyflow is not proposed.

7.2 Mode of action

Treatment of a hive with formic acid results in the diffusion of vapours through the hive. Formic acid acts as an inhibitor of the mitochondrial cytochrome oxidase complex, causing tissue suffocation and consequently cell death (Keyhani and Keyhani 1980).

The efficacy of formic acid depends on those parameters that affect the diffusion of the product inside the hive, such as the following:

- the method of application (e.g., applied as a liquid, gel, or impregnated in a fibre board);
- ambient temperature (the diffusion of formic acid is low below 10°C and increases with higher temperatures); and
- colony activity (activity helps to disperse the vapour throughout the hive).

In the context of varroa-mite control and regardless of the method of application, a full treatment must cover at least one period of pupal development of bees to ensure that all mites have been exposed to the miticide upon emergence from the capped cells. As the minimum duration of pupal development for workers and drones is 11 and 14 days, respectively, it is necessary to treat the hive for at least 14 days. However, in cool weather a longer period of treatment will be required, due to slower pupal development.

7.3 Effectiveness against pests

Three studies conducted in Ontario were provided to support label claims. Results demonstrate that the proposed product can reduce the tracheal and varroa mite populations in honeybee colonies, but data were not sufficient to support claims of "control" of tracheal and varroa mites. Since the level of efficacy against varroa mites is below that of other miticides (i.e., coumaphos and fluvalinate), label claims are limited to reduction of mite numbers.

7.4 Adverse effects on honeybees

At high concentrations formic acid is toxic not only to varroa and tracheal mites, but also to honeybees. If released in the hive too quickly, detrimental effects on the bees as a result of formic acid vapours can occur, including queen and worker mortality, extensive brood damage and absconding. Queen loss seems to occur more frequently with the use of higher concentrations of formic acid (e.g., 85%), with the following conditions:

- hot weather;
- when older queens are present; or
- when bees are not able to escape pockets of concentrated fumes.

Results demonstrate that up to 14 days of brood mortality can occur, especially in the smaller colonies (single brood chamber, less than seven frames of bees). However, colony health recovers by the end of treatment. The detrimental effects, including colony mortality and absconding, are exacerbated by hot ambient temperatures (30°C and above).

7.5 Survey of alternatives

7.5.1 Nonchemical control practices

Varroa mites – Alternate strategies, such as the use of drone-brood trapping, sticky boards and a Russian stock of bees that is resistant to varroa mite, are available to help manage the problem of varroa mite infestations. These are useful as components of an overall integrated pest management (IPM) program.

Tracheal mites – Non-chemical control strategies include selecting a resistant line of bees that exhibit a high level of self-grooming.

7.5.2 Chemical control practices

Varroa mites – The miticide Apistan (Reg. No. 23023; 10% fluvalinate) is the only product currently registered for control of varroa mites in honeybee colonies. Several provinces claim that some varroa mite populations are now resistant to fluvalinate, and that Apistan is no longer effective to control the varroa mite. Liquid formic acid (65%) is also available for use in Canada (proposed for exemption from registration and for regulation in the Note to CAPCO C94-05, under the authority of Schedule II of the PCP Regulations).

Tracheal mites – Liquid formic acid (65%) and menthol are the two miticides available in Canada for control of tracheal mites (both products are proposed for exemption from registration and for regulation under the authority of Schedule II of the PCP Regulations, in the Notes to CAPCO C94-05 and C92-05 [*Scheduling of Menthol for Honey Bee Tracheal Mite Control*], respectively).

7.6 Compatibility with current management practices including IPM

Mite-Away II™/NOD Formic Acid Pad is compatible with current IPM management practices. Varroa mite levels in colonies can be assessed by either monitoring the mite drop on sticky boards, or by washing mites from adult bees with alcohol or ether. To detect and monitor levels of tracheal mite infestations, a sample of adult bees must be collected and dissected under the microscope.

7.7 Contribution to risk reduction

The proposed EPs have value as there is no product currently registered for treatment against tracheal mites and resistance is building up in North American varroa mite populations to currently registered miticides (i.e., fluvalinate and coumaphos). Compared with the uses of liquid formic acid allowed in the Note to CAPCO C94-05, the application of this product saves time and effort, reduces disturbance to the colonies and reduces the risks of application to the apiculturist. Unlike currently registered miticides, formic acid is naturally present in honey.

7.8 Information on the occurrence or possible occurrence of developing resistance

There is no reason to suspect mites could develop resistance to formic acid based on the particular mode of action of this active ingredient (i.e., formic acid causes tissue suffocation). Therefore, no recommendations on resistance management should be required on the labels.

7.9 Summary

Efficacy data demonstrate that the proposed product can reduce the tracheal and varroa mite populations in honeybee colonies, but data were not sufficient to support claims of "control" of tracheal and varroa mites. Label claims are limited to the reduction of tracheal and varroa mite populations.

Table 7.9.1 Summary data

Product names	NOD Formic Acid Pad (Commercial Class) Mite-Away II™ Formic Acid Pad (Domestic Class)
Site/Host	Honeybee colonies (*Apis mellifera*)
Pest species	Tracheal mite (*Acarapis woodi*) Varroa mite (*Varroa destructor*)
Use claim	Reduction of tracheal and varroa mite populations
Method of application	By hand
Dosage	One pad per hive per period of treatment; each pad contains 250 mL of 65% formic acid
Duration of treatment	The pad remains in the hive for 21 days

Timing of application and special considerations for each period of treatment	**Spring and early fall:** Outside daytime maximum temperature should be between 10–25°C at the time of application; for single or double brood-chamber colonies (6–20 frames of bees). Do not apply while honey supers are on the hive. Complete the treatment before adding honey supers on the hive, or remove honey supers from the hive before starting a treatment. In addition, for treatments conducted before placing honey supers on the hive, allow at least two weeks between the end of treatment and the harvest of honey from the hive. It is recommended that pads be removed during heat waves and treatment resumed afterwards. **Late fall and winter (post-feeding, less than half a frame of brood):** Outside daytime maximum temperature should be above 4°C at the time of application; for single brood-chamber colonies (5–10 frames of bees) only. Cut a single slit in the top of the pouch (side opposing holes) when ambient temperature is below 15°C.
Interval between applications	Minimum of one month between applications
General consideration about the timing of application	Treat only if treatment thresholds are exceeded (refer to provincial guidelines)
Resistance management	Recommendations on resistance management are not required on the label

8.0 Toxic Substances Management Policy

During the review of NOD 65% Formic Acid Technical, the PMRA has considered the implications of the Toxic Substances Management Policy (TSMP) and its Regulatory Directive DIR99-03. It has been determined that this product does not meet TSMP Track 1 criteria for the following reasons:

- Formic acid is not bioaccumulative. Studies have shown that the *n*-octanol–water partition coefficient (log K_{ow}) is -1.55, which is below the TSMP Track 1 cut-off criterion of $\geq$5.0.
- The toxicity of formic acid is described in Section 3.1.
- Formic acid does not form any major transformation products that meet the TSMP Track 1 criteria.

- Formic acid (technical grade) does not contain any byproducts or microcontaminants that meet the TSMP Track 1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.
- The formulated product does not contain any formulants that are known to contain TSMP Track 1 substances.

9.0 Proposed regulatory decision

The PMRA has carried out an assessment of available information in accordance with Section 9 of the PCP Regulations and has found it sufficient, pursuant to Section 18(*b*), to allow a determination of safety, merit and value of formic acid and its EPs, NOD Formic Acid Pad and Mite-Away II™ Formic Acid Pad, manufactured by NOD Apiary Products Limited. The PMRA has concluded that the use of formic acid, NOD Formic Acid Pads and Mite-Away II™ Formic Acid Pads, in accordance with the label, has merit and value consistent with Section 18(*c*) of the PCP Regulations and does not entail an unacceptable risk of harm pursuant to Section 18(*d*). Therefore, based on the considerations outlined above, application of NOD Formic Acid Pad and Mite-Away II™ Formic Acid Pad may decrease damage caused by varroa and tracheal mites in/on honeybees. Therefore, the use of NOD Formic Acid Pad and Mite-Away II™ Formic Acid Pad is proposed for full registration, pursuant to Section 13 of the PCP Regulations.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

List of abbreviations

CAS	Chemical Abstracts Service
EP	end-use product
FDH	formic acid dehydrogenase
HDPE	high density polyethylene
HPLC	high-performance liquid chromatography
IPM	integrated pest management
IUPAC	International Union of Pure and Applied Chemistry
K_{ow}	*n*-octanol–water partition coefficient
LOD	limit of detection
OECD	Organisation for Economic Co-operation and Development
pK_a	dissociation constant
PCP	pest control product
ppm	parts per million
PMRA	Pest Management Regulatory Agency
STEL	short-term exposure limit
TGAI	technical grade active ingredient
TLV	threshold limit value
TSMP	Toxic Substances Management Policy
TWA	time-weighted average
UV	ultraviolet

References

Keyhani, J., and Keyhani E. 1980. EPR Study of the Effect of Formate on Cytochrome C Oxidase. *Biochemical and Biophysical Research Communications*. 92(1): 327–33.