Government of Canada Gouvernement du Canada

Screening Assessment

Formic Acid and Formates Substance Group

Chemical Abstracts Service Registry Numbers
64-18-6
107-31-3
109-94-4
141-53-7

Environment and Climate Change Canada
Health Canada

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Synopsis

Pursuant to sections 68 and 74 of the Canadian Environmental Protection Act, 1999 (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment of four substances referred to herein as the Formic Acid and Formates Substance Group. Substances in this group were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered as a priority on the basis of other human health concerns. The Chemical Abstracts Service Registry Number (CAS RN[1]), their Domestic Substances List (DSL) names and their common names are listed in the table below.

Substances in the Formic Acid and Formates Substance Group

CAS RN	Domestic Substances List name	Common name
64-18-6	Formic acid	Formic acid
107-31-3[a]	Formic acid, methyl ester	Methyl formate
109-94-4	Formic acid, ethyl ester	Ethyl formate
141-53-7	Formic acid, sodium salt	Sodium formate

[a] This substance was not identified under subsection 73(1) of CEPA but was included in this assessment as it was considered a priority on the basis of other human health concerns.

Formic acid occurs naturally in plants and is also a product of microbial metabolism of organic matter and of atmospheric photo-oxidation. In Canada, sources of formic acid and formates are mostly anthropogenic, and derive from industrial activities, disposal (down the drain) and use of cleaning products containing formic acid and sodium formate. In 2011, between 10 000 and 100 000 kg of methyl formate, between 100 and 1 000 kg of ethyl formate, and between 1 000 000 and 10 000 000 kg of sodium formate were imported into Canada. In addition, between 100 000 and 1 000 000 kg of sodium formate was manufactured in Canada. While recent quantities of formic acid in commerce are not available, it is a commodity chemical and expected to be in commerce in Canada in high quantities.

Formic acid and sodium formate can be found in products available to consumers, including cosmetics, fabric softeners, and laundry and dishwasher detergents; as well

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as in the manufacture of certain food packaging materials. In Canada, formic acid and ethyl formate are present as formulants in a limited number of pest control products; formic acid is also an active ingredient in mite treatment products for bee hives. Formic acid and ethyl formate may also be used as food flavourings. Other uses include chemical synthesis and industrial water treatment for sodium formate, and anti-rust treatment for formic acid. Methyl formate and ethyl formate are primarily used in chemical synthesis and agricultural products, respectively.

The ecological risk of substances in the Formic Acid and Formates Substance Group was characterized using the Ecological Risk Classification of organic substances (ERC). The ERC is a risk-based approach that employs multiple metrics for both hazard and exposure based on weighted consideration of multiple lines of evidence for determining risk classification. Hazard profiles are established based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Metrics considered in the exposure profiles include potential emission rate, overall persistence, and long-range transport potential. A risk matrix is used to assign a low, moderate or high level of potential concern for substances based on their hazard and exposure profiles. The ERC identified formic acid, methyl formate, ethyl formate and sodium formate as having low potential to cause ecological harm.

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from formic acid, methyl formate, ethyl formate and sodium formate. It is concluded that formic acid, methyl formate, ethyl formate and sodium formate do not meet the criteria under paragraphs 64(a) or (b) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Formic acid, sodium formate, methyl formate and ethyl formate break down to a common metabolite—formate ion; therefore, it is expected that the toxicological profiles of the acids and salts will be similar and a read-across approach is used to characterize hazard. The critical health effects identified for formic acid and sodium formate via the oral route are decreased body weight gain (at higher doses) based on read-across of oral repeated-dose toxicity data from potassium hydrogen diformate. No effects were observed in a long-term dietary study in rats administered ethyl formate at doses up to 500 mg/kg bw/day. For the inhalation route, localized toxicity to the nose was observed (i.e., squamous metaplasia and mild degeneration of the olfactory epithelium) for formic acid; no systemic toxicity was observed up to the highest dose tested.

Exposures of the general population to formic acid were estimated based on levels in air and food packaging materials, and from use of hair products; to sodium formate based on levels in food packaging materials and from use of body moisturizers; and to ethyl formate from its potential use as a food flavouring substance. Emissions from building materials may present a transient, low-level inhalation exposure to methyl formate, which is of low concern for human health.

Margins of exposure comparing effect levels for the critical hazard endpoints (noted above) and the estimates of exposure were considered adequate to address uncertainties in the health effects and exposure databases for formic acid, sodium formate and ethyl formate. Exposure to methyl formate is considered to be low, and the potential risk to human health is considered low.

On the basis of the adequacy of margins between critical effect levels and estimated exposures, and on information presented in this screening assessment, it is concluded that formic acid, methyl formate, ethyl formate and sodium formate do not meet the criteria under paragraph 64(c) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is concluded that formic acid, methyl formate, ethyl formate and sodium formate do not meet any of the criteria under section 64 of CEPA.

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Tables and Figures

1. Introduction

Pursuant to sections 68 and 74 of the Canadian Environmental Protection Act, 1999 (CEPA) (Canada 1999), the Minister of Environment and the Minister of Health have conducted a screening assessment of four substances referred to collectively as the Formic Acid and Formates Substance Group to determine whether these substances present or may present a risk to the environment or to human health.

The substances in this group were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other human health concerns (Environment and Climate Change Canada, Health Canada [modified 2007]). Methyl formate did not meet categorization criteria for human health, but was identified as a human health priority.

The ecological risk of substances in the Formic Acid and Formates Substance Group was characterized using the Ecological Risk Classification of organic substances (ERC) (ECCC 2016a). The ERC describes the hazard of a substance using key metrics including mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity and considers the possible exposure of organisms in the aquatic and terrestrial environments based on factors including potential emission rates, overall persistence and long-range transport potential in air. The various lines of evidence are combined to identify substances which warrant further evaluation of their potential to cause harm to the environment or which have a low likelihood of causing harm to the environment.

Formic acid, methyl formate and sodium formate were previously reviewed internationally through the High Production Volume (HPV) Chemicals Programme of the Organisation for Economic Co-operation and Development (OECD), and a Screening Information Data Set (SIDS) Initial Assessment Report (SIAR) is available (OECD 2008). These assessments undergo rigorous review and endorsement processes by international governmental authorities. Health Canada and Environment and Climate Change Canada are active participants in this process and consider these assessments to be reliable. In addition, the health effects of formic acid and ethyl formate when used as flavouring agents were previously evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA 1997), and Health Canada considers these assessments to be reliable.

The OECD SIAR was used as the basis for selecting critical health effects for characterizing risk to human health in this assessment, for formic acid, methyl formate and sodium formate. For these substances, a literature search was conducted from 2007, one year prior to the SIDS initial assessment meeting (SIAM; April 2008), to June 2016. For ethyl formate, the health effects assessment in this report is based on available hazard data. Given the structural similarities among the substances in the Formic Acid and Formates Substances Group, potential risk is assessed using a read-

across approach for hazard endpoints in the absence of substance-specific data; this approach was also used in the OECD SIAR (OECD 2008).

This screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposure, including additional information submitted by stakeholders. Relevant data were identified up to June 2016.

This screening assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The draft of this screening assessment (published December 31, 2016) was subject to a 60-day public comment period. The ERC approach (published July 30, 2016) was peer reviewed, and was also subject to a 60-day public comment period.

While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Environment and Climate Change Canada and Health Canada.

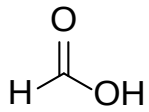
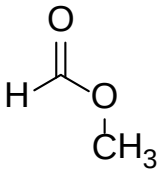
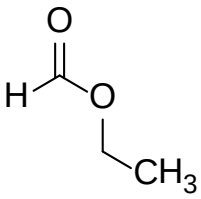
This screening assessment focuses on information critical to determining whether these substances meet the criteria as set out in section 64 of CEPA by examining scientific information and incorporating a weight of evidence approach and precaution[2]. The screening assessment presents the critical information and considerations and considerations on which the conclusions are based.

[2]A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products available to consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the Hazardous Products Regulations, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for hazardous products intended for workplace use, handling and storage. Similarly, a conclusion based on the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other Acts.

2. Identity of Substances

The Chemical Abstracts Service Registry Numbers (CAS RN[3]), Domestic Substances List (DSL) names and common names for the individual substances in the Formic Acid and Formates Substance Group are presented in Table 2-1.

Table 2-1. Substance identities

CAS RN (acronym)	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
64-18-6	Formic acid	 CH_2O_2	46
107-31-3	Formic acid, methyl ester (Methyl formate)	 $C_2H_4O_2$	60
109-94-4	Formic acid, ethyl ester (Ethyl formate)	 $C_3H_6O_2$	74

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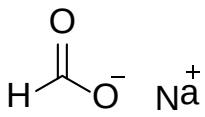
CAS RN (acronym)	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
141-53-7	Formic acid, sodium salt (Sodium formate)	 CH_2O_2Na	68

3. Physical and Chemical Properties

A summary of physical and chemical properties of the substances in the Formic Acid and Formates Substance Group is presented in Table 3-1, with the range of values indicated for each property. Additional physical and chemical properties are presented in ECCC (2016b).

Table 3-1. Experimental physical and chemical property values for the Formic Acid and Formates Substance Group

Property	Value or range	Type of data	Key reference(s)
Vapour pressure (mm Hg)	0–624.5	Calculated	Montgomery 2007; ECHA c2007-2015
Henry's law constant ($atm \cdot m^3/mol$)	1.67×10^{-7}–5×10^{-3}	Calculated	Howard 1993, 1997; Montgomery 2007
Water solubility (mg/L)	≥118 000	Experimental	Howard 1993, 1997; Montgomery 2007; Lide 2016
Log K_{ow} (dimensionless)	-1.8–0.33	Experimental Calculated	Howard 1993, 1997; Montgomery 2007; ECHA c2007-2015; Lide 2016
pK_a (dimensionless)	3.75–3.86	Experimental	ECHA c2007-2015; Lide 2016

Abbreviations: K_{ow}, octanol–water partition coefficient; pK_a, acid dissociation constant

4. Sources and Uses

Formic acid occurs naturally in plants and is also a product of microbial metabolism of organic matter and of atmospheric photo-oxidation (Howard 1997). The presence of formic acid, methyl formate and ethyl formate has been reported in certain foods, including fruits, honey, wine, roasted coffee, evaporated milk and cheese (OECD 2008; US FDA 1976), but there is a paucity of more recent information regarding levels. In Canada, sources of formic acid and formates are mostly anthropogenic, and derive from industrial activities, disposal (down the drain) and use of cleaning products containing formic acid and sodium formate.

On the basis of information submitted pursuant to section 71 of CEPA regarding commercial activity in Canada, only sodium formate was reported to be manufactured in Canada, while methyl formate, ethyl formate and sodium formate were all reported to be imported into Canada. Manufactured and imported quantities are summarized in Table 4-1 (Environment Canada 2013). While information on recent quantities of formic acid in commerce is not available, it is a commodity chemical and expected to be in commerce in Canada in high quantities. In the United States (US), greater than 28 947 451 lb (i.e., >13 000 000 kg) of formic acid was imported in 2012 (CDAT [modified 2014]).

Table 4-1. Summary of information submitted pursuant to section 71 of CEPA for methyl formate, ethyl formate and sodium formate in Canada in 2011[a]

Common name	Range of manufacture quantity (kg)	Range of import quantity (kg)
Methyl formate	0	10 000–100 000
Ethyl formate	0	100–1 000
Sodium formate	100 000–1 000 000	1 000 000–10 000 000

[a] Values reflect quantities reported in response to surveys conducted under section 71 of CEPA (Environment Canada 2013). See survey for specific inclusions and exclusions (Schedules 2 and 3).

In Canada, as well as globally, formic acid and sodium formate can be used as reagents for chemical synthesis, and as preservatives and pH regulators in fabric softeners, laundry and dishwasher detergents, cosmetics, and anti-rust treatment products (Household Products Database 1993-; Showell 2005; MSDS 2008; OECD 2008; CIR 2013; SkinDeep 2015). Sodium formate is used as a pH regulator in water treatment for industrial applications (BASF 2012; Environment Canada 2013). Methyl formate and ethyl formate are primarily used in the synthesis of chemical compounds and in agricultural products, respectively (OECD 2008; Montgomery 2007).

Table 4-2 presents a summary of Canadian uses for the three formates on the basis of information submitted pursuant to section 71 of CEPA (Environment Canada 2013). Other uses were also reported but are not indicated herein due to confidentiality.

Table 4-2. Summary of the major uses of methyl formate, ethyl formate and sodium formate in Canada (based on consumer and commercial DSL codes reported in a section 71 survey)

Major uses	Methyl formate	Ethyl formate	Sodium formate
Agricultural products, mixtures or manufactured items (non-pesticidal)	N	Y	N
Chemical synthesis	N	N	Y
Oil and natural gas extraction	N	N	Y
Paints and coatings	N	N	Y
Paper products, mixtures or manufactured items	N	N	Y
Water treatment	N	N	Y

The Food Chemicals Codex (FCC) indicates that formic acid is used as a flavouring agent and preservative, and ethyl formate is used as a flavouring agent (FCC USP 2016). Formic acid and ethyl formate are both listed in Fenaroli's Handbook of Flavor Ingredients (Burdock 2010). The US Food and Drug Administration permits the use of formic acid as a synthetic food flavouring substance and adjuvant (specified in 21CFR172.515; US FDA 2015a) and ethyl formate as a food flavouring agent and adjuvant (specified in 21CFR184.1295; US FDA 2015b). The European Union permits the use of methyl formate as a flavouring in food (EU Food Flavourings Database). No definitive information is available concerning the potential use of methyl formate or formic acid as food flavourings in Canada (personal communications, emails from Food Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada, dated 2015; unreferenced). According to one material safety data sheet, ethyl formate is used as a flavouring agent in bubble gum in Canada (MSDS 2011).

Canada regulates food preservatives as food additives. Although the FCC recognizes that formic acid can serve the function as a food preservative, Canada does not have a food additive provision that permits this use of formic acid.

Additional uses are listed in Table 4-3.

Table 4-3. Additional uses in Canada for the Formic Acid and Formates Substance Group

Use	Formic acid	Methyl formate	Ethyl formate	Sodium formate
Food packaging materials[a]	Y (coatings, epoxy-based materials, cellulose, paper and paperboard materials, melamine-formaldehyde resins and components in exterior inks)	N	N	Y (paper-based materials, melamine-formaldehyde resins and components in exterior inks)
Drug Product Database[b]	N	N	N	N
Natural Health Products Ingredients Database[c]	Y (non-medicinal role as flavour enhancer or antimicrobial preservative; homeopathic role)	N	Y (non-medicinal role as flavour enhancer)	Y (non-medicinal role as flavour enhancer)
Licensed Natural Health Products Database[d]	Y (as non-medicinal ingredient in a limited number of topical natural health products; as medicinal ingredient in a limited number of homeopathic medicines)	N	N	N
Reported to be present in cosmetics, based on notifications submitted under the Cosmetic Regulations to Health Canada[e]	Y (cleansers and soaps, shampoos, conditioners, hair dye, and hair styling products)	N	N	Y (moisturizers)
Formulant in pest control products	Y (e.g., acaracides, insecticides and a	N	Y (e.g., insect repellent,	N

Use	Formic acid	Methyl formate	Ethyl formate	Sodium formate
registered in Canada[f]	herbicide)		rodenticides and insecticides)	
Active ingredient in pest control product in Canada[g]	Y (mite treatment for bee hives)	N	N	N

Abbreviations: Y, Yes; N, No.

[a] June 2015 email from the Food Directorate, Health Canada to the Risk Management Bureau, Health Canada; unreferenced

[b] DPD [modified 2015]

[c] NHPID 2016– identified with an Acceptable Daily Intake of up to 3 mg/kg bw/day, expressed as formate equivalents

[d] LNHPD 2016

[e] June 2015 email from the Consumer Product Safety Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada

[f] September 2015 email from the Pest Management Regulatory Agency, Health Canada to the Risk Management Bureau, Health Canada; unreferenced

[g] Pesticide Label Search 2016

5. Potential to Cause Ecological Harm

5.1 Characterization of Ecological Risk

The ecological risks of substances in the Formic Acid and Formates Substance Group were characterized using the Ecological Risk Classification of organic substances (ERC) (ECCC 2016a). The ERC is a risk-based approach that considers multiple metrics for both hazard and exposure based on weighted consideration of multiple lines of evidence for determining risk classification. The various lines of evidence are combined to discriminate between substances of lower or higher potency and lower or higher potential for exposure in various media. This approach reduces the overall uncertainty with risk characterization compared to an approach that relies on a single metric in a single medium (e.g., LC_{50}) for characterization. The following summarizes the approach, which is described in detail in ECCC (2016a).

Data on physical-chemical properties, fate (chemical half-lives in various media and biota, partition coefficients, and fish bioconcentration), acute fish ecotoxicity, and chemical import or manufacture volume in Canada were collected from scientific literature, from available empirical databases (e.g., OECD QSAR Toolbox), and from surveys under section 71 of CEPA, or were generated using selected Quantitative Structure-Activity Relationship (QSAR) or mass-balance fate and bioaccumulation

models. These data were used as inputs to other mass-balance models or to complete the substance hazard and exposure profiles.

Hazard profiles were established based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Exposure profiles were also composed of multiple metrics including potential emission rate, overall persistence, and long-range transport potential. Hazard and exposure profiles were compared to decision criteria in order to classify the hazard and exposure potentials for each organic substance as low, moderate, or high. Additional rules were applied (e.g., classification consistency, margin of exposure) to refine the preliminary classifications of hazard or exposure.

A risk matrix was used to assign a low, moderate or high classification of potential risk for each substance based on its hazard and exposure classifications. ERC classifications of potential risk were verified using a two-step approach. The first step adjusted the risk classification outcomes from moderate or high to low for substances which had a low estimated rate of emission to water after wastewater treatment, representing a low potential for exposure. The second step reviewed low risk potential classification outcomes using relatively conservative, local-scale (i.e., in the area immediately surrounding a point-source of discharge) risk scenarios, designed to be protective of the environment, to determine whether the classification of potential risk should be increased.

ERC uses a weighted approach to minimize the potential for both over and under classification of hazard and exposure and subsequent risk. The balanced approaches for dealing with uncertainties are described in greater detail in ECCC 2016a. The following describes two of the more substantial areas of uncertainty. Error with empirical or modelled acute toxicity values could result in changes in classification of hazard, particularly metrics relying on tissue residue values (i.e., mode of toxic action), many of which are predicted values from QSAR models. However, the impact of this error is mitigated by the fact that overestimation of median lethality will result in a conservative (protective) tissue residue used for critical body residue (CBR) analysis. Error with underestimation of acute toxicity will be mitigated through the use of other hazard metrics such as structural profiling of mode of action, reactivity and/or estrogen binding affinity. Changes or errors in chemical quantity could result in differences in classification of exposure as the exposure and risk classifications are highly sensitive to emission rate and use quantity. The ERC classifications thus reflect exposure and risk in Canada based on what is believed to be the current use quantity, and may not reflect future trends.

Critical data and considerations used to develop the substance-specific profiles for the substances in the Formic Acid and Formates Substance Group, and the hazard, exposure and risk classification results, are presented in ECCC (2016b).

The hazard and exposure classifications for the Formic Acid and Formates Substance Group are summarized in Table 5-1.

Table 5-1. Ecological Risk Classification results for the Formic Acid and Formates Substance Group

Substance	ERC hazard classification	ERC exposure classification	ERC risk classification
Formic acid	Low	High	Low
Methyl formate	Low	Low	Low
Ethyl formate	Low	Low	Low
Sodium formate	Low	High	Low

Formic acid and sodium formate were classified as having high potential for exposures based on their potential emission rates and overall persistence and long-range transport potential in air. All four substances have been classified as presenting a low ecological hazard. The four substances in this group are classified as having a low potential for ecological risk. It is therefore unlikely that these substances result in concerns for organisms or the broader integrity of the environment in Canada.

6. Potential to Cause Harm to Human Health

6.1 Exposure Assessment

Potential exposures to formic acid and formates from environmental media, food and use of products are presented in this section. Additional details of the exposure scenarios are summarized in the appendices.

Environmental Media

Substances in this group were not measured in drinking water and soil in Canada or elsewhere; however, information relevant to these substances in air is presented below. Based on the quantities in commerce of these substances in Canada, any potential

release to water and soil would yield low concentrations (below nanogram-level) in the environment or low exposures for the general population. Hence, water and soil are not expected to be significant sources of exposure to formic acid, sodium formate, methyl formate and ethyl formate for the general population.

Formic Acid

Formic acid has high vapour pressure (i.e., 42.6 mm Hg) (Lide 2016) and can be measured in air. Table 6-1 summarizes the results from a 1993 study that measured indoor and outdoor air concentrations of formic acid over a 24-hour period in four residences during the winter and nine residences during the summer in Boston, United States (Reiss et al. 1995). Potential indoor sources of formic acid may include household cleaners, building materials, and atmospheric reactions (Zhang et al. 1994; Reiss et al. 1995).

Table 6-1. Summary of air measurements from Boston residences (Reiss et al. 1995)

Indoor or outdoor	Season	Number detected/Sample size	Mean concentration (ppb)	Range (ppb)	Detection limit (ppb)
Indoor	Winter	14/14	9.8	7.4–14.4	1.54
Indoor	Summer	26/26	17.8	8.6–33.1	1.82
Outdoor	Winter	7/8	3.1	ND–5.6	1.54
Outdoor[a]	Summer	17/17	3.9	1.1–7.2	1.82

Abbreviations: ND, not detected

[a] It is unclear why the minimum concentration is below the detection limit reported in the publication.

While other studies show similar findings (Tuazon et al. 1981; Lawrence and Koutrkis 1994; Zhang et al. 1994; Khwaja et al. 1995; Uchiyama et al. 2015), the Reiss et al. study (1995) is considered the most relevant for characterizing Canadian general population exposure to formic acid from indoor and outdoor air. The highest mean concentration of formic acid, 17.8 ppb (equivalent to 0.034 mg/m^3), is considered an appropriate value for characterizing potential exposure to formic acid in air.

Sodium Formate

Sodium formate is highly water soluble (94.9 g/100 mL; Lide 2016) and its evaporation (at 20ºC) is negligible (CDC [modified 2015]); therefore, exposure via inhalation is not expected.

Methyl Formate

In a report included in the Canadian National Research Council material emissions database, out of 58 materials tested in chamber studies, three new types of building materials (i.e., one medium density fiberboard and two oriented strand board flooring materials) were found to generate emissions of methyl formate (Won and Lusztyk 2011). Chamber testing of air samples (in accordance with ASTM International guidelines) demonstrated peak concentrations of methyl formate ranging from 0.09 to 0.13 µg/m^3 at the 24th hour, after which emissions decreased. These measured emission levels are considered to be low and would be rapidly removed from indoor environments by the ventilation system. Therefore, emissions from building materials may present a risk of transient, low-level inhalation exposure to methyl formate, which is of low concern for human health.

Ethyl Formate

Measured concentrations of ethyl formate in air in Canada or elsewhere were not identified. However, in an Environmental Compliance Approval granted in 2013 to a manufacturing facility in Ontario, it was stated that emissions to the atmosphere from this facility included ethyl formate (Environmental Registry 2013). Potential exposure, if any, from this source is not of concern since the facility demonstrated compliance on an ongoing basis with Ontario Regulation 419/05; hence, it is not considered further in this screening assessment.

Food and Food Packaging

The usual and maximum levels of use for formic acid as a food flavouring reported by the Flavor and Extract Manufacturers Association as indicated in Fenaroli's Handbook of Flavor Ingredients (Burdock 2010) are one to two orders of magnitude lower than the FDA limits for the use of ethyl formate as flavouring (specified in 21CFR184.1295; US FDA 2015b). Therefore, the potential dietary exposure to this formic acid use would be at least one to two orders of magnitude lower than the potential dietary exposure to ethyl formate (discussed below). Consequently, potential food flavouring use is not expected to be a significant source of exposure to formic acid.

Dietary exposure in Canada to ethyl formate as a result of its potential use as a food flavouring was estimated by assuming that (1) foods in which ethyl formate could be used as a flavouring in the US would contain the substance at the maximum level

permitted (as per 21CFR184.1295; US FDA 2015b)[4]; and (2) these foods are consumed at rates based on the most recent 24-hour dietary recall data from the Canadian Community Health Survey, Cycle 2.2, Nutrition (Statistics Canada 2004). For children and adults, the resulting mean estimated exposures (for all persons) are 1.29 mg formate/kg bw/day and 0.40 mg formate/kg bw/day, respectively, and the 90th percentile estimated exposures (for all persons) are 2.81 mg formate/kg bw/day and 0.94 mg formate/kg bw/day, respectively (personal communications, emails from Food Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada, dated 2015; unreferenced). These estimates are considered to be conservative.

In Canada, formic acid and sodium formate are used in certain food packaging materials, including some with direct food contact. However, estimated exposures from these uses are low (even assuming that all types of foods, except for alcoholic beverages and infant formula, would be in direct contact with the food packaging material): 0.000864 mg/kg bw/day and 0.00343 mg/kg bw/day for formic acid and sodium formate, respectively (personal communications, emails from Food Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada, dated 2015; unreferenced).

[4] Canada has not established a list of permitted food flavourings and their maximum levels of use.

Products Used by Consumers

Formic Acid and Sodium Formate

Exposures to formic acid and sodium formate in cosmetics were characterized and are presented in Table 6-2. Estimates were based on the reported concentration ranges in notifications submitted under the Cosmetic Regulations to Health Canada (2015 email from Consumer Product Safety Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). In the absence of dermal absorption data, dermal absorption from cosmetic uses was assumed to be 100%. Daily dermal exposure to formic acid is estimated from use of hair spray, while acute exposure from infrequent use is estimated based on the presence of this substance in permanent hair dye. The estimate of dermal exposure to sodium formate is based on use of body moisturizers. While inhalation may be a route of exposure to formic acid during use of hair sprays and hair dyes, these uses are not the predominant sources of inhalation exposures.

Table 6-2. Summary of estimates of dermal exposures of an adult to formic acid and sodium formate from use of cosmetics

Substance	Product type	Concentration (% w/w)[a]	Per application exposure (mg/kg bw)	Daily exposure (mg/kg bw/day)
Formic acid	Hair spray (aerosol)	≤0.3	≤0.0093	≤0.014
Formic acid	Permanent hair dye (wash-in)	0.1–0.3	0.14–0.42	NA
Sodium formate	Body moisturizer	≤0.1	≤0.062	≤0.068

Abbreviations: NA, not applicable

[a] Concentrations are based on notifications submitted under the Cosmetic Regulations to Health Canada (2015 email from Consumer Product Safety Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced)

Formic acid was identified as an ingredient in anti-rust sprays at concentrations up to 5%. Evaporation of formic acid from the treated area during use is expected to be minimal because formic acid reacts chemically with the rust. Therefore, any potential exposure is primarily from sprayed droplets remaining in the air. Acute inhalation exposure to formic acid may occur from anti-rust sprays when used indoors.

There is also potential formic acid exposure from use of fabric softeners and sodium formate exposure from the use of laundry and dishwasher detergents; such uses are not expected to result in significant exposures.

In contrast to formic acid and sodium formate, neither methyl nor ethyl formate are present in products used by consumers.

6.2 Health Effects Assessment

The OECD SIDS Initial Assessment Report (2008) summarizes the health effects literature and characterizes the hazard related to formic acid, methyl formate and sodium formate as part of the formates category. It was used to inform the hazard section of this assessment, including the selection of critical health effect levels.

Literature searches were conducted for the OECD 2008 category-derived substances (i.e., formic acid, sodium formate and methyl formate) as well as for ethyl formate. For the OECD 2008 category substances, the literature search was conducted from 2007, one year prior to the SIAM (April 2008), to June 2016. The literature search for ethyl formate covered the period 2000 to 2016.

In its category information, the OECD (2008) states that methyl formate and ethyl formate initially metabolize to formic acid, which then dissociates rapidly to formate (OECD 2008). Similarly, formate salts dissociate rapidly in biological surroundings to the common metabolite formate. Therefore, the substances in the Formic Acid and Formates Substance Group are considered to be similar for evaluation purposes by Health Canada, and can be used in a read-across approach. Data from the structurally and physiologically similar analogue potassium hydrogen diformate (CAS RN 20642-05-1), which exhibits similar physical-chemical properties and toxicokinetics, were also used to inform the human health assessment.

Formate, which is also formed endogenously, is eliminated primarily from the body as exhaled carbon monoxide, with a minor amount excreted unchanged in urine. Formate degradation is mediated through the tetrafolate system, which is slower in humans than in rodents. Another species difference is that ingestion of high amounts of formic acid can result in metabolic acidosis in humans, but this is unlikely to occur in rodents. Consequently, caution is advised when extrapolating animal study results for formic acid and its salts to humans (OECD 2008).

The acute toxicity of formic acid is considered to be moderate via the oral route, and low via inhalation (OECD 2008). Sodium formate is of low acute toxicity via the oral route and of slight acute toxicity via inhalation (CIR 2013). Methyl formate is of moderate acute toxicity via the oral route and of low acute toxicity via the inhalation and dermal routes of exposure (OECD 2008). Ethyl formate is considered to be of slight acutely

toxicity via the oral route and of low acute toxicity via the dermal and inhalation routes of exposure (Health Council of the Netherlands 2002).

Formic acid is considered to be corrosive to skin and eyes based on its physical and chemical properties (pH less than 2). In addition, acute (BASF AG 1980) and chronic (NTP 1992) inhalation toxicity studies show that formic acid can cause respiratory tract irritation. Skin irritation was not observed for sodium formate (Covance 1997; Bayer AG 1999), but transient eye irritation was noted (CIR 2013).

No skin irritation was observed for ethyl formate in rabbits exposed to up to 20 mg/kg bw (Smyth et al. 1954; DFG 2012) and in humans exposed to up to 4% ethyl formate under occlusive applications (Snyder 1992). An instillation of ethyl formate was corrosive to the eyes of rabbits (Smyth et al. 1954; DFG 2012) and slightly irritating to the eyes of human volunteers at 330 mL/m^3 (Flury and Zernik 1931). Moderate to severe nasal irritation was also noted in human volunteers (Flury and Zernik 1931).

No evidence of skin sensitization was observed for formic acid, sodium formate, methyl formate or ethyl formate (Health Council of the Netherlands 2002; OECD 2008; MSDS 2015).

In the 13-week inhalation study in mice and rats exposed to formic acid, localized toxicity to the nose was observed at 64 ppm and above (≥122 mg/m^3), including squamous metaplasia and mild degeneration of the olfactory epithelium. As such, the no-observed-adverse-effect-concentration (NOAEC) and the lowest-observed-adverse-effect-concentration (LOAEC) for local effects are 32 ppm (60 mg/m^3) and 64 ppm (122 mg/m^3), respectively. However, systemic toxicity was not observed up to the highest dose tested; therefore, the no-observed-effect-concentration (NOEC) for systemic toxicity was established at 128 ppm (244 mg/m^3) (NTP 1992).

For oral administration, long-term studies conducted with potassium hydrogen diformate in rats and mice were used as a read-across for formic acid. In an 80-week long-term carcinogenicity study in mice, non-statistically significant body weight gain was lower in male mice dosed at 2000 mg/kg bw/day. In addition, necropsy revealed an increased incidence of hyperplasia in the forestomach at the limiting ridge in high-dose male mice, but it was not considered relevant to humans. No treatment-related mortality or increased tumour incidence were observed. A lowest-observed-adverse-effect level (LOAEL) was not established, and the no-observed-effect-level (NOEL) was 2000 mg/kg bw/day (Covance 2002b).

In a 104-week long-term carcinogenicity dietary study in rats, glandular stomach thickening and lesions observed at a dose of 400 mg potassium hydrogen diformate/kg

bw/day (equivalent to 280 mg formate/kg bw/day) and above were attributed to the acidity of the test material, whereas concurrent forestomach hyperplasia was not considered relevant to humans (Covance 2002a). At the highest dose and a systemic LOAEL of 2000 mg/kg bw/day, there was decreased weight gain, as well as effects indicative of test material acidity (Brunner's gland hypertrophy in the duodenum and acinar cell hypertrophy in the salivary gland). The systemic no-observed-adverse-effect-level (NOAEL) was 400 mg/kg bw/day.

No observable effects were found in a long-term dietary study in rats given ethyl formate at levels of up to 10 000 ppm (500 mg/kg bw/day) (Hagan et al. 1967; US FDA 1976; IPCS 1980).

The Formic Acid and Formates Substance Group is not considered to be genotoxic or carcinogenic based on read-across from other long-term studies (Health Council of the Netherlands 2002; OECD 2008).

No developmental effects were observed in rats or rabbits at orally administered gavage doses of up to 945 mg/kg bw/day for sodium formate (BASF AG 2005). Similarly, no reproductive effects assessed by examining sperm motility and vaginal cytology were observed in rats and mice exposed via inhalation to formic acid at concentrations of up to 244 mg/m^3 (NTP 1992).

6.3 Characterization of Risk to Human Health

No evidence for genotoxicity or carcinogenicity was observed in the available empirical data for the Formic Acid and Formates Substance Group. Therefore, characterization of risk in this screening assessment is based on non-cancer effects. Tables 6-3 and 6-4 provide the relevant estimates of exposure and critical effect levels for formic acid and sodium formate, respectively, and the resulting margins of exposure (MOEs).

Table 6-3. Relevant exposure and hazard values for formic acid, as well as MOEs, for determination of risk

Exposure scenario	Estimated exposure	Critical effect level	MOE
Food packaging materials (daily, oral)	0.000864 mg/kg bw/day, equivalent to 0.000845 mg formate/kg bw/day	NOAEL (oral) = 400 mg potassium hydrogen diformate/kg bw/day, equivalent to 280 mg formate/kg bw/day	>331 000
Hair spray (daily,	0.014 mg/kg bw/day, equivalent to 0.014 mg	NOAEL (oral) = 400 mg potassium hydrogen	>20 000

Exposure scenario	Estimated exposure	Critical effect level	MOE
dermal)[a]	formate/kg bw/day	diformate/kg bw/day, equivalent to 280 mg formate/kg bw/day	
Permanent hair dye (per application, dermal)[a]	0.14–0.42 mg/kg bw	NOEL (oral, gavage) = 945 mg sodium formate/kg bw/day, equivalent to 626 mg formate/kg bw/day	1 490–4 470
Air (daily, inhalation)	0.034 mg/m^3	NOAEC (local) = 60 mg/m^3	1 760
Air (daily, inhalation)	0.034 mg/m^3	NOEC (systemic) = 244 mg/m^3	7 170

[a] In the absence of dermal absorption data, dermal absorption from cosmetic uses was assumed to be 100%.

Table 6-4 Relevant exposure and hazard values for sodium formate, as well as MOEs, for determination of risk

Exposure scenario	Estimated exposure	Critical effect level	MOE
Food packaging materials (daily, oral)	0.00343 mg/kg bw/day, equivalent to 0.00227 mg formate/kg bw/day	NOAEL (oral) = 400 mg potassium hydrogen diformate/kg bw/day, equivalent to 280 mg formate/kg bw/day	>123 000
Body moisturizer (daily, dermal)[a]	0.068 mg/kg bw/day, equivalent to 0.045 mg formate/kg bw/day	NOAEL (oral) = 400 mg potassium hydrogen diformate/kg bw/day, equivalent to 280 mg formate/kg bw/day	>6 220

[a] In the absence of dermal absorption data, dermal absorption from cosmetic uses was assumed to be 100%.

As shown in Table 6-3, comparison of estimated exposures to formic acid with the range of critical effect levels results in MOEs ranging from 1 490 to above 331 000. Comparison of estimated exposures to sodium formate with the oral NOAEL shown in Table 6-4, results in MOEs from 6 220 to above 123 000. These margins of exposure for formic acid and sodium formate are considered adequate to address uncertainties in the exposure and health effects databases.

Acute exposure to formic acid from use of anti-rust sprays in indoor environments is possible. The risk of exposure from use of anti-rust sprays is expected to be low, taking into account the following factors: anti-rust treatment is carried out infrequently (usually

once per year), exposure occurs for only a short time during application, anti-rust products are more likely to be used outdoors than indoors, a small fraction of spray particles are below the respirable range, and noticeable local effects (such as irritation) occur before adverse systemic effects do, thereby prompting the consumer to reduce usage or take precautions.

Acute dermal exposure to formic acid in permanent hair dyes was identified. An oral gavage developmental toxicity study was selected based on the appropriate time frame, and the NOEL was established at the highest dose tested (i.e., 945 mg/kg bw/day) due to the lack of systemic effects.

For ethyl formate, the mean estimated exposures from food flavouring use are 1.29 mg formate/kg bw/day for children and 0.40 mg formate/kg bw/day for adults; these estimates are considered to be conservative. Comparison of these estimated dietary exposures to the oral NOEL of 500 mg ethyl formate/kg bw/day, which is equivalent to 304 mg formate/kg bw/day, results in margins of exposure ranging from 235 to 760. These margins are considered adequate to address uncertainties in the exposure and health effects databases. Furthermore, the estimated dietary exposures are below the upper bound of the Acceptable Daily Intake of 0 to 3 mg/kg bw/day established for ethyl formate and formic acid by the Joint FAO/WHO Expert Committee on Food Additives (JECFA 1997). Overall, the risk from the potential use of ethyl formate as a food flavouring is expected to be very low.

6.4 Uncertainties in Evaluation of Risk to Human Health

The primary uncertainty in the estimation of dietary exposure to ethyl formate is that Health Canada does not have current, comprehensive data on the levels of this substance, if any, that are actually present in foods that are available in Canada today. As a surrogate for such data, the dietary exposure assessment for the use of ethyl formate as a food flavouring substance conservatively assumed that it is used as flavouring in all foods where the US permits such use and it is used in those foods at the maximum levels permitted by the appropriate authorities. On the basis of this conservative approach, there is high confidence that actual dietary exposures would be lower than the estimates.

Potential exposures from use of products by consumers were estimated using models and conservative assumptions, and are expected to be overestimates of actual exposures.

There is also inherent uncertainty in the use of read-across hazard data from one substance to another. Although potassium hydrogen diformate is known to have a similar toxicological profile to the substances under consideration, it is possible that the health effects endpoints and/or critical effect values are different.

As no dermal toxicity studies were identified, oral toxicity data were used to derive MOEs for dermal exposures. While uncertainty exists with use of route-to-route extrapolation, there is confidence that the margins are protective of human health as oral absorption is usually greater than dermal absorption, which was assumed to be 100% in this screening assessment but is likely less in reality.

There is uncertainty in the characterization of exposure to formic acid in air because the available data are limited and outdated (i.e., measured in 1993).

There is uncertainty associated with the risk characterization due to the duration of the study selected to characterize the risk of potential inhalation exposure to formic acid in air, which could be continuous (i.e., 24 h per day, every day). In the selected inhalation study, the dosing was 6 h per day, 5 days per week for 13 weeks. Despite this, the MOE, which is greater than 1760, is considered adequate to address this uncertainty.

7. Conclusion

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from formic acid, methyl formate, ethyl formate and sodium formate. It is concluded that formic acid, methyl formate, ethyl formate and sodium formate do not meet the criteria under paragraphs 64(a) or (b) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

On the basis of the information presented in this screening assessment, it is concluded that formic acid, methyl formate, ethyl formate and sodium formate do not meet the criteria under paragraph 64(c) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is concluded that formic acid, methyl formate, ethyl formate and sodium formate do not meet any of the criteria set out in section 64 of CEPA.

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Appendix A. Estimated oral exposure to ethyl formate used as a flavouring agent in foods

21CFR184.1295 in the United States' Code of Federal Regulations (US CFR) provides for and limits the use of ethyl formate in certain foods, and specifies numerical limits for good manufacturing practice in those food categories (i.e., 0.05% in baked goods; 0.04% in chewing gum, hard candy, and soft candy; 0.02% in frozen dairy desserts; 0.03% in gelatins, puddings, and fillings; and 0.01% in all other food categories) (US FDA 1984). Taking into account the formate moiety, the limits were converted to ppm and these maximum concentrations were used to estimate the dietary intake of ethyl formate as a flavouring agent from foods.

Table A-1. Limits of formate in certain foods according to the US CFR 21CFR184.1295 for ethyl formate

Food category	Maximum concentration of formate (ppm)
Bakery products	304
Confectionery (i.e., hard candy, soft candy, gum, candy bars)	243.2
Gelatins, puddings, and fillings	182.4
Frozen dairy desserts	121.6
Other flavoured foods	60.8

Appendix B. Estimated dermal exposures to formic acid and sodium formate

Exposures were estimated based on the assumed weight, 70.9 kg, of an adult (Health Canada 1998) and the use behaviours of an adult. Exposures were estimated using ConsExpo version 4.0 or algorithms from the model (ConsExpo 2006). In the absence of dermal absorption data, dermal absorption was assumed to be 100%.

Table B-1. Exposure parameter assumptions

Exposure scenario	Assumptions
Hair spray	Frequency: 1.49/day (Loretz et al. 2006) Product amount: 2.58 g/application (Loretz et al. 2006) Retention factor: 0.085 (Assuming 15% is loss from spray action and a transfer factor of 0.1 from hair to scalp)
Permanent hair dye	Exposure frequency: 0.02/day (7.99/year) (Statistics Canada

Exposure scenario	Assumptions
(wash-in)	2012) Product amount: 100 g/application (RIVM 2006) Overall retention factor: 0.10 (SCCS 2012)
Body moisturizer	Exposure frequency: 1.1/day (Loretz et al. 2005) Product amount: 4.4 g/application (Loretz et al. 2005)