Government of Canada Gouvernement du Canada

Risk Management Approach

for

Carbamic acid, ethyl ester

(Ethyl carbamate)

Chemical Abstracts Service Registry Number (CAS RN):

51-79-6

Health Canada

June 2016

Canada

Summary of Proposed Risk Management

This document builds on the previously published risk management scope document and outlines the proposed risk management actions for ethyl carbamate. In particular, the Government of Canada is proposing to:

- Review the existing Canadian standards (Maximum Levels) for ethyl carbamate in certain alcoholic beverages and consider amending them, if warranted;
- Continue to support the development and implementation of additional techniques or tools available to industry that will minimize ethyl carbamate formation in alcoholic beverages;
- Continue encouraging industry to adopt ethyl carbamate reduction strategies;
- Consider developing information documents and/or consumption advice for consumers of certain alcoholic beverages that have the potential to contain higher concentrations of ethyl carbamate; and
- Assess the impact of Canada's Low-Risk Alcohol Drinking Guidelines on reducing exposure to ethyl carbamate.

In addition to these proposed actions, in September 2013, Health Canada enabled the use of the enzyme urease in the manufacture of wine and sake to reduce formation of ethyl carbamate. Future monitoring data will be evaluated and used by Health Canada to determine the effectiveness of this action in reducing exposure to ethyl carbamate.

Information or comments on the items above should be provided (on or before July 27, 2016), to the contact details identified in section 8 of this document, to inform risk management decision-making.

The risk management options outlined in this document may evolve from additional information obtained from the public comment period or through the consideration of assessments and risk management options published for other substances under the Chemicals Management Plan. This will help to ensure effective, coordinated, and consistent risk management decision-making.

Note: The above summary is an abridged list of actions proposed to manage this substance. Please refer to section 3 of this document for more complete details.

Table of Contents

1. Context

The *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999) provides the authority for the Minister of the Environment and the Minister of Health (the Ministers) to conduct assessments to determine if substances are toxic to the environment and/or to human health as set out in section 64 of CEPA [1,2], and, if so, to manage the associated risks.

As part of the second phase of the Chemicals Management Plan (CMP), the Ministers plan to assess and manage, where appropriate, the potential health and ecological risks associated with approximately 500 substances in 9 Substance Groupings (Canada 2011). The substance carbamic acid, ethyl ester, hereinafter referred to as ethyl carbamate, is one of the six substances included in the Internationally Classified Substance Grouping of the CMP.

2. Issue

2.1 Final Screening Assessment Report Conclusion

Health Canada and Environment Canada conducted a joint scientific assessment relevant to the evaluation of ethyl carbamate in Canada. A notice summarizing the scientific considerations of the final screening assessment for this substance was published in the *Canada Gazette*, Part I, on May 28, 2016 (Canada 2016a).

[1] Section 64 [of CEPA]: *For the purposes of* [Parts 5 and 6 of CEPA]*, except where the expression "inherently toxic" appears, a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that*

(a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;

(b) constitute or may constitute a danger to the environment on which life depends; or

(c) constitute or may constitute a danger in Canada to human life or health.

[2] A determination of whether one or more of the criteria of section 64 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 the use of consumer products. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Hazardous Products Regulations* and the *Controlled Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. 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.

Based on the information available, the final screening assessment concludes that ethyl carbamate meets the criterion under section 64(*c*) of CEPA , because it is 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 (Canada 2016b).

The critical effect for characterization of risk associated with exposure to ethyl carbamate is carcinogenicity. The exposure of concern for human health is from consumption of alcoholic beverages. As such, this document will focus on this source of exposure (see section 5).

The proposed risk management options described in this document may be subject to change. For further information on the final screening assessment for ethyl carbamate, refer to http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=C24225A8-1.

2.2 Recommendation under CEPA

Based on the findings of the final screening assessment conducted under section 68 of CEPA, the Ministers propose[3] to take no further action under CEPA on ethyl carbamate at this time. Health Canada currently has risk management actions in place and others are being proposed under the *Food and Drugs Act* (Canada 1985) to reduce human exposure to ethyl carbamate from alcoholic beverages. The Minister of Health is releasing this risk management document to continue discussions with stakeholders on the manner in which Health Canada intends to implement preventive or control actions in relation to the substance.

2.3 Public Comment Period on the Risk Management Scope

The risk management scope document for ethyl carbamate, which summarized the risk management actions under consideration at that time, was published on July 19, 2014 as part of the Internationally Classified Substance Grouping. Industry and other interested stakeholders were invited to submit comments on the risk management scope document during a 60-day comment period. No public comments were received for ethyl carbamate.

[3] When a substance is found to meet one or more of the criteria under section 64 of CEPA, the Ministers can propose to take no further action under CEPA with respect to the substance, add the substance to the Priority Substances List for further assessment, or recommend the addition of the substance to the List of Toxic Substances in Schedule 1 of the Act.

3. Proposed Risk Management

3.1 Proposed Human Health Objective

Proposed human health objectives are quantitative or qualitative statements of what should be achieved to address human health concerns.

For ethyl carbamate, the proposed objective is focused on addressing the exposure sources of concern outlined in section 5 of this document. As such, the proposed human health objective for ethyl carbamate is to decrease human exposure from dietary sources.

3.2 Proposed Risk Management Objective and Proposed Actions

Proposed risk management objectives set quantitative or qualitative targets to be achieved by the implementation of risk management regulations, instrument(s) and/or tool(s) for a given substance or substances. The proposed risk management objective for ethyl carbamate is to reduce exposure that occurs as a result of consumption of alcoholic beverages.

To achieve the proposed risk management objective and to work towards achieving the proposed human health objective, the proposed risk management actions for ethyl carbamate are to:

- Review the existing Canadian standards (Maximum Levels) for ethyl carbamate in certain alcoholic beverages and consider amending them, if warranted;

- Continue to support the development and implementation of additional techniques or tools available to industry that will minimize ethyl carbamate formation in alcoholic beverages. This action includes prioritizing the evaluation of food additives that may reduce the formation of ethyl carbamate;

- Continue to encourage industry to adopt ethyl carbamate reduction strategies, such as those described in the *Codex Alimentarius Code of Practice for the Prevention and Reduction of Ethyl Carbamate Contamination in Stone Fruit Distillates.* This action will be done through direct stakeholder outreach or through messaging on the Health Canada website;

- Consider developing information documents and/or consumption advice for consumers of certain alcoholic beverages that have the potential to contain higher concentrations of ethyl carbamate; and

- Assess the impact of Canada's Low-Risk Alcohol Drinking Guidelines (LRDG) on reducing exposure to ethyl carbamate. The LRDG were developed by a team of independent Canadian and international experts on behalf of the National Alcohol Strategy Advisory Committee and published by the Canadian Centre on Substance Abuse (CCSA). The guidelines are found at the CCSA website: http://www.ccsa.ca/Eng/topics/alcohol/drinking-guidelines/Pages/default.aspx

In addition to these proposed actions, Health Canada has enabled the use of the enzyme urease in the manufacture of wine and sake to reduce the formation of ethyl carbamate. This action became effective on September 3, 2013 and is reflected in the *List of Permitted Food Enzymes*, incorporated by reference in the *Marketing Authorization for Food Additives that May be Used as Food Enzymes*, issued under the authority of the *Food and Drugs Act*. Future monitoring data of ethyl carbamate levels in these alcoholic beverages, collected by provincial liquor control boards and the Canadian Food Inspection Agency, will be evaluated by Health Canada and used to determine the effectiveness of this recent risk management action in reducing exposure to ethyl carbamate.

Following the publication of this risk management approach document, each risk management action presented in this document will be assessed in detail by Health Canada. The results of that assessment and information submitted through the public comment period, as well as any other pertinent information will be used in the selection and development of risk management.

3.3 Risk Management Information Gaps

At this time, no additional information is required from industry; however, monitoring of ethyl carbamate levels in alcoholic beverages will continue. These monitoring data may provide information on the use and effectiveness of ethyl carbamate reduction tools and strategies, such as enabling the use of urease in the manufacture of wine and sake and the adoption of the Codex *Code of Practice for the Prevention and Reduction of Ethyl Carbamate Contamination in Stone Fruit Distillates* by industry.

4. Background

4.1 Current Uses

Based on information obtained from stakeholder consultation in 2012-2013, no single company has been identified as having imported or used ethyl carbamate above the reporting threshold of 100 kg per year in Canada. In Canada and internationally, the current uses of ethyl carbamate are limited to medical research on laboratory animals where it is used for its anaesthetic or neoplastic properties (Canada 2016b).

5. Exposure Sources and Identified Risks

Ethyl carbamate is a by-product of the fermentation process and has been detected in many types of fermented foods and beverages. It is also a constituent of tobacco plants and present in main stream tobacco smoke. Exposure of the general population of Canada to ethyl carbamate is primarily from the diet, particularly from alcoholic beverages which typically have the highest reported ethyl carbamate levels of all foods.

The formation of ethyl carbamate in alcoholic beverages is dependent on the chemical precursors and potential catalysts available in the raw material, among other factors. In wine, for example, arginine is a naturally occurring amino acid in grapes and is a food source for yeast (Zimmerli and Schlatter 1991). Yeast consumes arginine and produces urea, which reacts with ethanol produced during alcoholic fermentation to form ethyl carbamate. In stone fruit brandies, naturally-present hydrogen cyanide (also called hydrocyanic acid) is a key precursor in the formation of ethyl carbamate.

The critical effect for characterization of risk to human health associated with exposure to ethyl carbamate is carcinogenicity. There is also strong evidence that ethyl carbamate is genotoxic and a multisite carcinogen. Modelling was used in the exposure assessment (Canada 2016b). The margins between critical effects and the upper limits of dietary exposure for adults from alcohol consumption were deemed of potential concern to human health for long-term exposure. Corresponding margins of exposure for the general population, excluding alcohol consumption, were not of concern to human health.

The Government of Canada considered, where available, risk assessment information relevant to children’s exposure to this substance. As part of the CMP, the Government asked industry and interested stakeholders to submit any information on the substance that may be used to inform risk assessment, risk

management and product stewardship. In particular, stakeholders were asked if any of the products or manufactured items containing the substance were intended for use by children. No manufactured items or consumer products containing ethyl carbamate were reported. As ethyl carbamate can be found in fermented foods likely consumed by children, exposure estimates were calculated in the screening assessment. However, the margins between critical effects and the estimate of daily intake of ethyl carbamate by children were not considered to be of concern to human health.

Implicated sectors, based on the main sources of exposure, include those associated with the food industry, particularly the alcoholic beverage industry.

6. Alternatives and Socio-economic Considerations for Risk Management

Since ethyl carbamate is a by-product formed in foods (including alcoholic beverages), information on alternatives is not relevant. In Canada and internationally, the current uses of ethyl carbamate are limited to medical research on laboratory animals.

The Government of Canada will take socio-economic considerations into account when selecting and developing a regulation, instrument, or tool to address concerns related to ethyl carbamate.

7. Overview of Existing Risk Management

7.1 Related Canadian Risk Management Context

Federal

The enzyme urease is on the *List of Permitted Food Enzymes*, incorporated by reference in the *Marketing Authorization for Food Additives that May be Used as Food Enzymes*, issued under the authority of the *Food and Drugs Act*. Urease is permitted to be used in the manufacture of wine and sake to reduce the formation of ethyl carbamate (Health Canada 2013a).

Ethyl carbamate is listed in the *Canadian Standards (maximum levels) for Various Chemical Contaminants in Foods* where maximum levels have been established for certain alcoholic beverages (Health Canada 2013b). The Canadian Standards (maximum levels)[4,5] for ethyl carbamate are:

- 30 ppb in table wines;
- 100 ppb in fortified wines;
- 150 ppb in distilled spirits;
- 400 ppb in fruit brandies and liqueurs; and
- 200 ppb in sake.

More information may be found at: http://www.hc-sc.gc.ca/fn-an/securit/chem-chim/contaminants-guidelines-directives-eng.php

Provincial

Provincial and Territorial liquor boards oversee the control, distribution and sale of alcoholic beverages. The liquor boards may establish separate maximum levels[5] for ethyl carbamate and monitor alcoholic beverages to ensure maximum levels are not exceed.

La Société des alcools du Québec (SAQ) has established maximum levels[5] for ethyl carbamate in alcoholic beverages similar to Health Canada, with the addition of levels for beer. The SAQ maximum levels[4] are as follows:

- 30 ppb in wine;
- 100 ppb in fortified wines;
- 15 ppb in beer;
- 30 ppb in strong and extra-strong beer (SAQ, 2014).

More information may be found at: http://marketing.globalwinespirits.com/SAQ_B2B/Gestion%20Qualite/Guide_constitution_et_stabilit%C3%A9%20ANG.pdf

The Liquor Control Board of Ontario (LCBO) also has established maximum levels[5] for ethyl carbamate in alcoholic beverages similar to Health Canada. The LCBO has a lower level for sake containing less than 14% alcohol and has established maximum levels for other types of alcoholic beverages. The LCBO maximum levels[4] are as follows:

- 30 ppb in table wine;
- 100 ppb in fortified wine;
- 30 ppb in sake;

[4] The units reported in the original documentation by Health Canada, the LCBO, and the SAQ are all reported in this document in ppb for ease of comparison. Note that ppb (parts per billion) is equivalent to µg/kg (microgram per kilogram) and µg/L (microgram per litre).

[5] The terms “levels”, “limits”, “concentrations”, and “guidelines” are all used to describe the maximum amounts of ethyl carbamate established by various organizations. The term “levels” has been used in this document for consistency.

- 15 ppb in regular beer;
- 30 ppb in extra strong beer with >8.5% alc./vol.;
- 30 ppb in cider;
- 15 ppb in cooler/ready-to-drink (beverages);
- 100 ppb in dairy based coolers;
- 150 ppb in spirits; and
- 400 ppb in fruit spirit.

The following exceptions to the LCBO maximum levels also apply and are under review by Health Canada:

- All wines priced greater than $30.00 per bottle (retail) and in quantities less than 200 cases per year will fall under the maximum level of 150 ppb ethyl carbamate;
- Rare sherries and other fortified wine products where the price exceeds $70.00 per case (wholesale) and in quantities less than 200 cases per year will fall under the maximum level of 400 ppb ethyl carbamate.
- Sake with at least 14% declared alcohol will fall under the maximum level of 200 ppb ethyl carbamate.
- Pre-shipment or submission samples of all future orders will be tested, and accepted, only if the ethyl carbamate reading is below 85% of the maximum level. (LCBO, 2014).

More information may be found at:
http://www.doingbusinesswithlcbo.com/tro/Packaging-Quality/Downloads/PPS_EN.pdf

7.2 Pertinent International Risk Management Context

United States

Urease is listed as an acceptable wine additive “to reduce levels of naturally occurring urea in wine to help prevent the formation of ethyl carbamate” in the United States (U.S.) Code of Federal Regulations Title 27, *Section 24.246: Materials authorized for the treatment of wine and juice* (CFR 2010). Urease is also listed as an ingredient generally recognized as safe in food (wine), to reduce the formation of ethyl carbamate, according to the U.S. Code of Federal Regulations Title 21, *Section 184.1924: Urease enzyme preparation from lactobacillus fermentum* (CFR 2013).

The U.S. Food and Drug Administration makes available the *Ethyl Carbamate Preventative Action Manual* prepared by the University of California. This manual identifies control measures wineries may implement to reduce levels of ethyl carbamate (UC Davis 1997).

European Union

The concentration of hydrocyanic acid, an important precursor of ethyl carbamate formation, is regulated in stone fruit spirits and stone fruit marc spirits in *Regulation (EC) No 110/2008 on the definition, description, presentation, labelling and the protection of geographical indications of sprit drinks* (EC 2008a).

The enzyme urease is permitted to be used in winemaking, in the European Union, to reduce formation of ethyl carbamate (EC 2008b).

The Commission Recommendation (the Recommendation) on *the prevention and reduction of ethyl carbamate contamination in stone fruit spirits and stone fruit marc spirits and on the monitoring of ethyl carbamate levels in these beverages (2010/133/EU)* recommends member states adopt the Code of Practice (the Code) included in the Annex of the Recommendation, to reduce ethyl carbamate levels in fruit spirits. The recommended practices in the Code are based on Good Manufacturing Practices and notes that an ethyl carbamate target level of 1 mg/L (1000 ppb) in the ready to drink spirit is realistic and achievable (EC 2010).

Codex Alimentarius Commission (World Health Organization and the Food and Agriculture Organization of the United Nations)

The Codex Alimentarius Commission has published a *Code of Practice for the Prevention and Reduction of Ethyl Carbamate Contamination in Stone Fruit Distillates in 2011* (Codex Alimentarius 2011).

8. Next Steps

8.1 Public Comment Period

Industry and other interested stakeholders are invited to submit comments on the content of this risk management approach document or other information that would help to inform decision-making. Please submit additional information and comments prior to July 27, 2016.

Comments and information should be submitted to the following address:

Environment and Climate Change Canada
Gatineau, Quebec K1A 0H3
Tel: 1-800-567-1999 (in Canada) / 819-938-3232
Fax: 819-938-5212
Email: ec.substances.ec@canada.ca

Companies who have a business interest in ethyl carbamate or are the target of risk management actions, which in this case is the alcoholic beverages sector, are encouraged to identify themselves as stakeholders. Stakeholders will be informed of future decisions regarding ethyl carbamate and may be contacted for further information.

Following the public comment period on the risk management approach document, the Government of Canada will initiate the development of the specific risk management actions, where necessary. Comments received on the risk management approach document will be taken into consideration in the selection and development of risk management actions. Consultation will also take place as instruments or tools are developed.

8.2 Timing of Actions

Electronic consultation on the risk management approach: May 28, 2016 to July 27, 2016

Publication of responses to public comments on the risk management approach document: On or before May 2018

Implementation of the final risk management tool(s): On or before November 2019

9. References

Canada. 1985. *Food and Drugs Act*. R.S.C. 1985, c.F-27. Available from: http://laws-lois.justice.gc.ca/eng/acts/f-27/

Canada. 1999. *Canadian Environmental Protection Act, 1999*. S.C., 1999, ch. 33. Canada Gazette. Part III. vol. 22, no. 3. Ottawa: Queen's Printer. Available from: http://laws-lois.justice.gc.ca/eng/acts/C-15.31/

Canada. 2011. Dept. of the Environment. *Canadian Environmental Protection Act, 1999: Announcement of planned actions to assess and manage, where appropriate, the risks posed by certain substances to the health of Canadians and the environment*. Canada Gazette, Part I, vol. 145, no. 41 – October 8, 2011, p. 3125-3129. Available from: http://www.gazette.gc.ca/rp-pr/p1/2011/2011-10-08/html/notice-avis-eng.html#d127

Canada. 2016a. Dept. of the Environment, Dept. of Health. *Canadian Environmental Protection Act, 1999:* Publication of final decision after screening assessment of a substance — carbamic acid, ethyl ester (ethyl carbamate), CAS RN 51-79-6 — specified on the *Domestic Substances List* [paragraphs 68(*b*) and 68(*c*) of the *Canadian Environmental Protection Act, 1999*]. Canada Gazette, Part I, vol. 150, no. 22, p. [1661 – 1664]. Available from: http://www.gazette.gc.ca/rp-pr/p1/2016/2016-05-28/html/notice-avis-eng.php#nl7

Canada. 2016b. Dept. of the Environment, Dept. of Health. Final Screening Assessment Report for the Substance Groupings Initiative, Carbamic acid, ethyl ester (Ethyl carbamate), Chemical Abstracts Service Registry Number (CAS RN) 51-79-6. Available from: http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=C24225A8-1

[CFR] US Code of Federal Regulations. 2010. Title 21, *Section 24.246: Materials authorized for the treatment of wine and juice*. Available from: http://www.gpo.gov/fdsys/pkg/CFR-2012-title27-vol1/pdf/CFR-2012-title27-vol1-sec24-246.pdf.

[CFR] US Code of Federal Regulations. 2013. Title 21, Volume 3, *Section 184.1924: Urease enzyme preparation from Lactobacillus fermentum*. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=184.1924.

Codex Alimentarius. 2011. *Code of Practice for the Prevention and Reduction of Ethyl Carbamate Contamination in Stone Fruit Distillates*. CAC/RCP 70-2011. Available from: http://www.codexalimentarius.org/standards/list-of-standards/en/?provide=standards&orderField=fullReference&sort=asc&num1=CAC/RCP.

[EC] European Commission. 2008a. *Regulation (EC) No 110/2008 on the definition, description, presentation, labelling and the protection of geographical indications of spirit drinks*. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:039:0016:0054:EN:PDF.

[EC] European Commission. 2008b. *Regulation (EC) No 1332/2008 on food enzymes and amending Council Directive 83/417/EEC, Council Regulation (EC) No 1493/1999, Directive 2000/13/EC, Council Directive 2001/112/EC and Regulation (EC) No 258/97*. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:354:0007:0015:en:PDF.

[EC] European Commission. 2010. *Commission Recommendation on the prevention and reduction of ethyl carbamate contamination in stone fruit spirits and stone fruit marc spirits and on the monitoring of ethyl carbamate levels in these beverages (2010/133/EU).* Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:052:0053:0057:EN:PDF.

Health Canada. 2013a. List of Permitted Food Enzymes. Available from: http://www.hc-sc.gc.ca/fn-an/securit/addit/list/5-enzymes-eng.php.

Health Canada. 2013b. Canadian Standards (Maximum Levels) for Various Chemical Contaminants in Foods. Available from: http://www.hc-sc.gc.ca/fn-an/securit/chem-chim/contaminants-guidelines-directives-eng.php.

LCBO (Liquor Control Board of Ontario). 2014. *LCBO Product Packaging Standards & Guidelines for Chemical Analysis*. March, 1998; revised February, 2013. Accessed Dec. 5, 2014: http://www.doingbusinesswithlcbo.com/tro/Packaging-Quality/ProductPackagingStandards.shtml

SAQ (Société des alcools du Québec). 2014, GUIDE Standards – Constitution and Stability, last update July 31, 2014. Accessed Dec. 5, 2014: http://marketing.globalwinespirits.com/SAQ_B2B/Gestion%20Qualite/Guide_constitution_et_stabilit%C3%A9%20ANG.pdf

[UC Davis] University of California, Davis. 1997. Ethyl Carbamate Preventative Action Manual. Available from: http://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm078521.htm

Zimmerli B, Schlatter J. 1991. Ethyl carbamate: analytical methodology, occurrence, formation, biological activity and risk assessment. *Mutat. Res.* 259(3–4):325–350.