Canadian Environmental Protection Act, 1999

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

FOLLOW-UP TO THE STATE OF SCIENCE REPORT, 2000

Aluminum Chloride
Aluminum Nitrate
Aluminum Sulphate

Chemical Abstracts Service Registry Numbers
7446-70-0
13473-90-0
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Environment Canada
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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ACRONYMS AND ABBREVIATIONS

Aβ	amyloid beta
ACH	aluminum chlorohydrate
AD	Alzheimer's disease
AD_{AF}	chemical-specific animal to human toxicodynamic adjustment factor
ADP	adenosine diphosphate
ADRDA	Alzheimer's Disease and Related Disorders Association
AK_{AF}	chemical-specific animal to human toxicokinetic adjustment factor
AMS	accelerator mass spectrometry
ApoE	apolipoprotein E
ASFA	Aquatic Sciences and Fisheries Abstracts (World Health Organization Food and Agricultural Organization)
ATP	adenosine triphosphate
ATPase	class of enzymes that catalyze the decomposition of ATP into ADP
ATSDR	Agency for Toxic Substances and Disease Registry (U.S. Department of Health and Human Services)
BAF	bioaccumulation factor
BCF	bioconcentration factor
BIOSIS	Biosciences Information Services
CAplus	Chemical Abstracts Plus
CAB	Commonwealth Agricultural Bureaux
cAMP	cyclic adenosine monophosphate
CAS	Chemical Abstracts Service
CASReact	CAS Reaction
CBTB	Canadian Brain Tissue Bank
CEPA	Canadian Environmental Protection Act
CEPA 1999	Canadian Environmental Protection Act, 1999
CESARS	Chemical Evaluation Search and Retrieval System (Ontario Ministry of the Environment and Michigan Department of Natural Resources)
cGMP	cyclic guanosine monophosphate
ChemCats	Chemical Catalogs online
Chemlist	regulated Chemicals Listing
CHRIS	Chemical Hazard Release Information System
CI	confidence interval
CSHA	Canadian Study of Health and Aging
CT	computer tomography
CTV	Critical Toxicity Value
D_a	administered dose
D_b	base diet dose

D_c	cumulative dose
DIN	Drug Identification Number
DNA	deoxyribonucleic acid
DOC	dissolved organic carbon
DOM	dissolved organic material
DSM	Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association)
dw	dry weight
DWTP	drinking water treatment plant
EC_{50}	median effective concentration
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
EDI	estimated daily intake
EEM	Environmental Effects Monitoring
ELIAS	Environmental Library Integrated Automated System (Environment Canada library)
EPA	Environmental Protection Agency (U.S.)
ETAAS	electrothermal atomic absorption spectroscopy
FAO	Food and Agricultural Organization (United Nations)
GD	gestational day
GEOREF	Geo Reference Information System (American Geological Institute)
GLP	good laboratory practice
GVRD	Greater Vancouver Regional District
GVS&DD	Greater Vancouver Sewerage & Drainage District
HD_{AF}	chemical-specific human variability toxicodynamic adjustment factor
HK_{AF}	chemical-specific human variability toxicokinetic adjustment factor
HSDB	Hazardous Substances Data Bank (U.S. National Library of Medicine)
ICD	International Classification of Diseases (World Health Organization)
IM	intramuscular
IPCS	International Programme on Chemical Safety (World Health Organization)
IV	intravenous
JECFA	Joint FAO/WHO Expert Committee on Food Additives
KASAL	alkaline aluminum phosphate and dibasic sodium phosphate

LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEC	lowest observed adverse effect concentration
LOEC	lowest observed effect concentration
LOEL	lowest observed effect level
LSA	Ontario Longitudinal study of Aging
MEDLINE	Medical Literature Analysis and Retrieval System Online (U.S. National Library of Medicine)
MINEQL+	chemical equilibrium modeling software
MMAD	mass median aerodynamic diameter
MMSE	Mini-Mental State Examination
MOE	margin of exposure
mRNA	messenger ribonucleic acid
MS	multiple sclerosis
MWWTP	municipal wastewater treatment plant
NADPH	nicotinamide adenine dinucleotide phosphate
NATES	National Analysis of Trends in Emergencies System
NEMISIS	National Enforcement Management Information System and Intelligence System
NFT	neurofibrillary tangles
NICNAS	National Industrial Chemicals Notification and Assessment Scheme (Australian Government Department of Health and Aging)
NIH	National Institutes of Health (U.S. Department of Health and Human Services)
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NOEC	no observed effect concentration
NOEL	no observed effect level
NTIS	National Technical Information Service (U.S. Department of Commerce)
OECD	Organisation for Economic Co-Operation and Development
OR	odds ratio
p value	the probability of obtaining a value of the test statistic at least as extreme as the one that was actually observed, given that the null hypothesis is true
PAC	polyaluminum chloride
PAQUID	Principle lifetime occupation and cognitive impairment in a French elderly
PAS	polyaluminum sulphate
PASS	polyaluminum silicate sulphate
PEC	Predicted Environmental Concentration
PM	particulate matter

$PM_{2.5}$	particulate matter less than 2.5 micrometers in aerodynamic diameter
PM_{10}	particulate matter less than 10 micrometers in aerodynamic diameter
PND	postnatal day
PNEC	Predicted No-Effect Concentration
POLTOX	Cambridge Scientific Abstracts (U.S. National Library of Medicine)
PPP2	Protein Phosphatase 2
PSL	Priority Substances List
PTEAM	Particle Total Exposure Assessment Methodology
PubMed	free Internet access to MEDLINE
RMOC	Regional Municipality of Ottawa-Carleton
RR	relative risk
RTECS	Registry of Toxic Effects of Chemical Substances (U.S. National Institute for Occupational Safety and Health)
SALP	sodium aluminum phosphate
SOS	State of the Science
$t_{½}$	half-life
TDI	total dietary intake
Tf	transferrin
$TNF^{-\infty}$	alpha tumour necrosis factor
TOXLINE	toxicology database (U.S. National Library of Medicine)
TRI93	Toxic Chemical Release Inventory (U.S. Environmental Protection Agency, Office of Toxic Substances)
TSS	total suspended solids
USEPA-ASTER	Assessment Tools for the Evaluation of Risk (U.S. Environmental Protection Agency)
V_d	volumes of distribution
WASTEINFO	Waste Management Information (Bureau of the American Energy Agency)
WHAM	Windermere Humic-Aqueous Model software designed to calculate equilibrium chemical speciation in surface and ground waters, sediments and soils
WHO	World Health Organization

SYNOPSIS

The three aluminum salts, aluminum chloride, aluminum nitrate and aluminum sulphate, were included as a substance on the Priority Substances List under the *Canadian Environmental Protection Act, 1999* (CEPA 1999) in order to assess the potential environmental and human health risks posed by exposure to aluminum derived from these three salts in Canada.

In December 2000, the assessment of the three aluminum salts was formally suspended due to limitations in the available data for assessing health effects. At the same time, a State of the Science report (Environment Canada and Health Canada 2000) on the three aluminum salts was released, providing an in-depth review of toxicity and exposure information relating to human health and the environment. During the suspension period, additional health effects information was published in the scientific literature, and they are considered here.

In Canada, municipal water treatment facilities are the major users of aluminum chloride and aluminum sulphate, accounting for 78% of the estimated 16.1 kilotonnes of the 2006 domestic consumption. Industrial water and wastewater treatment, and use in the pulp and paper industry, account for an additional 20 %. Aluminum sulphate and aluminum chloride are also used as ingredients in drugs and cosmetics, such as antiperspirants and topical creams. Aluminum sulphate is permitted as a food additive in a limited number of products. Aluminum nitrate, used in far less quantities than the sulphate and chloride salts, may be used in fertilizers, and as a chemical reagent in various industries.

Aluminum salts occur naturally in small quantities in restricted geological environments and aluminum can be released into the Canadian environment from these natural sources. However, since aluminum is present in relatively large amounts in most rocks, dominantly in aluminosilicate minerals, which weather and slowly release aluminum to the surface environment, the small amounts of aluminum in surface waters resulting from weathering of aluminum salts such as aluminum sulphate cannot be distinguished from other natural aluminum releases.

During their use in water treatment, aluminum salts react rapidly, producing dissolved and solid forms of aluminum with some release of these to Canadian surface waters. The amount of anthropogenic aluminum released nationally in Canada is small compared with estimated natural aluminum releases; however anthropogenic releases can dominate locally near strong point sources. Most direct release into surface waters of aluminum derived from the use of aluminum salts in water treatment processes originates from drinking water treatment plants (DWTPs). However, direct releases of process waters from DWTPs are regulated by many provincial and territorial authorities, and these releases typically occur in circumneutral water, where the solubility of aluminum is minimal. Disposal of sludge produced by municipal and industrial water treatment facilities on land through landfarming practices is a source of aluminum to the terrestrial environment. However, the presence of dissolved organic matter and inorganic chelating agents will lower the amount of bioavailable aluminum in both the terrestrial and aquatic environments.

While extensive recent data on total aluminum concentrations in Canadian surface waters are available, few data exist on levels in areas close to sites where releases occur. The situation for sediment and soil is similar, in that data exist for the Canadian environment in general, but not for areas where releases occur. A large number of environmental toxicity data are available for acidified environments, but relatively few exist for circumneutral environments similar to those where most releases occur.

Based on a comparison of highest measured and estimated aluminum levels present in both aquatic and terrestrial environments in Canada that receive direct inputs of aluminum from the use of the three aluminum salts, and Predicted No-Effect Concentrations (PNECs) derived from experimental data for aquatic and terrestrial biota, it is considered that, in general, it is unlikely that organisms are exposed to harmful levels of aluminum resulting from the use of aluminum salts in Canada. However, it is acknowledged that under some release conditions there is potential for local impacts to benthic organisms related to the settling of aluminum sludge from DWTPs onto the sediment surface. As such, it is concluded that the three aluminum salts (i.e., aluminum chloride, aluminum nitrate, aluminum sulphate) 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.

With respect to human health, both epidemiological and experimental animal data were reviewed. Considering experimental animal studies, the dose at which neurotoxic, reproductive, and developmental effects have been repeatedly observed was used to establish an exposure level of concern.

General population exposure to total aluminum was quantified. With respect to the three salts—aluminum chloride, aluminum nitrate, and aluminum sulphate—their contribution to total aluminum exposure can only be qualitatively estimated, however, the only media in which the mean concentration may be significantly affected by the use of these salts is drinking water, in which aluminum sulphate or aluminum chloride may be added during the treatment process. As a surrogate for quantitative exposure estimation, it was assumed that all aluminum in drinking water is derived from aluminum chloride and aluminum sulphate. Comparison of the exposure level of concern to the age-group with the highest average daily intake of total aluminum from drinking water results in a margin of exposure that is considered adequate.

Based on the information available for human health and the environment, it is concluded that the three aluminum salts, aluminum chloride, aluminum nitrate, aluminum sulphate, 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. It is also concluded that aluminum from aluminum chloride, aluminum nitrate and aluminum sulphate, 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. It is therefore concluded that aluminum chloride, aluminum nitrate and aluminum sulphate do not meet the definition of "toxic" under section 64 of the *Canadian Environmental Protection Act, 1999*.

1 INTRODUCTION

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires the Ministers of the Environment and of Health to prepare and publish a Priority Substances List (PSL) that identifies substances (including chemicals, groups of chemicals, effluents and wastes) that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances to determine whether they meet or are capable of meeting the criteria as defined in section 64 of the Act. A substance meets the criteria under CEPA 1999 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.

For substances deemed to meet the criteria defined in section 64, risk management measures are identified and implemented in consultation with stakeholders, in order to reduce or eliminate the risks posed to human health or the environment. These measures may include regulations, guidelines, pollution prevention plans or codes of practice to control any aspect of the life cycle of the substance, from the research and development stage through to manufacture, use, storage, transport and ultimate disposal.

Based on initial screening of readily accessible information, the rationale provided by the Ministers' Expert Advisory Panel in 1995 for including aluminum chloride, aluminum nitrate and aluminum sulphate on the Second Priority Substances List was as follows (Environment Canada and Health Canada 2000):

> *"Aluminum, from both natural and man-made sources, is widespread in the Canadian environment. Intakes of aluminum among the human population and ambient airborne concentrations in some parts of the country are close to those that have induced developmental and pulmonary effects in animal studies. Epidemiological studies have indicated that there may be a link between exposure to aluminum in the environment and effects in humans. Aluminum compounds are bioaccumulative, and can cause adverse ecological effects, especially in acidic environments. The Panel identifies three aluminum compounds as being of particular concern. An assessment is needed to establish the weight of evidence for the various effects, the extent of exposure and the aluminum compounds involved. If necessary, the assessment could be expanded to include other aluminum compounds."*

A preliminary report was completed for the three aluminum salts and released as a State of the Science (SOS) report in December 2000. With respect to immediate or long term harmful effects of the three aluminum salts on the environment or its biological diversity, the

report proposed that, based on measured and estimated aluminum levels in Canadian aquatic and terrestrial environments receiving direct inputs of aluminum from the use of aluminum salts and on the Predicted No-Effect Concentrations (PNECs) derived from experimental data for aquatic and terrestrial biota, it is in general unlikely that organisms are exposed to harmful levels of aluminum resulting from the use of aluminum salts in Canada.

With respect to human health, a conclusion regarding section 64(c) could not be reached in 2000, owing to the limitations in the available data for assessing health effects. Therefore, the assessment of aluminum salts was suspended in December 2000 for a period of six years to allow for the development of additional human health effects data in order that Health Canada could reach a conclusion on whether aluminum salts (chloride, nitrate and sulphate) should be considered as "toxic" under CEPA 1999.

In terms of this PSL assessment, the conclusions made under section 64 of CEPA 1999 relate directly to the three aluminum salts nominated by the Ministers' Expert Advisory Panel (aluminum chloride, nitrate, and sulphate). However, different approaches are taken by Environment Canada and Health Canada in evaluating the potential for risk.

In characterizing the potential for risk to the environment, data relevant to the entry of the three listed salts into the Canadian environment from local point sources (e.g., drinking water treatment plants) were examined in conjunction with data on environmental fate and exposure. The focus was on assessing potential for effects on the environment near point sources. This evaluation formed the basis for determining whether the three aluminum salts identified by the Ministers' Expert Advisory Panel (chloride, nitrate and sulphate) are "toxic" under section 64 of CEPA 1999.

The human health risk characterization consists of a two-stage evaluation. In the first stage, exposure of the general Canadian population to total aluminum in air, drinking water, diet, and soil is quantified. In the second stage, the relative contribution of each of the three listed aluminum salts (chloride, nitrate, and sulphate) to this total aluminum exposure is qualitatively evaluated, and a recommendation with respect to section 64(c) of CEPA is made for the three salts.

Health Canada chose this two-stage approach on the basis of both scientific and practical considerations. First, overall exposure to the aluminum moiety (Al^{3+}), and not exposure to a particular aluminum compound, is the critical parameter for evaluating potential toxicological risk[1]. Second, concentrations of aluminum in foods, soil, drinking water, and air are generally reported as total aluminum, and not in terms of specific salts, consequently it is difficult to determine with great precision the relative contribution of the three salt forms being considered. Although information on sources and uses of aluminum-containing

[1] Note, however, that different aluminum salts are absorbed into the bloodstream to different degrees (Yokel et al. 2006) and this aspect is considered in this assessment within section 2.3.3.1.

compounds are used to characterize total aluminum exposure, the risk characterization is limited to the three specific aluminum salts.

The search strategies employed in the identification of relevant data are presented in Appendix A. All original studies that form the basis for decision making have been critically evaluated and are described in the assessment. For issues relevant to the environmental and human health effects of aluminum, but outside the scope of the present assessment, the information is summarized briefly and the reader is referred to recent critical reviews published in the scientific literature for a more detailed discussion.

The human health components of the present document were prepared by the Safe Environments Programme- Quebec Region, in collaboration with the Existing Substances Division of the Safe Environments Programme (National Capital Region) and other Health Canada programs. The environmental components were prepared by the Existing Substances Division of the Science and Technology Branch.

The human health components of this assessment have been peer reviewed by the following external experts:

Dr. Diane Benford, Food Standards Agency, United Kingdom
Dr. Nicola Cherry, University of Alberta, Edmonton, Alberta
Dr. Rajendra Chhabra, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina
Dr. Herman Gibb, Sciences International, Arlington, Virginia
Dr. Lesbia Smith, Environmental and Occupational Health Plus, Toronto, Ontario
Dr. Robert Yokel, University of Kentucky, Lexington, Kentucky

Information relevant to environmental components of this assessment has been reviewed by the following external experts:

Dr. Pierre-André Côté, Canadian Water and Wastewater Association, Québec, Quebec
Mr. André Germain, Environment Canda, Montréal, Quebec.
Mr. Robert Garrett, Geological Survey of Canada, Ottawa, Ontario
Dr. William Hendershot, McGill University, Montréal, Quebec
Mr. Christopher Lind, General Chemical Corporation, Newark, New Jersey
Mr. Robert Roy, Fisheries and Oceans Canada, Mont-Joli, Quebec
Mr. James Brown, Reynolds Metals Company, Richmond, Virginia
Mr. Scott Brown, National Water Research Institute, Burlington, Ontario
Mr. Christopher Cronan, University of Maine, Orono, Maine
Dr. Lawrence Curtis, Oregon State University, Corvallis, Oregon
Mr. Richard Lapointe, Société d'électrolyse et de chimie Alcan Ltée, Montréal, Quebec
Dr. Stéphanie McFadyen, Canadian Water and Wastewater Association, Ottawa, Ontario
Dr. Wayne Wagner, Natural Resources Canada, Ottawa, Ontario

While external peer review comments were taken into consideration, the final content and outcome of the risk assessment remain the responsibility of Health Canada and Environment Canada.

2 SUMMARY OF INFORMATION CRITICAL TO ASSESSMENT OF "TOXIC" UNDER CEPA 1999

2.1 Identity and physical/chemical properties

Aluminum chloride is also known as aluminum trichloride, aluminum chloride (1:3) and trichloroaluminum (ATSDR 2006). It has the Chemical Abstracts Service (CAS) registry number 7446-70-0 and a chemical formula of $AlCl_3$. In its hydrated form, $AlCl_3 \cdot 6H_2O$, it is called hexahydrated aluminum chloride (CAS No. 7784-13-6). Trade names include Aluwets, Anhydrol and Drichlor.

Synonyms for aluminum nitrate include aluminum trinitrate and aluminum (III) nitrate (1:3). The CAS registry number is 13473-90-0 and the chemical formula is $Al(NO_3)_3$. The nonahydrate aluminum nitrate, $Al(NO_3)_3 \cdot 9H_2O$ (CAS No. 7784-27-2), is the stable form of this compound.

Aluminum sulphate can also be identified as alum, alumsulphate (2:3), aluminum trisulphate, dialuminum sulphate and dialuminum trisulphate. The CAS registry number for aluminum sulphate is 10043-01-3 and the chemical formula is $Al_2(SO_4)_3$. Alum is often represented as $Al_2(SO_4)_3 \cdot 14H_2O$. It may be found in different hydrated forms. The commercial product, called cake alum or patent alum, is an octadecahydrate aluminum sulphate, $Al_2(SO_4)_3 \cdot 18H_2O$.

In addition to these three compounds, aluminum polymers such as polyaluminum sulphate (PAS) and polyaluminum chloride (PAC) are used in water treatment. The general formula for PAS is $Al_a(OH)_b(SO_4)_c$, where $b + 2c = 3a$; for PAC, the general formula is $Al_a(OH)_bCl_c$, where b/a is usually about 2.5 (e.g., $Al_2(OH)_5Cl$). Mixed aluminum polymers may also be used; their general formula is $Al_a(OH)_bCl_c(SO_4)_d$, and b/a varies between 0.4 and 0.6.

Physicochemical properties of the three aluminum salts are presented in Table 2.1.

Table 2.1 Physicochemical properties of aluminum chloride, aluminum nitrate and aluminum sulphate [1]

Property	Aluminum chloride	Aluminum nitrate	Aluminum sulphate
CAS No.	7446-70-0	13473-90-0	10043-01-3
Molecular formula	$AlCl_3$	$Al(NO_3)_3$	$Al_2(SO_4)_3$
Molecular weight	133.34	213.00	342.14
Colour	White when pure, ordinarily gray or yellow to greenish	Colourless[2]	White, lustrous
Physical state	White hexagonal deliquescent or moisture sensitive plates	Rhombic crystals[2]	Crystals, pieces, granules or powder
Density (g/mL)	2.48	No data	1.61
Melting point (°C)	194 at 527 kPa	73[2]	Decomposes at 770
Boiling point (°C)	182.7 (1.00×10^5 Pa or 752 mm Hg; sublimation temperature)	Decomposes at 135°C[2]	No data, substance has no boiling point
Solubility in water (g/100 mL)	69.86 (15°C) (Reacts violently with water)	63.7 (25°C)	36.4 (20°C)
Solubility in other solvents	Soluble in benzene, carbon tetrachloride, chloroform	Very soluble in alcohol; slightly soluble in acetone almost insoluble in ethyl acetate, pyridine[2]	Insoluble in ethanol
pH	No data	Aqueous solution is acidic	No data
Vapour pressure (Pa)	100 (20°C)	No data	0 (20°C) substance has no vapour pressure

[1] Taken from Perry and Green (1984), Budaveri et al. (1989), Lewis (1992), European Commission (2000a,b) and ATSDR (2006)

[2] Refers to aluminum nitrate nonahydrate (CAS No. 7784-27-2)

2.2 Entry characterization

2.2.1 Production, import, export and use

Aluminum sulphate and aluminum chloride are produced in Canada, while aluminum nitrate is imported. Information on sources and emissions of aluminum salts or aluminum resulting from the use of aluminum salts was initially obtained through an industry survey carried out under the authority of section 16 of CEPA (CEPA 1988; Environment Canada 1997). Information regarding the use of aluminum chloride and aluminum sulphate in water treatment plants was obtained on a voluntary basis from Canadian municipalities with the help of provincial and territorial authorities. In 2007, additional research was conducted in order to review use patterns and quantities of aluminum derived from sources identified in the original assessment, as well as to identify and quantify potential new sources of aluminum to the

environment resulting from the application of aluminum salts in Canada (Cheminfo Services Inc. 2008).

Table 2.2 provides estimated production, import, export and consumption values for the year 2006, based largely on input from Canadian aluminum salt producers. Unless otherwise stated, quantities reported in Table 2.2 and the accompanying text represent the amount of elemental aluminum present in the respective salts rather than the total amount of the salt. Polymeric forms of the chloride and sulphate are detailed separately, as these salts were found to be commonly used individually or in combination with other salts in water treatment processes. No producers or users of aluminum nitrate were identified for 2006 and, therefore, while it is likely that very small quantities were being imported into Canada in that year for a variety of low volume applications, no numerical data were available. Total Canadian consumption of aluminum as aluminum salts in 2006 was estimated at 16.1 kilotonnes, with aluminum sulphate accounting for approximately 80% of this demand, and PAC for the majority of the remainder (Cheminfo Services Inc. 2008). Approximately 80% of the total aluminum demand was for the treatment of drinking water and wastewater at municipalities. Industrial fresh water and wastewater treatment facilities accounted for the majority of the remaining demand in Canada.

Table 2.2 Estimated production, import, export and consumption of aluminum in the form of aluminum salts in Canada for 2006
(kilotonnes elemental aluminum; Cheminfo Services Inc. 2008)[1]

	Aluminum Sulphate	**Aluminum Chloride**	**Other[2]**	**Total**
Production	11.9	0.1	4.6	16.6
Imports	0.6	0.2	1.0	1.8
Total supply	**12.5**	**0.3**	**5.6**	**18.4**
Demand				
Municipal Drinking Water Treatment Plants	4.3	0.1	2.4	6.8
Municipal Wastewater Treatment Plants	5.7	0.03	0.07	5.8
Industrial Fresh Water Treatment	0.3	0.03	0.67	1.0
Industrial Wastewater Treatment	0.5	0.03	0.44	0.9
Pulp and Paper Additive	1.1	0.01	0.16	1.3
Miscellaneous	0.1	0.1	0.1	0.3
Total Domestic Consumption	12.0	0.3	3.8	16.1
Exports	0.5	0.0	1.8	2.3
Total Disposition	**12.5**	**0.3**	**5.6**	**18.4**

[1] Quantities reported represent elemental aluminum present in the respective aluminum salts.

[2] This quantity represents the combined total of polyaluminum sulphate, polyaluminum chloride, aluminum chlorohydrate and sodium aluminate.

Five companies produced most of the aluminum salts used in Canada in 2006 (Cheminfo Services Inc. 2008). Imports and exports were roughly in balance, with imports representing approximately 10% of 2006 domestic consumption and exports representing approximately 14% of 2006 production. Alum, PAC and aluminum chlorohydrate (ACH) were the major imported aluminum salts, while PAC and alum were exported.

Total Canadian demand for aluminum salts remained relatively constant between 2000 and 2006 (Cheminfo Services Inc. 2008). Canada's salt producers indicate that the demand for alum and sodium aluminate declined during this period, while PAC, ACH and polyaluminum silicate sulphate (PASS) increased in use. While overall aluminum salts demand for municipal water treatment has increased slightly, use in the pulp and paper industry has dropped. The overall total amount of aluminum contained in the salts used in Canada has remained constant at close to 16 kilotonnes per year (Cheminfo Services Inc. 2008).

2.2.1.1 Aluminum chloride

Aluminum chloride is used in either anhydrous or hydrated form. In the anhydrous form, it is used as a catalyst, in Friedel-Crafts reactions, in the manufacture of rubber, the cracking of petroleum, and the manufacture of lubricants. In its hydrated form, it is used by the pharmaceutical industry as an active ingredient in deodorants and antiperspirants, as well as in wood preservation, and in the manufacture of adhesives, paint pigments, resins, fertilizers and astringents (Germain et al. 2000; Pichard 2005; Merck 2006). Polymeric forms, primarily polyaluminum chloride (PAC) and the more concentrated and highly charged aluminum chlorohydrate (ACH), are used as coagulants and flocculants in water treatment.

PAC has the highest Canadian production and use volumes of the three aluminum chloride salts. PAC demand increased over the period 2000 to 2006, with greatest quantities being used in the treatment of drinking water (Cheminfo Services Inc. 2008). Similar increased demand was evident in other applications, including industrial freshwater treatment, municipal and industrial wastewater treatment, and as a pulp and paper additive (Cheminfo Services Inc. 2008). Production and demand were substantially lower for both aluminum chloride and ACH. Canadian consumption of aluminum chloride remained stable from 2000 to 2006, while ACH demand increased substantially (Cheminfo Services Inc. 2008). Most of the increased demand was associated with increased applications in industrial wastewater treatment, with slower rates of growth in other applications.

2.2.1.2 Aluminum nitrate

Aluminum nitrate is used as a chemical reagent (catalyst), in the leather tanning industry, as an antiperspirant, as a corrosion inhibitor, and in the manufacture of abrasives, refractories, ceramics, electric insulation, catalysts, paper, candles, pots, artificial precious stones and heat-resistant fibres (Budaveri et al. 1989; Pichard 2005). It is also used as an adsorbent in chromatography for the production of filter membranes, in radiation protection dosimetry in the uranium extraction sector, and as a nitrating agent in the food industry (Merck 2006).

There are no known producers of aluminum nitrate in Canada, and only one user was identified in a survey done in 1997 by Environment Canada (1997). This user reported that less than 400 kg of aluminum nitrate was included in fertilizers for export to the United States. It is likely that very small quantities of aluminum nitrate are being imported into Canada for a variety of low volume applications, including laboratory uses, leather manufacturing, manufacturing of fire works, and other minor applications (Cheminfo Services Inc. 2008).

2.2.1.3 Aluminum sulphate

In Canada, aluminum sulphate is used primarily as a coagulant and flocculant in water and wastewater treatment. There are other applications, however, in the leather industry, the paper industry, as a mordant in dyeing, in the fireproofing and waterproofing of textiles, in resin manufacture, and in the preparation of fertilizers and paint pigments (Germain et al. 2000; Pichard 2005; Merck 2006). The Canadian Fertilizers Product Forum advises that aluminum sulphate (alum) is used as a soil pH adjuster in the Lawn and Garden industry (2008 email from The Canadian Fertilizers Product Forum to J. Pasternak, Environment Canada; unreferenced). Aluminum sulphate can also be used to waterproof concrete, decolorize petroleum products, and as a formulant in antiperspirants and pesticides (Budaveri et al. 1989). Aluminum sulphate or alum is used in the treatment of eutrophic or mesotrophic lakes, to reduce the amount of nutrients present in the water. Both alum ($Al_2(SO_4)_3$) and sodium aluminate ($Na_2Al_2O_4$) are highly effective coagulants and flocculants that adsorb and precipitate soluble phosphorus and other compounds such as organic matter, forming clumps that settle to the bottom of the lake. In saturated solutions, aluminum sulphate is considered a mild corrosive and can be applied to ulcers in concentrations of 5% to 10% to prevent mucous secretion (Pichard 2005). The substance is also used as a food additive and some foods, such as baking powder.

It is estimated that approximately 276 kilotonnes of aluminum sulphate (11.9 kilotonnes on an aluminum basis) were produced in Canada in 2006, 15 kilotonnes (0.6 kilotonnes of aluminum) were imported and 12 kilotonnes (0.5 kilotonnes of aluminum) exported (Table 2.2). Municipal drinking water and wastewater treatment plants were the main users, comprising almost 84% of the total demand for that year. Industrial water treatment facilities and the pulp and paper sector accounted for most of the remaining consumption (15.8%).

2.2.2 Sources and releases

Aluminum sulphate minerals such as aluminite and alunite occur naturally in Canada in certain restricted geological environments. Aluminum chloride and aluminum nitrate do not occur naturally in the environment. Aluminum can be released from natural aluminum sulphate minerals. Since aluminum is a common constituent of rocks, where it occurs dominantly in aluminosilicate minerals (e.g., kaolinite, boehmite, clay, gibbsite, feldspar, etc.), weathering can slowly release aluminum to the surface environment. Aluminum present in surface waters due to human activites cannot be distinguished from natural aluminum released during weathering of aluminum-bearing minerals.

While aluminum chloride, aluminum nitrate and aluminum sulphate have many commercial applications in Canada, releases of aluminum to the environment from most

commercial applications are expected to be small. However, there is potential for release of relatively large amounts of aluminum resulting from the use of aluminum chloride and aluminum sulphate in water treatment plants (industrial water, drinking water or wastewater). In this application, aluminum will react rapidly, producing sludge, usually in the form of aluminum hydroxide ($Al(OH)_3$). Most sludge produced by municipal wastewater treatment plants (MWWTPs) or industries is sent to landfills or spread on land, with the remainder being composted, held in permanent lagoons, or incinerated prior to landfilling (Germain et al. 2000). Most provinces control DWTP waste flows through their respective systems of permits and/or approvals. Sludge purged from clarifiers or accumulated in sedimentation basins of drinking water treatment plants (DWTPs) cannot be released directly to the aquatic environment in many provinces. It may be sent to sewers, incinerated with wastewater sludge and landfilled, held in permanent lagoons, spread on land or landfilled. Likewise, backwash waters (used to clean filters) cannot be discharged directly into open water bodies in many provinces where these discharges are often subjected to requirements for pretreatment (e.g., diversion to sedimentation ponds) or diversion to MWWTPs. While many provinces do not generally allow direct discharge to surface water of any DWTP effluents containing sludges or backwash waters (e.g., Alberta, Manitoba, Ontario and New Brunswick), some of their existing plants may continue to discharge effluents directly to surface waters. Communication with provincial agencies indicates that these provinces are generally requiring some type of environmental impact assessments of the subject discharges with consideration of alternatives to direct discharge. Some existing large plants in these provinces have recently removed their DWTP direct discharges from surface water (e.g., Britannia DWTP and Lemieux Island DWTP in Ottawa, ON), or are developing plans for alternatives to direct discharge to surface waters (e.g., certain plants in Alberta). In other provinces, direct discharge may be allowed through provincial approvals systems if it is shown that the discharge results in no adverse effects (defined based on varying criteria) on the receiving body of water (e.g., Saskatchewan, Nova Scotia and Newfoundland). It should be noted that some provinces and territories either do not have any coagulant usage for drinking water treatment, or they only use very small amounts and have requirements for DWTP effluent treatment destined for surface water (e.g., Prince Edward Island, Yukon Territory, Northwest Territories and Nunavut Territory) (Environment Canada unpublished 2008a)

While most aluminum is released in particulate form, a certain proportion occurs as the dissolved metal and it is this form that is considered easily absorbed and therefore bioavailable to aquatic organisms. The following section therefore discusses aluminum releases in general, with additional emphasis given to dissolved forms. This approach was necessary because very few studies examine monomeric aluminum levels in the environment or in anthropogenic releases.

2.2.2.1 Natural Sources

Atmospheric deposition of aluminum on land or water is small compared with internal releases by weathering and erosion of rock, soil and sediment (Driscoll et al. 1994). Weathering and erosion of “alum”-containing rocks will release aluminum into soils and streams, in part as Al^{3+} and other dissolved cationic and anionic species, depending on pH and the availability of complexing ions (Garrett 1998). These releases will be small, however, in relation to releases from weathering and erosion of aluminosilicate minerals.

There are no reliable estimates of the quantities of aluminum released to the environment by natural processes on a global scale, most of which comes from natural aluminosilicate minerals. Quantification of total or dissolved aluminum releases in Canada and elsewhere is very difficult and can provide only a rough estimate. Using Garrels et al.'s (1975) proposed global stream flux of 2.05 g/m^2 per year, total aluminum releases (including particulate material) were estimated to be approximately 20.45 million tonnes per year for Canada. Studies of weathering flux in selected Canadian and U.S. catchments (e.g., Likens et al. 1977; Kirkwood and Nesbitt 1991) yield similar or somewhat lower estimates (2 to 20 million tonnes per year) when extrapolated to the whole of Canada.

2.2.2.2 Anthropogenic sources

Very limited information is available on historical releases of the three aluminum salts. Accidental releases are reported to Environment Canada's National Analysis of Trends in Emergencies System (NATES) database and, more recently, the National Enforcement Management Information System and Intelligence System (NEMISIS). Between 1974 and 1991, 24 events released 316.2 tonnes of aluminum sulphate, mainly to land, and approximately 80% of the spilled material was recovered. Four accidental releases of aluminum chloride occurred in 1986 and 1987, and the product was not recovered on two occasions, resulting in a total release of 18.18 tonnes (Environment Canada 1995). Six spills involving the three aluminum salts subject to this assessment were reported from 1992 to 2008, all for aluminum sulphate. Approximately 40,000 liters of aluminum sulphate were released during these events, to both land and surface water, with no identified recovery of the spilled material. None of the reported incidents related to municipal or industrial effluent discharges (Environment Canada 2008b).

Municipal drinking water and wastewater treatment plants are the main users of aluminum sulphate, aluminum chloride and other aluminum-based polymeric products. Aluminum salts are used as coagulants and flocculants to cause fine materials that are suspended, soluble or both to agglomerate, for subsequent removal via sedimentation and filtration. As part of this agglomeration or coagulation process, most of the aluminum associated with the added aluminum salt hydrolyses to aluminum hydroxide, which precipitates and becomes part of the floc structure. As such, it makes up a part of the sludge generated by the treatment process. A small amount of the aluminum added may stay with the finished water in either colloidal particulate ($Al(OH)_3$) or soluble form (e.g., $AlOH^{2+}$, $Al(OH)_2^{+}$, $Al(OH)_3$, $Al(OH)_4^{-}$), dictated by the conditions of the treatment process and in particular, the pH (see Figure 2.1 below and from Stumm and Morgan 1981) .

While no comprehensive inventory of releases of aluminum associated with commercial use of aluminum salts exists, order-of-magnitude estimates derived from information provided by Canadian producers and users confirm that most releases are associated with wastewater treatment processes (approximately 43% in 2006), with drinking water treatment plants accounting for the majority of the remainder (about 36%; Table 2.3; Cheminfo Services Inc. 2008). All other sources are relatively minor. Again, most quantities are reported in terms of the elemental aluminum present in the respective salts. Approximately three quarters of the releases are to land, including: landfill, application on farms, and permanent lagoons. It is estimated that 5% of the aluminum used at pulp and paper mills for paper sizing is released to water courses (rivers or lakes), while 95% is contained on the paper,

which is assumed to receive eventual disposal to landfills and composting in a minor, but growing proportion (2008 email from Canadian Wastewater Association to J. Pasternak, Environment Canada; unreferenced).

Table 2.3 Estimated total releases in Canada of aluminum from aluminum salts[1] for 2006, by application (kilotonnes aluminum; Cheminfo Services Inc. 2008)

	Drinking Water	**Receiving Water**	**Storage in Lagoon**	**Landfill**	**Farms**	**Total**
	Water	Water	Land	Land	Land	
Municipal Drinking Water Treatment Plants[2]	0.1	3.2	0.1	2.2		5.7
Municipal Wastewater Treatment Plants[3]		0.4	0.06	2.0	4.5	6.9
Industrial Fresh Water Treatment	0.02	0.5	0.02	0.4		1.0
Industrial Wastewater Treatment		0.06	0.01	0.3	0.6	0.9
Pulp and Paper Additive		0.1		1.2		1.2
Miscellaneous				0.2		0.2
Total	0.12	4.3	0.2	6.3	5.1	16.0
Percent of Total						
Municipal Drinking Water Treatment Plants	1%	20%	1%	14%		36%
Municipal Wastewater Treatment Plants		3%	0.4%	12%	28%	43%
Industrial Fresh Water Treatment	0.1%	3%	0.1%	2%		6%
Industrial Wastewater Treatment		0.3%	0.05%	2%	4%	6%
Pulp and Paper Additive		0.4%		7%		8%
Miscellaneous				2%		2%
Total	1%	27%	1%	39%	32%	100%

[1] Includes aluminum sulphate, aluminum chloride, polyaluminum sulphate, polyaluminum chloride, aluminum chlorohydrate and sodium aluminate. Quantities reported represent elemental aluminum released from the aluminum salts.

[2] This excludes aluminum that is contained in effluents sent to wastewater treatment plants

[3] This includes aluminum that is contained in effluents obtained from drinking water treatment plants

Most of the aluminum releases are from the use of aluminum sulphate, which is the aluminum salt having the highest quantity of consumption in Canada (Table 2.4; Cheminfo Services Inc. 2008).

Table 2.4 Estimated total releases of aluminum, by salt, for 2006 (kilotonnes aluminum; Cheminfo Services Inc. 2008)[1]

	Drinking Water	Receiving Water	Storage in Lagoon	Landfill	Farms	Total
Aluminum Sulphate	0.1	3.6	0.2	5.0	3.1	12.0
Polyaluminum Chloride	0.02	0.7	0.03	0.9	0.6	2.3
Aluminum Chlorohydrate	0.01	0.1	0.01	0.2	0.1	0.5
Polyaluminum Sulphate	0.003	0.1	0.005	0.1	0.1	0.3
Sodium Aluminate	0.01	0.2	0.01	0.3	0.2	0.7
Aluminum Chloride	0.004	0.1	0.00	0.1	0.1	0.3
Total	0.2	4.8	0.2	6.6	4.2	16.0

[1] Quantities reported represent elemental aluminum released by the respective aluminum salts.

Approximately 2% of the total aluminum used by municipalities for drinking water treatment (6.8 kilotonnes; see Table 2.2) ends up in drinking water (Table 2.3; Cheminfo Services Inc. 2008). A survey of 102 Canadian water treatment facilities conducted in 2006 found that over 80% of drinking water treatment plants (DWTPs) that use aluminum salts as coagulants and flocculants measure the concentration of aluminum in the treated water. The survey considered data from municipal drinking water and wastewater treatment facilities across Canada, primarily from larger municipalities (population > 100,000), although a small sample of small-to-medium sized municipalities was included (population range 20,000-100,000; Cheminfo Services Inc. 2008). Outlet concentrations in drinking water at the surveyed DWTPs which used aluminum ranged from 0.005 to 0.2 mg/L, with an average value of 0.067 mg/L. For comparison, Health Canada's *Guidelines for Canadian Drinking Water Quality* are 0.1 mg/L for conventional treatment plants using aluminum-based coagulants and 0.2 mg/L for other treatment systems using aluminum-based coagulants (Health Canada 2007a).

Less than half of the aluminum used at drinking water plants is released to receiving waters – mostly as solid aluminum hydroxide sludge (Cheminfo Services Inc. 2008). Notable examples of this practice occur in water treatment plants in Toronto. Most of the remaining aluminum is contained in sludge that is sent to landfill. Some of the sludge from drinking water facilities (commonly called "filter backwash solids"), in dilute form, may also be sent to wastewater treatment facilities in the municipality. Results from the 2006 survey suggest that approximately 16% of the aluminum used at drinking water treatment facilities is contained in sludge sent to nearby wastewater treatment facilities. A very small portion (~2%) remains permanently stored in lagoons, which for assessment purposes has been assumed to be a land destination. The 2006 survey did not identify any sludge from drinking water treatment plants going to farms; however, it is possible that some disposal by this method may be occurring in Canada as a small proportion of DWTP sludge was identified for landfarming in the earlier survey conducted for 1995 and 1996 (Germain et al. 2000).

In a study done with sludge from Calgary and Edmonton, AEC (1987) found that less than 0.02% of aluminum bound with sludge (containing 78,187 mg Al/kg dw) was released in water (i.e., 0.20 to 0.32 mg/L). Srinivasan et al. (1998) studied the speciation of aluminum at

six different stages of water treatment at Calgary's DWTP. Total aluminum concentrations ranged from 0.038 to 5.760 mg/L, and dissolved inorganic aluminum concentrations varied from 0.002 to 0.013 mg/L. George et al. (1991) measured monomeric aluminum concentrations of less than 0.06 mg/L in alum sludge from ten different DWTPs containing up to a total of 2,900 mg Al/L; Calgary's DWTP was one of the plants studied.

Calgary's DWTP reported the aluminum content in backwash water following the cleaning of its filters. Dissolved aluminum levels ranged from 0.07 to 0.44 mg/L, and total aluminum concentrations varied from 0.76 to 3.3 mg/L. The backwash waters from this DWTP were not released to the river but were treated and sold as fertilizer (Do 1999).

Most of the aluminum discharged from municipal wastewater treatment plants (MWWTPs) surveyed in the 2006 study is associated with sludge. Approximately two thirds of the aluminum in MWWTP sludge is applied to farmland, with most of the balance (around 30%) being sent to landfill. About 5% of total aluminum releases are to surface waters and a very small proportion (less than 1%) is stored permanently in lagoons (Table 2.3). In Quebec City, the sludge from the drinking water treatment plant is directed to MWWTP where the resulting sludge is dried and incinerated with residential waste (co-incineration). The mineral and non-combustible component of the sludge is then landfilled (2008 email from Canadian Wastewater Association to J. Pasternak, Environment Canada; unreferenced). In most cases, the sludge sent to landfills was first sent for anaerobic digestion (where methane gas is generated from the organic content and used for plant energy) and the remaining solids concentrated to remove excess water. Some provinces (e.g., Alberta, Ontario and Quebec) have guidelines for the disposal of sewage sludge on agricultural land; spreading on agricultural land is permitted only when the pH is greater than 6.0 or when liming and fertilization (if necessary) are done. Although not a common practice, a few of the municipalities participating in the 2006 survey provided measured concentrations for aluminum present in sludge solids from their plants. In general, these values were in the range of 10 to 60 mg per gram of solids (dry basis) (Cheminfo Services Inc. 2008).

Final effluent concentrations of aluminum were not always available for MWWTPs participating in the 2006 survey (Cheminfo Services Inc. 2008). Where data were available, reported concentrations ranged from 0.013 to 1.200 mg/L, with an average value (weighted by water volume treated) of 0.816 mg/L. The form of the aluminum measured was not specified. Many of the MWWTPs surveyed relied on substances other than aluminum to treat wastewater, such as iron salts (ferrous and ferric chloride) and/or polyacrylamides, while others did not use any chemicals in their water treatment process.

Only two respondents to the 2006 survey provided information on aluminum concentrations in receiving waters in the vicinity of their effluent outfalls. The typical background level of dissolved aluminum in Lake Ontario in the vicinity of Toronto was reported to be approximately 0.010 mg/L, while typical concentrations in the North Saskatchewan River near Edmonton were 0.020 to 0.040 mg/L (Cheminfo Services Inc. 2008). These data are insufficient to determine in a useful way the contribution of aluminum from aluminum salt consumption in receiving waters. In the original State of the Science (SOS) report (Environment Canada and Health Canada 2000), it was determined that while extensive data on total aluminum concentrations in Canadian surface water are available, few data exist

in areas close to sites where releases occur. The situation for sediment and soil is similar, in that data exist for the Canadian environment in general, but not for areas where releases occur. The state of available relevant concentration data has not changed since 2000.

In addition, changes in policies and procedures relating to the direct release of treatment plant effluents into surface waters have occurred since the publication of the original SOS report. In 1993, a total aluminum concentration of 36 mg/L was measured just downstream of the Regional Municipality of Ottawa-Carleton's (RMOC) DWTP discharge pipe, while the concentration 200 m downstream of the plant was 0.5 mg/L (Germain et al. 2000). Similarly, in 1998, sediment concentrations in the Ottawa River were 125,160, 51,428 and 41,331 mg/kg dw at points closest to, 300 m, and 500 m downstream of the DWTP, respectively, and were significantly elevated compared with control and upstream values of 17,543 and 20,603 mg/kg dw, respectively. In 2008, all wastes from the plant were diverted to a nearby MWWTP, effectively eliminating the direct discharge of aluminum-bearing sludge into the river (Environment Canada 2008c). However, it will likely take some time before conditions in bottom sediment in the vicinity of the DWTP outfall return to those in line with non-impacted areas.

Germain et al. (2000) reported mean total aluminum levels in the effluent of some MWWTPs using aluminum salts. Concentrations varied from 0.03 to 0.84 mg/L, and the maximum value reported by one plant reached 1.8 mg/L. These figures are in the same order of magnitude as those reported by Orr et al. (1992) for 10 Ontario MWWTPs and by MEF and Environnement Canada (1998) for 15 Quebec MWWTPs, and agree well with those of Cheminfo Services Inc. (2008) reported above. Some plants do not use aluminum-based coagulants and flocculants but still reported aluminum levels in their effluents; their mean total aluminum levels ranged from 0.003 to 0.90 mg/L (Germain et al. 2000). Many wastewater treatment plants, such as those in Quebec, receive influents from combined sewers which collect both wastewater and stormwater. In these cases, part of the solids content of the influent will come from urban drainage that could contain aluminum-bearing solids from erosion processes and other sources. The content of wastewater treatment plant influents is determined by the nature and proportions of their primary inputs (i.e., residential, commercial, institutional, industrial) and contaminants present in these waters may also appear in the effluent, depending on the treatment process (2008 email from Canadian Wastewater Association to J. Pasternak, Environment Canada; unreferenced).

Federal, provincial/territorial and municipal governments all play a role in managing treated drinking water quality in Canada (Cheminfo Services Inc. 2008). Voluntary guidelines have been established for aluminum concentrations in drinking water, and while provincial/territorial and municipal government authorities recognize these guidelines, they have not been adopted as mandatory standards. For example, in British Columbia, Alberta, Newfoundland and Manitoba, the *Guidelines for Canadian Drinking Water Quality - Technical Documents: Aluminum* as specified by Health Canada (i.e., 0.1 mg/L for conventional treatment plants using aluminum-based coagulants and 0.2 mg/L for other treatment systems using aluminum-based coagulants) are recognized, but specific standards have not yet been fully incorporated into operating permits for treatment facilities. In Ontario, Certificates of Approval with a limit of 0.1 mg/L are issued to drinking water treatment plants; however, this limit is included as a guideline rather than a standard. In Quebec, no limits on

aluminum content in drinking water are found in the provincial regulations (including the Regulation Respecting the Quality of Drinking Water), and operating approvals are not required by wastewater treatment facilities (Cheminfo Services Inc. 2008).

Similarly, no federal legislation specific to municipal wastewater effluent discharges is in place (Cheminfo Services Inc. 2008). The federal government enforces CEPA (1999) that governs the releases of toxic substances to the environment, and the *Fisheries Act* that protects Canadian waters against the deposit of deleterious substances into fish habitat. In recent years, federal, provincial, and territorial governments have been working to develop a *Canada-wide Strategy for the Management of Municipal Wastewater Effluent* through the Canadian Council of Ministers of the Environment (CCME 2008); however, release standards for aluminum are not currently proposed or under development under the Strategy.

Less information is available on industrial releases of aluminum salts. The pulp and paper sector is the primary industrial user of aluminum salts, with applications in water treatment and as a paper additive. Alum is more commonly used for water treatment at mills in the warmer months of the year, while polyaluminum chloride (PAC) and polyaluminum silicate sulphate (PASS) have been found to be more effective winter coagulants. Recent quantitative release data for industrial uses are not available, although average concentrations of residual aluminum in treated water are estimated to be in the range of 0.02 mg/L (Cheminfo Services Inc. 2008). A 35% to 40% decrease in use of aluminum salts as a pulp and paper additive has been reported for the period 2000 to 2006, indicating a significant reduction in demand for this application (Cheminfo Services Inc. 2008).

Germain et al. (2000) reported mean total aluminum levels ranging from 0.46 to 4.8 mg/L in wastewaters released into rivers by the pulp and paper industry over the period 1990 to 1997. Mean total aluminum levels measured for other types of industries ranged from 0.01 to 2.3 mg/L. Since 1995, pulp and paper mills have been subject to the *Pulp and Paper Effluent Regulations* passed in 1992 under the *Fisheries Act*. In Quebec, for example, implementation of these regulations has led to a mean reduction of approximately 60% in total aluminum concentrations present in effluents (Germain et al. 2000). Environmental Effects Monitoring (EEM) reports published by the pulp and paper industry provide information on the distance from point of discharge that is required to dilute an effluent to less than 1% in the receiving water body. In some cases, only a few metres were needed, while in others, up to 300 km was required. In these cases, water input from other watercourses was needed to achieve dilution to 1%.

Sludge containing aluminum from the salts used in industrial water treatment can be sent to landfill or to steam boilers and co-generation units that handle bark, sludge, or other fuels (Cheminfo Services Inc. 2008). Aluminum may be present in the fly ash after burning of the sludge, although a small portion may also be emitted to air along with particulate matter (PM) emissions. No data are available on aluminum concentrations in fly ash; however, potential PM emissions are usually controlled with baghouses, electrostatic precipitators or other PM control systems.

The use of sludge derived from aluminum-based water treatment facilities as a soil amendment is the primary pathway by which aluminum salts enter the terrestrial environment.

It is likely that the amount of aluminum added to soil through this practice is small in comparison with aluminum naturally present in soil. Sludge disposal guidelines specifying maximum application rates and soil pH requirements exist for a number of provinces. In Ontario, sludge application rates cannot exceed 8 tonnes solids/ha/5 years and the pH of the receiving soil must be greater than 6.0 or liming is required (ME and MAFRA 1996). Still, potential exists for the release of aluminum into soil due to high amounts of the metal present in sludge residuals (Mortula et al. 2007). In addition, a shift in soil pH at the site of sludge application could mobilize aluminum in the sludge by shifting the chemical equilibrium towards more soluble forms of the metal. Soil acidification may occur during high water discharge events (e.g., storm events), when water entering the sludge deposition area has interacted with organic matter or travelled through more acidic upper mineral soils (Pellerin et al. 2002). Aluminum solubilized in this process is then available to be transported to adjacent soils or water bodies along shallow flow paths in the soil.

2.3 Exposure Characterization

2.3.1 Environmental Fate

The sections below summarize the information available on the distribution and fate of aluminum and the three aluminum salts, aluminum chloride, aluminum nitrate and aluminum sulphate, in the environment. A more detailed discussion on environmental fate can be found in Bélanger et al. (1999), Germain et al. (2000) and Roy (1999a).

2.3.1.1 Air

In air, hydrated aluminum chloride will react with moisture to produce hydrochloric acid and aluminum oxide (Vasiloff 1991). Aluminum nitrate and aluminum sulphate are likely to react in the same way, forming nitric and sulfuric acids, respectively. As the three aluminum salts that are the subject of this assessment are not usually emitted to air, the amount of aluminum present in air due to these salts is expected to be negligible compared with amounts coming from the natural erosion of soil (Environment Canada and Health Canada 2000).

2.3.1.2 Water

Natural sources of aluminum release to aquatic systems include weathering of rocks, glacial deposits and soils and their derivative minerals, and atmospheric deposition of dust particles. The most obvious increases in aluminum concentrations have consistently been associated with environmental acidification (Driscoll and Schecher 1988; Nelson and Campbell 1991). For this reason, recently observed changes in global climate and alterations in the acidity of atmospheric and oceanic systems, both resulting at least in part from human activities, have the potential to influence the presence and mobility of aluminum in the environment (Pidwirny and Gow 2002; Crane et al. 2005). The relationship is complex, however, and more research is needed in order to elicit the nature of potential impacts and their consequences for biota. Crane et al. (2005) postulated that increasingly severe weather patterns occurring as a consequence of global climate change, such as an increased incidence of prolonged heavy rainfall in some areas, may intensify physical and chemical weathering processes. When combined with the effects of acidification of waters, this could lead to significant changes in the speciation and mobility of aluminum and other metals.

Soil minerals such as gibbsite ($Al(OH)_3$) and jurbanite ($AlSO_4(OH)•5H_2O$) are considered the primary sources of aluminum release to the aqueous environment, especially in poorly buffered watersheds (Driscoll and Schecher 1990; Campbell et al. 1992; Kram et al. 1995). In more buffered watersheds, a solid-phase humic sorbent in soil is involved in the release of aluminum (Cronan et al. 1986; Bertsch 1990; Cronan and Schofield 1990; Cronan et al. 1990; Seip et al. 1990; Taugbol and Seip 1994; Lee et al. 1995; Rustad and Cronan 1995).

The three aluminum salts—chloride, nitrate and sulphate—are highly soluble and will form various dissolved species on contact with water. The fate and behaviour of aluminum in the aquatic environment are very complex. Aluminum speciation, which refers to the partitioning of aluminum among different physical and chemical forms, and aluminum solubility are affected by a wide variety of environmental parameters, including pH, solution temperature, dissolved organic carbon (DOC) content, and the presence and concentrations of numerous ligands. Metals in solution may be present as dissolved complexes, as "free" or aquo ions, in association with particles, as colloids or as solids in the process of precipitating. Colloidal particles (i.e., those in the range of 0.001 to 1 μm) are important in the transport of metals in stream ecosystems (Kimball et al. 1995; Schemel et al. 2000), as well as the accumulation of metals in sediment (Church et al. 1997) and biofilm (Besser et al. 2001), and the transfer to biota. Farag et al. (2007) proposed that colloids and biofilm may play critical roles in the pathway of metals to the food chain. The reactivity of aluminum, as well as geochemical behaviour, bioavailability and toxicity, are dependent upon its speciation (Neville et al. 1988; Gagnon and Turcotte 2007).

There are two general types of ligands that can form strong complexes with aluminum in solution. Inorganic ligands include anions such as sulphate (SO_4^{2-}), fluoride (F^-), phosphate (PO_4^{3-}), bicarbonate (HCO_3^-) and hydroxide (OH^-), among others. Organic ligands include oxalic, humic and fulvic acids (Driscoll et al. 1980; Sparling and Lowe 1996). The relative concentrations of the inorganic and organic ligands generally determine the proportions and type of complexes that are formed in solution.

Interactions with pH (Campbell and Stokes 1985; Hutchinson and Sprague 1987; Schindler 1988; Driscoll and Postek 1996) and DOC (Hutchinson and Sprague 1987; Kullberg et al. 1993) are of primary importance to the fate and behaviour of aluminum. DOC will complex with aluminum in water, forming aluminum-organic complexes and reducing concentrations of monomeric forms of aluminum (Farag et al. 1993; Parent et al. 1996). At a pH of 4.5, a concentration of 1 mg DOC/L can complex approximately 0.025 mg Al/L, with this complexing capacity increasing as pH increases (Neville et al. 1988). Fractions of dissolved organic aluminum were estimated for various rivers in Canada using the MINEQL+ (Schecher and McAvoy 1994) and WHAM (Tipping 1994) models; the results suggested that the importance of complexation with dissolved organic material (DOM) decreased over the pH range 7.0 to 8.5, likely due to reduced concentrations of the Al^{3+} and $AlOH^{2+}$ species which can associate with DOM (Fortin and Campbell 1999).

Aluminum is a strongly hydrolysing metal and is relatively insoluble in the neutral pH range (6.0–8.0) (Figure 2.1). In the presence of complexing ligands and under acidic ($pH < 6$) and alkaline ($pH > 8$) conditions, aluminum solubility is enhanced. At low pH values,

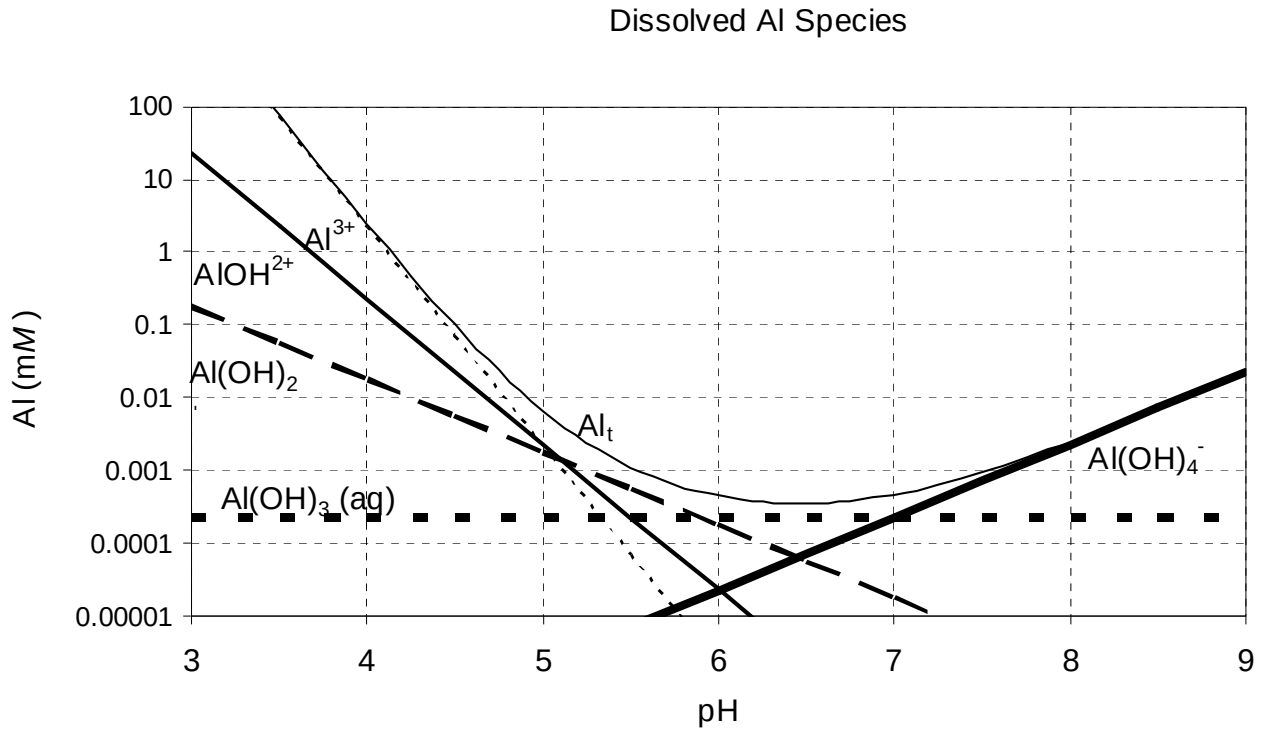
dissolved aluminum is present mainly in the aquo form (Al^{3+}). Hydrolysis occurs as pH rises, resulting in a series of less soluble hydroxide complexes (e.g., $Al(OH)^{2+}$, $Al(OH)_2^{+}$). Aluminum solubility is at a minimum near pH 6.5 at 20°C and then increases as the anion, $Al(OH)_4^{-}$, begins to form at higher pH (Driscoll and Schecher 1990; Witters et al. 1996). Thus, at 20°C and pH < 5.7, aluminum is present primarily in the forms Al^{3+} and $Al(OH)^{2+}$. In the pH range 5.7 to 6.7, aluminum hydroxide species dominate, including $Al(OH)^{2+}$ and $Al(OH)_2^{+}$, and then $Al(OH)_3$. Typically, at a pH of approximately 6.5, $Al(OH)_3$ predominates over all the other species. In this range, aluminum solubility is low, and availability to aquatic biota should also be low. At pH > 6.7, $Al(OH)_4^{-}$ becomes the dominant species. Aluminum-hydroxide complexes predominate over aluminum-fluoride complexes under alkaline conditions. However, the aluminum speciation determined for some rivers in Canada indicated that only one river, of pH less than 7, had a significant concentration (> 1%) of aluminum-fluoride complexes (Fortin and Campbell 1999). It is important to note that the various aluminum species described above are always present simultaneously at any pH value. The influence of pH in aquatic systems is mainly to change the proportion of all the species as the pH changes (2008 email from Canadian Wastewater Association to J. Pasternak, Environment Canada; unreferenced).

Mononuclear aluminum hydrolytic products combine to form polynuclear species in solution (Bertsch and Parker 1996). Aluminum begins to polymerize when the pH of an acidic solution increases to over 4.5:

$$2Al(OH)(H_2O)_5^{2+} \rightleftharpoons Al_2(OH)_2(H_2O)_8^{4+} + 2H_2O$$

Polymerization gradually proceeds to larger structures, eventually leading to the formation of the Al_{13} polycation (Parker and Bertsch 1992a, 1992b). In nature, conditions that favour the formation of polynuclear forms of aluminum can occur during the liming of acidic aluminum-rich watersheds (Weatherley et al. 1991; Lacroix 1992; Rosseland et al. 1992) and possibly during the addition of alum to circumneutral waters (Neville et al. 1988; LaZerte et al. 1997).

Figure 2.1 Solubility of aluminum species (and total aluminum, Al_t) in relation to pH in a system in equilibrium with microcrystalline gibbsite
(0.001 mM = 0.027 mg/L; Driscoll and Schecher 1990)



Temperature has been shown to influence the solubility, hydrolysis and molecular weight distribution of aqueous aluminum species as well as the pH of solutions. Lydersen et al. (1990b) reported a higher degree of aluminum hydrolysis and greater polymerization to high molecular weight species in inorganic aluminum solutions stored for one month at 25°C compared with those stored for an equivalent period at 2°C. The researchers hypothesized that more advanced polymerization evident at the higher temperature resulted in more deprotonation and condensation reactions, possibly accounting for the observed lower pH of the 25°C test solutions (range 4.83 to 5.07 versus 5.64 to 5.78 in the solutions at 2°C). Solubility and sedimentation were significantly higher at 25°C, with dissolution controlled by microcrystalline gibbsite. While substantial amounts of high molecular weight aluminum species were present in the solution at 2°C, little sedimentation was observed. Dissolution at the lower temperature appeared controlled by an amorphous $Al(OH)_3(s)$ with much higher solubility and, therefore, a high proportion of the high molecular weight inorganic aluminum species remained as colloids in the solution. The effects of low temperature on the coagulation efficiency of aluminum sulphate have been studied in relation to water treatment processes (Braul et al. 2001; Wobma et al. 2001; Kundert et al. 2004). The results provide further evidence that temperature-dependent fluctuations in the predominant aluminum species present in an aquatic system may occur in regions of Canada that experience marked seasonal fluctuations in temperature.

When released into water, for example within a drinking water treatment plant (DWTP), most of the aluminum associated with the aluminum salts considered in this report

hydrolyses to form aluminum hydroxides (Hossain and Bache 1991). Reactions between aluminum salts, water and associated "impurities" result in the formation of a floc, which separates from the water phase to form alum sludge. A small fraction of the aluminum can stay in the water in either colloidal or dissolved form. Barnes (1985) describes the different reactions involved in the formation of aluminum hydroxide in aqueous solution; the overall reaction can be represented by the following equation:

$$Al_2(SO_4)_3 + 6H_2O \rightleftharpoons 2Al(OH)_3^0 + 3H_2SO_4$$

The aluminum hydroxide present in sludge is expected to remain mostly solid following release into surface water. Ramamoorthy (1988) showed that less than 0.2% of the aluminum hydroxide present in sludge was released in supernatant water at a pH of 6 and less than 0.0013% was released at pH 7.65. In both cases, aluminum hydroxide was present mostly in particulate form. At these pH values, aluminum solubility is low and kinetics favour the formation of solid aluminum hydroxide.

When used to treat sewage water, alum will also react with phosphate, as shown in the following reaction (Romano 1971; Barnes 1985):

$$Al_2(SO_4)_3 + 2PO_4^{3-} \rightleftharpoons AlPO_4(s) + 3SO_4^{2-}$$

This process has been used for many years to treat phosphorus in wastewaters, as well as to reduce phosphorus levels in runoff from land fertilized with poultry litter and restore phosphorus-enriched eutrophic lakes (Lewandowski et al. 2003).

Kopáček et al. (2001) examined the possible role of aluminum in influencing the natural cycling of phosphorus, which is often a limiting nutrient in aquatic systems. The researchers postulated that aluminum from nearby lower pH soils may enter circumneutral water bodies during episodic acidification events, such as spring melt, leading to the formation of colloidal aluminum oxyhydroxide flocs which will strongly adsorb orthophosphate in the water column. The phosphate-bound particulate aluminum settles onto the lake bottom, removing the bioavailability of this phosphorus to organisms in the water column. The increasing sediment concentrations of aluminum-phosphorus floc disrupt the redox-dependent cycling of phosphorus in the lake, indicating that while aluminum does not enter directly into biotic cycles, it is capable of influencing the biogeochemical cycles of substances that are integral to living systems. Based on the solubility characteristics of aluminum (see

Figure 2.1), this process may also occur when acidic waters, which generally contain the most aluminum (Gensemer and Playle 1999), enter downstream waters of higher pH.

The cycling and availability of other trace elements (e.g., nitrogen) and of organic carbon may also be influenced by the adsorption and coagulation properties of aluminum (Driscoll and Schecher 1990; Lee and Westerhoff 2006). Dissolved organic carbon (DOC) has been shown to provide an important weak acid/base buffering system that aids in the regulation of pH in dilute acidic waters and removal of DOC by adsorption to aluminum could adversely affect pH conditions in a water body (Johannessen 1980; Driscoll and Bisogni 1984). As well, coagulation and removal of DOC and other light attenuating materials may alter patterns of water column heating, resulting in decreased thermal stability in a water body (Almer et al. 1974; Malley et al. 1982). Changes to the heating pattern and thermal stratification of a lake can profoundly impact ecosystems by altering the vertical transport of solutes and restricting coldwater fisheries (Driscoll and Schecher 1990).

Aluminum is highly reactive in seawater and will be rapidly scavenged by particulate matter when released into this medium (Nozaki 1997). The mean oceanic residence time for aluminum is predicted to be short compared to some other elements, in the range of 100 to 200 years, with vertical distribution dictated by terrestrial and atmospheric inputs at the surface, intense particle scavenging throughout the water column, and some regeneration in bottom waters (Orians and Bruland 1985). The higher ionic strength and relative magnitude of individual ion concentrations in saline waters compared with freshwaters lead to differences in coagulation reactions with aluminum salts. Duan et al. (2002) identified distinctly different characteristics between the two water types with respect to colloid destabilization, coagulation mechanisms, and colloidal removal. These differences can become important when water treatment processes include release of effluent or backwash materials into marine or brackish waters.

2.3.1.3 Sediment

Sediment, where metals are generally considered less biologically available, is nonetheless an important medium for aluminum (Stumm and Morgan 1981; Campbell et al. 1988; Tessier and Campbell 1990). Aluminum occurs naturally in aluminosilicates, mainly as silt and clay particles, and can be bound to organic matter (fulvic and humic acids) in sediments (Stumm and Morgan 1981). At $pH > 5.0$, dissolved organic matter (DOM) can co-precipitate with aluminum, thereby controlling its concentrations in lakes with elevated concentrations of DOM (Urban et al. 1990). DOM plays a similar role in peatlands (Bendell-Young and Pick 1995). At $pH < 5.0$, the cycling of aluminum in lakes is controlled by the solubility of mineral phases such as microcrystalline gibbsite (Urban et al. 1990). Lakes receiving drainage from acidified watersheds can act as a sink for aluminum (Troutman and Peters 1982; Dillon et al. 1988; Dave 1992).

Experimental acidification of lakes and limnocorrals has shown that aqueous aluminum concentrations rapidly increase in response to acidification (Schindler et al. 1980; Santschi et al. 1986; Brezonick et al. 1990). Mass-balance studies have demonstrated that retention of aluminum by sediments decreases as pH decreases (Dillon et al. 1988; Nilsson 1988). Under such conditions, sediments in acidified watersheds can provide a source of aluminum to the

water column (Nriagu and Wong 1986). Based on calculation of fluxes in acidic lakes, Wong et al. (1989) suggested that sediment is a source of aluminum to the overlying water column.

The release of aluminum hydroxide sludge from drinking water treatment plants (DWTPs) directly to surface waters is the primary pathway by which aluminum from aluminum salts enters sediment. If water velocity is low at the point of discharge, much of the released sludge will settle onto the surface of local sediment. Since, in Canada, the waters receiving such discharges are typically circumneutral, the solubility of aluminum in the sludge will generally be minimal (Environment Canada and Health Canada 2000).

2.3.1.4 Soil

Atmospheric deposition of aluminum to soil is attributed mostly to the deposition of dust particles and is generally low (Driscoll et al. 1994). Volcanic activity can also act as a major natural source of aluminum to soil (Pichard 2005). Aluminum is the third most abundant element in the earth's crust, making up approximately 8% of rocks and minerals and accounting for about 1% of the total mass of the Earth (Landry and Mercier 1992; Skinner and Porter 1989). Approximately 75% of Canada is covered by glacial till (Landry and Mercier 1992); examples of aluminum-bearing minerals inherited from glacial till (i.e., primary minerals) are feldspars, micas, amphiboles and pyroxenes. Transformation of primary minerals by chemical weathering reactions results in new solid phases (i.e., secondary minerals). Aluminum-bearing secondary minerals such as smectite, vermiculite and chlorite are often found in Canadian soils developed on glacial till.

Inputs of aluminum into soil solutions usually occur by mobilization of aluminum derived from the chemical weathering of soil minerals. The most important reaction in the chemical weathering of the common silicate minerals is hydrolysis. However, aluminum is not very soluble over the normal soil pH range; thus, it generally remains near its site of release to form clay minerals or precipitate as amorphous or crystalline oxides, hydroxides or hydrous oxides. Silica is much more soluble than aluminum at normal soil pH and is always in excess of the amount used to form most clay minerals, so that some is removed from the soil system in leachates (Birkeland 1984). In some parts of the world, the extent of chemical transformation by chelation is believed to exceed that by hydrolysis alone. In forest soils of cold and humid regions, such as those of eastern Canada, aluminum is believed to be transported from upper to lower mineral soil horizons by organic acids leached from foliage and the slow decomposition of organic matter in the forest floor (Courchesne and Hendershot 1997). The movement of aluminum-organic complexes stops when the soil solution becomes saturated (or when the aluminum-to-organic-carbon ratio reaches a critical value), thereby reducing their solubility. In pristine conditions, aluminum is normally retained within the B horizon of the soil. A third important reaction involving aluminum is the transformation of one mineral into another through the exchange of interlayer cations (Sposito 1996).

Although the dissolution and precipitation reactions of aluminum-bearing minerals are often good indicators of the solubility of aluminum in soils, they are by no means the only pedogenic processes controlling the concentrations of aluminum in soil solutions. Many other processes may partly control the uptake of aluminum by plants and soil organisms. Aluminum may be 1) adsorbed on cation exchange sites, 2) incorporated into soil organic matter, 3) absorbed by vegetation or 4) leached out of the soil system (Ritchie 1995). Aluminum can

form stable complexes with various types of soluble and insoluble organic matter, from simple low-molecular weight organic acids to humic and fulvic acids (Vance et al. 1996; Ritchie 1995). Organic ligands play an important role in the speciation of aluminum in soil solutions (David and Driscoll 1984; Driscoll et al. 1985; Ares 1986).

In eastern Canada, the atmospheric deposition of strong acids, such as nitric acid and sulfuric acid, has accelerated the natural acidification of soil. The increased H^+ activity (lower pH) in the soil solution creates a new equilibrium where more Al^{3+} is dissolved in the soil solution, cation nutrients (Ca^{2+}, Mg^{2+} and K^+) are replaced on the soil exchange complex by Al^{3+} and the base cations are eventually leached out of the soil.

There may be significant variation in Al^{3+} solubility with depth in a soil profile (Hendershot et al. 1995). In the surface horizons, the soil solutions tend to be undersaturated with respect to aluminum-bearing minerals; in the lower B and C horizons, aluminum in soil solutions can be expected to be near equilibrium with some aluminum solids. Although the equilibrium concentration is close to that which would be expected if gibbsite were controlling equilibrium, gibbsite has generally not been identified in Canadian soils. Other forms of aluminum, for example, hydroxy interlayered vermiculite, may control aluminum solubility at values close to those of gibbsite. Amorphous aluminum complexed with organic matter may also have a similar pH solubility curve that is a function of the pH-dependent variation in the number of binding sites.

Fluoride and hydroxide complexes are the two strongest groups of inorganic ion associations with aluminum in soil solutions (Nordstrom and May 1995). In very acidic soils, aluminum in the soil solution is present mainly as free Al^{3+}; as pH increases, free Al^{3+} hydrolyses to form complexes with OH^- ions (e.g., $AlOH^{2+}$, $Al(OH)_2^+$, $Al(OH)_3^0$). Near pH 6.5, aluminum solubility is at a minimum, but it increases at neutral to alkaline conditions because of the formation of $Al(OH)_4^-$ (Driscoll and Postek 1996). According to Lindsay et al. (1989), fluorine, the most electronegative and one of the most reactive elements, is released as fluoride ion through the dissolution of fluoride-bearing minerals. In acidic soils ($pH < 5.5$), low-ligand-number complexes such as AlF^{2+} are normally formed. In neutral to alkaline conditions, it is more difficult for F^- to compete with OH^- for aluminum in the soil solution because of the increased level of OH^- and probably the presence of calcium that tends to link with fluoride (CaF_2). Consequently, aluminum-hydroxide complexes predominate over aluminum-fluoride complexes in alkaline conditions.

The complexation of aluminum with sulphate is weaker than that with fluoride. However, in acidic soils where the sulphate concentration is high, aluminum may also form aluminum-sulphate complexes (Driscoll and Postek 1996). At low sulphate concentrations, $AlSO_4^+$ is the dominant aqueous form, whereas $Al(SO_4)_2^-$ is predominant in soil solutions with higher sulphate concentrations. Brown and Driscoll (1992) showed that several aluminosilicate complexes, including $AlSiO(OH)_3^{2+}$, are present in various regions of the eastern U.S. and Canada.

It has been shown that most dissolved aluminum in soil solution of the forest floor is organically bound and that these aluminum-organic complexes become less abundant with increasing soil depth (Nilsson and Bergkvist 1983; David and Driscoll 1984; Driscoll et al.

1985). In the Adirondacks of New York, David and Driscoll (1984) found that 82% and 93% of the total dissolved aluminum in the organic horizons of conifer and hardwood stands, respectively, were organically complexed. The proportion of organic to inorganic aluminum decreased at both sites from the organic to the upper mineral horizons and from the upper to the lower mineral horizons. In the soil solutions of the mineral horizons, aluminum-organic complexes accounted for 67% and 58% of the total aluminum in the conifer and hardwood sites, respectively, which indicates the importance of aluminum-organic complexes in humus-rich forest soils of eastern North America.

2.3.1.5 Biota

In general terms, a substance is considered to be bioavailable if, under the conditions of exposure, it can be taken up by organisms (Environment Canada 1996). The bioavailability of a substance is determined by its chemical form, the physical and chemical characteristics of the media (e.g., water, soil, food) in which it occurs, the receptor species, and the route of the exposure (e.g., dermal contact, ingestion, inhalation). For metals such as aluminum, the "free" or hydrated dissolved ions (i.e., Al^{3+}, $Al(OH)^{2+}$ and $Al(OH)_2^{+}$) are normally considered to be the principal bioavailable forms (Newman and Jagoe 1994). However, there is evidence that some other forms of a metal, such as organometallic compounds (e.g., of mercury and tin), oxyanions of the metal (e.g., CrO_4^{2-}, AsO_4^{3-}), and dissolved organic and inorganic metal complexes (e.g., colloidal and polynuclear aluminum complexes) can also be taken up by organisms (Parker and Bertsch 1992b; Benson et al. 1994; Campbell 1995).

Bioavailability directly influences the potential for bioconcentration, bioaccumulation and biomagnification of a substance in organisms. ICMM (2007) defines bioconcentration as the increase in concentration of a substance in an organism (or specified tissues thereof) relative to the concentration of the substance in the environmental medium (generally water) to which it is exposed, bioaccumulation as the amount of a substance taken up by an organism from water (bioconcentration) as well as through ingestion via the diet and inhalation, and biomagnification as the process by which the tissue concentration of a bioaccumulated substance increases as it passes up the food chain through at least two levels (Parametrix 1995). The three processes are significant indicators of the propensity of a substance to impart toxicity to individual organisms and at higher trophic levels in the food chain. However, bioaccumulation of essential elements (such as some metals) in organisms is typically subject to metabolic regulation (ICMM 2007).

Bioconcentration factors (BCFs) and bioaccumulation factors (BAFs) are unitless values derived by dividing steady state tissue concentrations of a substance by the steady state environmental concentration (ICMM 2007). For synthetic organic compounds, the use of a BCF and BAF threshold value (such as that of 5000 specified in the CEPA 1999 *Persistence and Bioaccumulation Regulations*; Canada 2000) provides valuable information for the evaluation of hazard and risk. Bioaccumulation is more complex for naturally occurring inorganic substances such as metals, however, as processes such as adaptation and acclimation can modulate both accumulation and potential toxic impact (ICMM 2007). All biota will naturally accumulate metals to some degree without deleterious effect and as some metals are essential elements, bioaccumulation does not necessarily indicate the potential for adverse effects (McGreer et al. 2003). While metal bioaccumulation is homeostatically regulated for

metals essential to biological function (Adams et al. 2000), non-essential metals may also be regulated to some degree as these homeostatic mechanisms are not metal-specific (ICMM 2007).

Thus, interpretation of the toxicological significance of bioaccumulation data for metals such as aluminum is complex. A more complete discussion of aluminum bioavailability and the implications for bioaccumulation and toxicity can be found in Roy (1999a) and Bélanger et al. (1999).

Few studies have examined the uptake and accumulation of aluminum by algae. While the algal bioassays conducted by Parent and Campbell (1994) were not specifically designed to determine the effect of pH on aluminum bioaccumulation, their data indicated that the accumulation of aluminum by *Chlorella pyrenoidosa* increased with the concentration of inorganic monomeric aluminum. In addition, the comparison of assays performed at the same concentration of aluminum but at different pH values showed that aluminum accumulation was suppressed at low pH (Parent and Campbell 1994). Aquatic invertebrates can also accumulate substantial quantities of aluminum, yet there is evidence that most of the metal is adsorbed to external surfaces and is not internalized (Havas 1985; Frick and Hermann 1990). Using the results of Havas (1985), the bioconcentration factor (BCF) for *Daphnia magna* varied from 10,000 at pH 6.5 down to 0 at pH 4.5. Similar results, i.e., decreasing accumulation of aluminum with decreasing pH, were reported for crayfish (Malley et al. 1988), caddisfly (Otto and Svensson 1983), unionoid clams (Servos et al. 1985) and a chironomid (Young and Harvey 1991). Other studies with clams and benthic insects showed no relationship between water pH and tissue accumulation (Sadler and Lynam 1985; Servos et al. 1985). Frick and Herrmann (1990) found that the largest portion (70%) of the aluminum was present in the exuvia of the mayfly, *Heptagenia sulphurea*, indicating that the metal was largely adsorbed and was not incorporated into the organism.

BCFs for fish were calculated to range from 400 to 1,365 based on results presented in Roy (1999a). Numerous field and laboratory studies have demonstrated that fish accumulate aluminum in and on the gill. It has been suggested that the rate of transfer of aluminum into the body of fish is either slow or negligible under natural environmental conditions (Spry and Wiener 1991). The initial uptake of aluminum by fish essentially takes place not on the gill surface but mainly on the gill mucous layer (Wilkinson and Campbell 1993). Fish may rapidly eliminate mucus and the bound aluminum following the exposure episode. For example, Wilkinson and Campbell (1993) and Lacroix et al. (1993) found that depuration of aluminum from the gills of Atlantic salmon (*Salmo salar*) was extremely rapid once fish were transferred into clean water. The authors suggested that the rapid loss is due to expulsion of aluminum bound to mucus.

Far fewer studies have examined aluminum accumulation in benthic organisms. However, chironomids do not appear to accumulate aluminum to the same degree as other aquatic invertebrates. Krantzberg (1989) reported that the concentration of aluminum in chironomids was < 0.3 nmol/g dw for the entire body and < 0.1 nmol/g dw for the internal structures. Most aluminum is either adsorbed externally or is associated with the gut contents of chironomids (Krantzberg and Stokes 1988; Bendell-Young et al. 1994).

BCFs for terrestrial plants were calculated based on data cited in the review by Bélanger et al. (1999). For both hardwood and coniferous species, the calculated BCF ranged from 5 to 1,300 for foliage and from 20 to 79,600 for roots in studies done with aluminum solutions. For those conducted with soil, BCFs were lower for both foliage (0.03–1.3) and roots (325–3,526). BCFs calculated for grain and forage crops ranged from 4 to 1,260 in foliage and from 200 to 6,000 in roots for experiments done with solutions. For soil experiments, the foliar BCF varied from 0.07 to 0.7.

2.3.2 Environmental concentrations

To determine aluminum concentrations in various environmental media in Canada, the most recent available data in Canada were used where possible, although data from other countries were examined as well. Concentrations in environmental media to be used as input into the human exposure assessment (i.e., air, drinking water, soil, and food) are estimated based on total aluminum. Although other sources of aluminum are also presented (e.g., consumer products) to provide an overview of aluminum exposures, they are not used to estimate general population exposure (see section 3.2.1). Bioavailability of aluminum in different media in relation to absorption in humans is considered separately in section 2.3.3. Data presented below are also relevant to the assessment of ecotoxicological effects.

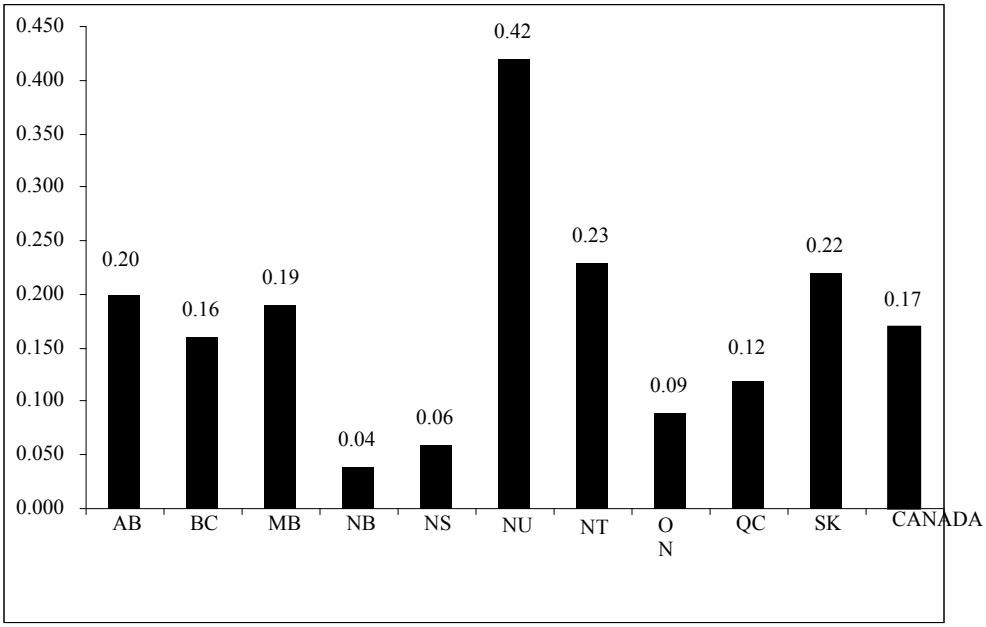
2.3.2.1 Air

2.3.2.1.1 Ambient air

Ambient air at more than 40 Canadian sites, primarily in urban areas, was sampled over a period of ten years (1996–2006). More than 10,000 samples were measured at different sites throughout Canada, although the number varied from year to year. In 2006, only 25 sites were measured, resulting in 1,400 samples, 96% of which had levels greater than the detection limit (approximately 0.001 $\mu g/m^3$).

Total aluminum concentrations measured in individual samples of PM_{10} (i.e., particulate matter smaller than 10 μm in diameter) ranged from the detection limit to 24.94 $\mu g/m^3$, with the lowest concentration being measured in Saint John, New Brunswick and the highest in Vancouver, British Columbia (Dann 2007). Figure 2.2 shows estimated mean aluminum concentrations measured in ambient air for all sampling sites by province for the ten-year period. On the basis of these measurements from across Canada, the estimated provincial/territorial mean aluminum concentration in PM_{10} is 0.17 $\mu g/m^3$. This value was used for the purpose of assessing exposure of the Canadian population to aluminum in ambient air.

Figure 2.2 Mean aluminum concentrations in PM_{10} in outdoor air from provinces and territories across Canada (μg/m^3) (1996–2006)



For most of the Canadian sites where PM_{10} measurements were carried out, data were also available for $PM_{2.5}$ particles (i.e., smaller than 2.5 μm in diameter). Close to 20,000 measurements were available from 1998 to 2006, 77% of which had levels greater than the detection limit. Using all available data, the mean aluminum concentration in $PM_{2.5}$ in Canada is approximately 0.069 μg/m^3, with a maximum aluminum concentration of 9.24 μg/m^3 measured in Vancouver, British Columbia (Dann 2007).

No published data were available on aluminum levels in ambient air in the vicinity of aluminum smelters or other industries in Canada, and limited data from other countries were identified. In an industrial area of the province of Turin in Italy, levels of 1.12 and 0.4 μg/m^3 of aluminum were measured during industrial activity and during holidays, respectively, (Polizzi et al. 2007). According to JECFA (2007), the concentration of aluminum in ambient air of industrial areas may range from 25 to 2,500 μg/m^3. It should be noted that the three aluminum salts—chloride, nitrate and sulphate—are unlikely to have contributed significantly to total concentrations measured in ambient air, as their use does not generally result in air emissions of aluminum.

2.3.2.1.2 Indoor air

Few data on aluminum concentrations in indoor air in residential dwellings were identified for Canada. Studies in the U.S. did provide data on aluminum in indoor air. These findings are summarized below.

In 1990, a Particle Total Exposure Assessment Methodology (PTEAM) study was conducted in Riverside, California, in which samples were collected from 178 non-smokers over ten years of age. In addition to the personal sampling (portable sampler), stationary samplers were set up inside the residential dwellings and outside near the entrance door.

Airborne particle (PM_{10} and $PM_{2.5}$) samples were collected for two 12-hour periods (nighttime and daytime), and more than 2,900 samples were analyzed (Clayton et al. 1993; Thomas et al. 1993). In this study, the aluminum concentrations exceeded the reporting limit of 0.5 $\mu g/m^3$ in more than half of the personal PM_{10} samples taken during the two periods. In the case of $PM_{2.5}$, only 20% of the measurements exceeded the reporting limit. Estimated daytime median concentrations of aluminum for the PM_{10} indoor, outdoor and personal exposure monitors were 1.9, 2.5 and 3.4 $\mu g/m^3$, respectively; the corresponding nighttime median concentrations were 0.99, 1.7 and 1.0 $\mu g/m^3$. Based on the average daytime and nighttime concentrations of aluminum in PM_{10} particles, the estimated mean concentration of aluminum in indoor air was about 1.49 $\mu g/m^3$.

For the purpose of assessing exposure for the general Canadian population, this estimated mean concentration of aluminum in PM_{10} particles of 1.49 $\mu g/m^3$ was considered to represent the typical indoor air concentration of aluminum in Canada. As in the case of ambient air, the three aluminum salts—chloride, nitrate and sulphate—are unlikely to have contributed significantly to total aluminum concentrations measured in indoor air.

2.3.2.2 Water

2.3.2.2.1 Surface water

Aluminum is a naturally occurring element and is present in all water bodies in Canada and elsewhere. Aluminum can be analysed under different forms, but historically results were reported mostly as total aluminum because of the low cost and ease of analysis. In many cases, results are also available for extractable or dissolved aluminum. Total aluminum represents all the aluminum present in a water sample, including the particulate fraction. Extractable aluminum includes both the "dissolved" fraction and weakly bound or sorbed aluminum on particles, and "dissolved" aluminum represents the fraction present in a sample filtered through a 0.45 µm membrane. All the bioavailable aluminum is considered to be present in this fraction, but not all the dissolved aluminum is bioavailable. Colloidal aluminum (0.01 to 0.1 µm) and organic aluminum (aluminum bound with soluble organic ligands) that are included in this fraction are generally thought to be less bioavailable than truly dissolved forms of the metal (Roy 1999a).

At reference lake and river sites across Canada that have not been influenced by effluents from facilities using aluminum salts, mean total aluminum concentrations ranged from 0.05 to 0.47 mg/L, with a maximum value of 10.4 mg/L, measured in British Columbia. Mean extractable aluminum concentrations ranged from 0.004 to 0.18 mg/L, with a maximum value of 0.52 mg/L found in a lake in the Abitibi region of Quebec. Mean dissolved aluminum concentrations varied from 0.01 to 0.08 mg/L and the highest dissolved aluminum value reported was 0.9 mg/L in British Columbia (Germain et al. 2000).

Aluminum was measured in water taken both upstream and downstream of facilities using aluminum salts and releasing aluminum or aluminum salts, but sampling stations were typically not located close enough to sources to allow the local impact of the effluents to be assessed. Mean total aluminum levels generally varied from 0.002 to 2.15 mg/L, with a maximum value of 28.7 mg/L, measured in the Oldman River, 40 km downstream of Lethbridge, Alberta. Total aluminum levels are usually higher in the Prairies, in rivers with

high total particulate matter content. Mean extractable aluminum concentrations ranged from 0.03 to 0.62 mg/L, and the maximum value of 7.23 mg/L was reached in the Red Deer River, at Drumheller, Alberta. Mean dissolved aluminum concentrations were much lower, ranging from 0.01 to 0.06 mg/L. In surface water, the maximum dissolved aluminum concentration (0.24 mg/L) was measured in the Peace River, Alberta (Germain et al. 2000). Concentrations in downstream locations were not consistently elevated in relation to concentrations in upstream locations, suggesting that the impacts of releases of aluminum salts are mostly local.

Although information on the forms of dissolved aluminum present at these monitoring locations was not identified, results of equilibrium modelling suggest that most dissolved aluminum in waters with pH values of 8.0 and higher is in inorganic monomeric forms (Fortin and Campbell 1999). For the 12 Prairie locations where dissolved and total aluminum levels were reported, pH levels were 8.0 or higher, and dissolved aluminum represented less than 3% of total aluminum (Roy 1999b). The overall average concentration of dissolved aluminum at these sites was 0.022 mg/L, similar to levels of inorganic monomeric aluminum reported in comparatively pristine Adirondack surface waters (pH from ~5.8 to ~7.2), where most values were around 0.027 mg/L (Driscoll and Schecher 1990).

Empirical data indicating an increase in aluminum levels in ambient water receiving inputs of aluminum salts were available for only a few locations. A total aluminum concentration of 36 mg/L was attained just downstream of the discharge pipe of a Regional Municipality of Ottawa-Carleton's (RMOC) DWTP in water samples taken following a rountine release of backwash in 1993; samples taken 200 m downstream of the discharge pipe showed a total aluminum level of 0.5 mg/L In 1994, the total aluminum level reached 11.3 mg/L just downstream of the discharge. In 2008, all wastes previously destined for the Ottawa River from RMOC DWTPs were diverted completely to the local sewage treatment plant for treatment prior to discharge (Wier, pers. comm. 2008). In the Kaministiquia River, the increase in mean total aluminum noted from upstream to downstream stations corresponds approximately to the inputs from the pulp and paper mill located in Thunder Bay, Ontario. The mean difference of 0.071 mg/L observed in total aluminum concentrations for samples taken on the same day at both stations for the period 1990–1996 is equivalent to the predicted aluminum increase of 0.069 mg/L calculated with the aluminum releases reported by the mill (Germain et al. 2000). For the Ottawa and Kaministiquia rivers, estimated dissolved monomeric aluminum levels were 0.027 mg/L and 0.040 mg/L, respectively. These values were obtained using the MINEQL+ model and estimated concentrations in effluents, assuming solubility controlled by microcrystalline gibbsite (Fortin and Campbell 1999). Using boehmite as the controlling phase provides lower dissolved inorganic aluminum levels (0.005 mg/L and 0.007 mg/L, respectively).

The Quebec Environment Ministry, now Ministère du Développement Durable, de l'Environnement et des Parcs, and Environment Canada examined the toxic potential of effluents generated by 15 municipal wastewater treatment plants in Quebec (Ministère de l'Environnement du Québec and Environment Canada 2001). The plants were considered to represent treatment methods used most commonly in Quebec and serviced over 50% of the province's population. Whole effluent sampling was conducted twice a year, during summer and winter operating conditions, over the period 1996 to 1999. Total aluminum concentrations in the effluents ranged from below the detection limit (0.002 to 0.1 mg/L) to 3.57 mg/L in

summer and up to 4.25 mg/L under winter operating conditions. Concentrations remained at or below 1 mg/L year-round in all but two of the plants; however, 20 out of 45 summer readings and 25 out of 39 winter readings exceeded the maximum interim water quality guideline of 0.156 mg/L for the protection of freshwater life (water pH equal to or greater than 6.4) as recommended by CCME (2003). The study concluded that ammonia nitrogen and surfactants were mainly responsible for the observed effluent toxicity, with pesticides possibly a factor during summer months; however, the presence of aluminum in the effluents at levels above background may also have contributed to some extent. The results suggest that periodic episodes of aluminum toxicity are possible in some receiving waters; however, the nature of the collected data makes concluding on potential risk to the environment difficult. The study was designed to evaluate the toxic potential of whole effluents and did not include consideration of factors such as dilution effects, interactions between constituents in the effluents, and natural background levels of aluminum in the receiving environments. Therefore, while effluent concentrations may have exceeded the recommended water quality guideline, it is uncertain whether these guidelines were also exceeded in the surface waters receiving these effluents. In addition, it is likely that a large fraction of the total aluminum present in the effluents was associated with particulates that would settle out of the water column upon release into surface waters (Germain et al. 2000). This would substantially reduce the potential for adverse impacts to pelagic organisms, although negative impacts to benthic organisms could still occur. These impacts could relate directly to aluminum toxicity or be associated with physical aspects such as blanketing effects and/or the presence of other toxic contaminants.

Agencies such as the Greater Vancouver Regional District (GVRD; now Metro Vancouver) routinely monitor wastewater products generated at municipal treatment plants, in order to evaluate effluent quality and ensure compliance with provincial regulations such as the Environmental Management Act. Wastewater monitoring in the GVRD is conducted by the Greater Vancouver Sewerage & Drainage District (GVS&DD) and includes determination of total and dissolved aluminum concentrations in wastewater treatment plant influents and effluents, as well as estimates for influent and effluent loading of aluminum. Monthly data summaries are provided on the GVRD website and these are compiled annually into a Quality Control Report (http://www.metrovancouver.org/services/wastewater/treatment/Pages/montoring.aspx). For 2006, the latest report available on the website, influent concentrations measured at the five wastewater treatment plants operating in the GVRD ranged from 0.47 to 2.74 mg/L and 0.04 to 0.25 mg/L for total and dissolved aluminum, respectively (GVRD 2006), while effluent values were 0.05 to 0.97 mg/L and 0.02 to 0.16 mg/L. While influent concentrations of total aluminum were generally comparable between primary and secondary wastewater treatment plants, mean total aluminum concentrations were higher in primary treatment effluents as compared with those from plants using secondary treatment, likely reflecting greater removal of particulate aluminum from the water phase during the coagulation and flocculation process of secondary treatment. In general, influent concentrations of both total and dissolved aluminum were comparable between the two types of wastewater treatment. However, estimated loading rates varied widely between the plants and annually within each plant, with influents ranging from 7.8 to 1,380 kg/d total and 1.0 to 98 kg/d dissolved aluminum, and effluent rates 0.9 to 943 kg/d and 0.2 to 59 kg/d for total and dissolved aluminum, respectively. An analysis of total aluminum concentrations in treatment plant effluents from

1997 to 2006 indicated that levels had remained generally stable around 0.1 to 1.0 mg/L or decreased steadily during this period. A marked reduction in total aluminum was observed at two plants following the implementation of secondary treatment in 1998 and 1999, confirming the efficacy of this process in removing particulate aluminum from water.

2.3.2.2.2 Drinking water

Many drinking water treatment plants in Canada using surface water supplies add aluminum salts (aluminum sulphate, aluminum chloride or polymer forms) as a coagulant/flocculent to eliminate organic compounds, micro-organisms and suspended particulate matter. Treatment with aluminum salts may not necessarily increase the total aluminum concentration in finished drinking water, as the aluminum associated with suspended solids is removed. However, aluminum salt addition does appear to increase the concentration of low-molecular-weight, dissolved aluminum species, which may potentially present a higher bioavailability (Health Canada 1998b). More information on the bioavailability of aluminum from drinking water can be found in section 2.3.3.1.1.

For most provinces and territories, data on concentrations of aluminum in drinking water were obtained directly from municipalities that use aluminum salts in drinking water treatment (Health Canada 2007b). Data were also obtained from monitoring programs carried out in five provinces and territories from 1990 to 1998 (Environment Canada and Health Canada 2000). Over 10,000 drinking water samples from approximately 1,200 sites across Canada were analyzed over the past 20 years. The majority of the data analyzed was collected over ten years, in some cases up to 2007 (Health Canada 2007c).

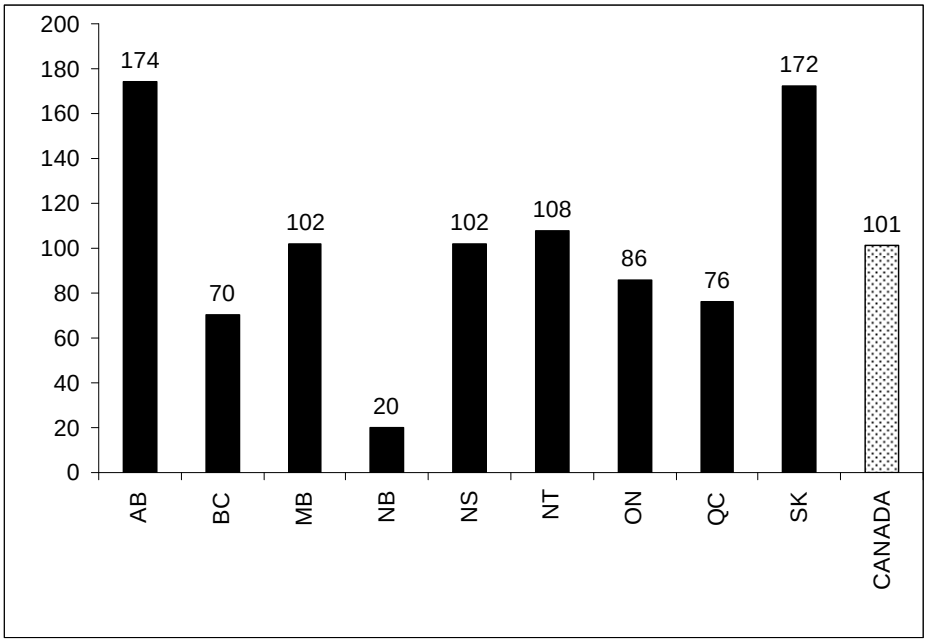
In drinking water treatment systems in Canada that have surface water sources and use aluminum salts, the mean total aluminum concentration was estimated at 101 µg/L.[2] Mean concentrations for the different provinces (see Figure 2.3) varied from 20.0 µg/L in New Brunswick (between 1995 and 2007) to 174 µg/L in Alberta (between 1990 and 2002).

In addition to the analysis of alum-treated drinking water, more than 2,800 samples of drinking water derived from groundwater sources from various Canadian municipalities were analyzed. Aluminum salts are not used in treatment of groundwater, except in the case of certain sites in the Northwest Territories. New Brunswick private wells had the highest mean total aluminum concentrations at approximately 40.0 µg/L, whereas Ontario had the lowest concentrations of about 10.0 µg/L. On the basis of all the data from about 30 drinking water treatment systems in Canada, the mean aluminum concentration is estimated to be 25.2 µg/L in groundwater sources, which is four times lower than that estimated for surface water treated with alum.

[2] An arithmetic mean was made with all available data per province or territory which provided total aluminum concentrations from water treatment systems that have surface water sources and use aluminum salts. Then an average of these values from the nine provinces/territories was calculated to represent the Canadian average (101 µg/L).

The average value of 101 μg/L, associated with the various aluminum salt-treated water supplies was used for the purpose of assessing exposure of the Canadian population to aluminum in drinking water.

Figure 2.3 Mean total aluminum concentrations in aluminum-treated drinking water from provinces and territories across Canada (μg/L) (1990–2007)



2.3.2.3 Sediment

Based on limited data, total aluminum levels in Canadian sediments are of the same order of magnitude as those measured in soils (see Section 2.3.2.4), with levels varying between 0.9% and 12.8%. The highest levels were found in Lake St. Louis, Quebec. Of particular interest are aluminum levels measured in sediment of the Ottawa River less than 300 m downstream of a location where backwash water (from the Britannia DWTP)_ had been discharged for approximately 27 years (Environment Canada 2008c). In 1989, the mean total aluminum content of sediment collected from a control site situated 100 m off the treatment plant effluent plume was 17,543 mg/kg dw, while the value closest to the outfall was 125,160 mg/kg dw (Germain et al. 2000). Mean concentrations measured 300 m and 500 m downstream of the plant discharge point were 51,428 and 41,331 mg/kg dw, respectively, still elevated compared with the control site and that of an upstream location (mean concentration 20,603 mg/kg dw). In a follow-up study conducted in 2000 (City of Ottawa 2002), sampling confirmed that concentrations of aluminum were highest in riverbed sediment located at the discharge outlet of the Britannia DWTP (approximate mean of 150,000 mg/kg dw), then declined over 500 m to approximately 12,000 mg/kg dw. This concentration was not appreciably higher than the sampling location 150 m upstream from the discharge outlet (10,000 mg/kg). The aluminum concentration then increased to approximately 61,000 mg/kg at the 1,500 m sampling site indicating that this was likely a far-field zone of deposition. Waste discharges of aluminum-bearing sludge from Ottawa DWTPs previously destined for

the Ottawa River have been diverted in 2008 to the local WWTP for treatment (Environment Canada 2008c).

2.3.2.4 Soil

Aluminum is the third most abundant element in the earth's crust, after oxygen and silicon, occurring as aluminosilicates and other minerals. The data on soil aluminum concentrations presented below come from soil surveys covering various geographic areas, and generally represent naturally-occurring aluminum concentrations.

In Canada, soil sampling has been carried out since the 1930s, but analysis for aluminum has only occurred in the past 20 years. Data for more than 40 studies based on over 40,000 soil samples across Canada from the past 20 years are thus available and were used to estimate the average total aluminum concentration in soil. Two studies cover all of Canada, while others focus on specific regions such as the Prairies, a province, or a municipality, in connection with local industries, types of soil, soil horizons, soil groups, or land use. In addition, some Canadian data on aluminum in dust from inside residential dwellings were available for consideration. More detailed information describing the available soil concentration data may be found in the supporting documentation for this assessment (Health Canada 2008a).

The estimated exposure to the Canadian population is based on data representing surface soil horizons, or in the first few decimetres, and not on data measured in the C horizon (primary environment; Reimann and Garrett 2005). The surficial concentrations of natural elements are, nonetheless, directly related to their concentration in the primary environment.

Some researchers have maintained that background concentrations[3] should not be expressed as an absolute value but rather a range of values varying by sampling location and scale (Choinière and Beaumier 1997; Reimann and Garrett 2005). For the purposes of the present assessment, however, the concentration of aluminum in surface soil has been based on the arithmetic mean of all available data, and not based on a concentration range.

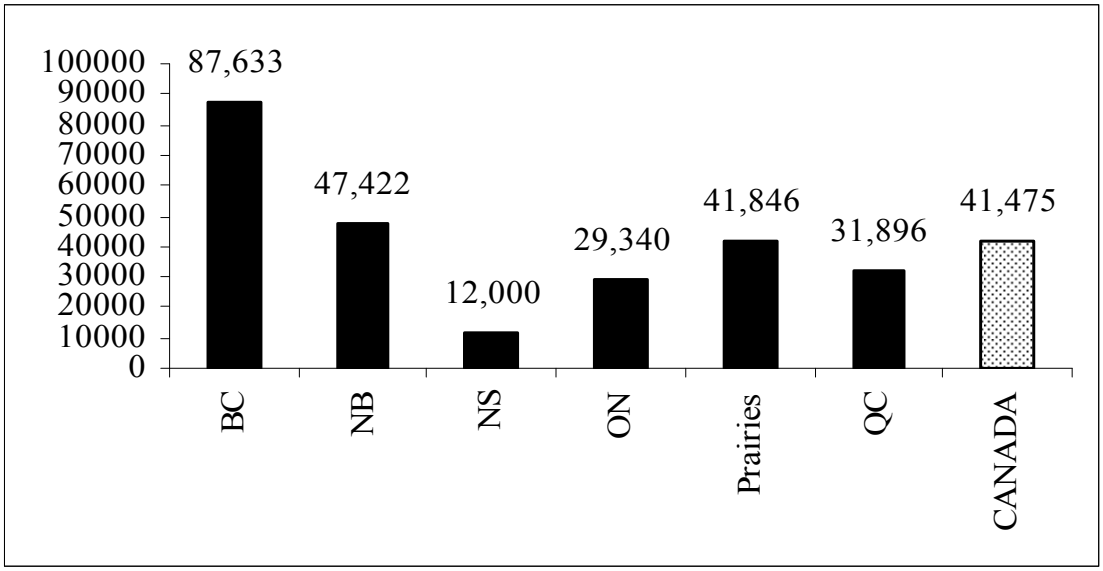
The mean total aluminum concentration in Canada is estimated to be 41,475 mg/kg[4]. Figure 2.4 summarizes the mean total aluminum concentrations in soils by province and for Canada as a whole. The mean concentrations of total aluminum ranged from 12,000 mg/kg in Nova Scotia to 87,633 mg/kg in British Columbia. While a single estimate of aluminum concentration in soil has been calculated for the purpose of the present assessment, it is important to recognize that aluminum concentrations in soil vary extensively from one region to another.

[3] Background concentration is a term used in geochemical exploration that refers to the natural abundance of a sterile element from the Earth's crust (Hawkes and Webb 1962).

[4] Average of the results obtained from over 40 studies covering ten provinces.

In recent years, Health Canada initiated research in the Ottawa region comparing mean aluminum concentrations in residential gardens with concentrations in dust from inside residential dwellings. The results showed that mean aluminum concentrations were about 26,000 mg/kg inside residential dwellings, but more than double that (55,841 mg/kg) in gardens (Rasmussen et al. 2001).

Figure 2.4 Comparison of mean total aluminum concentrations in soils from provinces across Canada (mg/kg) (1987–2007)



Measures of extractable and dissolved aluminum in soil

In general, unless the soil pH falls below 4, levels of the more soluble Al^{3+} form (i.e., the form considered to be more readily taken up by organisms) in the soil pore fluids are likely to be low. Hendershot and Courchesne (1991) measured aluminum in soil solution at St. Hippolyte, Quebec. The median total dissolved aluminum level was 0.570 mg/L, the median inorganic aluminum level 0.190 mg/L and the median Al^{3+} level 0.0003 mg/L in samples collected at a depth of 25 cm (pH = 5.5). Total dissolved aluminum was also measured in soil solution in the Niagara, Ontario, region; its level reached 1.214 mg/L (pH 4.2) in untreated soil. Following treatment with lime, aluminum was not detected in soil pore waters, and the pH increased to 4.8–5.5 prior to planting alfalfa (*Medicago sativa* L.). After three cuts of alfalfa, the pH was elevated to 6.0 in control plots and to 7.5–8.0 in limed plots; the mean total dissolved aluminum level was 0.335 mg/L in pore waters in the control plots and 0.016 to 0.397 mg/L in limed plots (Su and Evans 1996).

Turmel and Courchesne (2007) reported concentrations of 16.5 to 18.5 mg/kg dw total recoverable aluminum (from nitric acid digestion) in surface soil samples (pH 5.2) collected in 2005 from an abandoned agricultural field near a zinc plant in the Valleyfield area of Quebec. Soil collected under a nearby forest stand (pH 6.0) contained from 8.8 to 11.7 mg/kg dw total recoverable aluminum. The water soluble fraction of aluminum for the soils was 0.477 to 0.507 mg/L and 0.403 to 0.424 mg/L for the agricultural and forest soil samples, respectively.

Data relating to aluminum levels in soils treated with aluminum hydroxide sludges are limited. Near Regina, Saskatchewan, 1100 tonnes of alum sludge from a DWTP were spread on 16 ha of soil at a rate of 75 tonnes per hectare. There was no statistical difference in the mean acid-extractable aluminum level in both control (4.0%) and treated (4.1%) soil (Bergman and Boots 1997). In a study done for the American Water Works Association, Novak et al. (1995) measured the aluminum content of soil before (pH 4.7 and 5.5 at two sites) and after application of water treatment residuals. The PAC residual contained 2,330 mg Al/kg dw, and the alum residual, 6,350 mg/kg dw. In cropland soil treated according to the Mehlich III extraction procedure, which estimates the amount of aluminum available for uptake by organisms, concentrations of this available aluminum varied between 405 and 543 mg/kg dw (or 0.04% and 0.05%) before the application of the water treatment residuals. Addition of PAC and alum residuals resulted in an increase of available aluminum to 770 mg/kg dw and 1115 mg/kg dw, respectively. In another experiment, alum residual containing 150,000 mg Al/kg dw was applied to forest soil (pH 4.7). Soil analyses done 30 months later showed no differences between the control and the treatment plots for bioavailable and total aluminum.

2.3.2.5 Biota

Aluminum concentrations in vegetation related to the production or use of the aluminum salts considered in this report were available for only a few locations in Canada. Vasiloff (1991, 1992) reported aluminum levels in bur oak (*Quercus macrocarpa*) foliage collected from trees near an aluminum chloride producer in Sarnia, Ontario. Total aluminum levels ranged from 25 to 170 mg/kg dw in 1989 and from 57 to 395 mg/kg dw in 1991. Levels were higher in the foliage of trees closer to the aluminum chloride plant. These levels were below the Ontario Rural Upper Limit of Normal for aluminum in tree foliage (Vasiloff 1992). Fugitive emissions of aluminum chloride and subsequent hydrolysis, resulting in the formation of hydrochloric acid, were responsible for the damage to trees, including death that was observed at one location. The company ceased its operations in the mid-1990s. No such damage was reported near aluminum sulphate plants.

Novak et al. (1995) measured aluminum levels in soils before (pH 4.7 and 5.5 at two sites) and after the application of water treatment residuals (PAC and alum sludge), as well as aluminum contents in tissues of corn (*Zea mays*), wheat (*Triticum aestivum*) and loblolly pine (*Pinus taeda*) in control and treated soils. Statistical differences in aluminum contents were noted only in corn tissues. Aluminum levels were lower (15.1 mg/kg dw versus 18.6 to 19.6 mg/kg dw) in plants grown in soil treated with 2.5% of PAC water residual than in plants grown in soil treated with 1.34% alum or in controls; however, crop yields (kg/ha) were not lower. Aluminum levels in loblolly pine tissues were not statistically different in trees grown in control (270 mg/kg dw) and treated (152 to 170 mg/kg dw) soil.

No information was found relating concentrations in animals with aluminum entering the environment from direct production or use of the three salts subject to this assessment.

Morrissey et al. (2005) reported mean levels of 55 mg/kg dw in feathers and 2780 mg/kg dw in feces of American dippers (*Cinclus mexicanus*) residing in the Chilliwack watershed of British Columbia. The samples were collected over the period 1999 to 2001, and

were considered to represent overall exposure to both natural and anthropogenic sources in the region. Benthic invertebrates (primarily insect larvae) and salmon fry, both key dietary items for the birds, contained mean concentrations of around 1,500 mg/kg dw and 165 mg/kg dw, respectively. Aluminum was present in all invertebrate (n = 30), fish (n = 9) and bird fecal samples (n = 14), but only 16% of the feather samples (n = 82). Based on a calculated total dietary intake (TDI) value of 26 mg/kg bw/d, derived using procedures described in CCME (1998), the researchers hypothesized that dipper populations in the region may be subject to chronic exposure effects of aluminum.

2.3.2.6 Food

Most foods, whether of plant or animal origin, contain a certain amount of aluminum originating from: (a) naturally-occurring aluminum in the soil, (b) the addition of aluminum salt-based food additives, and (c) the migration from aluminum-containing materials in contact with food (InVS-Afssa-Afssaps 2003). More than 80% of total aluminum concentrations found in foods and beverages range from 0.1 to 10 mg/kg wet weight. Some foods containing additives can exceed aluminum concentrations of 100 mg/kg.[5]

Selection of data for foods in Canada

Data on the concentrations of aluminum in Canadian foodstuffs are collected through Canadian Total Diet Studies, carried out by the Health Products and Food Branch of Health Canada, with the fifth Total Diet Study being the most recent. The Total Diet Study estimates the concentrations of more than 15 trace metals (both essential and non-essential) in foods commonly consumed by Canadians.

Estimating quantities of aluminum ingested by an individual is complicated by the fact that foods are composite materials, and the components have very different aluminum concentrations. In the Total Diet studies, foods bought in grocery stores are prepared to reflect the Canadian diet; hence raw meat is cooked, and vegetables are peeled, trimmed or otherwise cleaned for serving, if not cooked. Processed foods or mixes are prepared as directed.

While the Total Diet Study provides data on total aluminum concentrations in foods, it does not allow estimation of the proportion of naturally-occurring aluminum versus the proportion of added aluminum salts. Some qualitative information in this regard is, however, included below.

With respect to aluminum originating from the contact of food with packaging material, this source would be included in the total aluminum concentration measured in the food item in the Total Diet Study. Aluminum utensils, pots and pans are not used to prepare the food, and so this potential source is not reflected in the measured concentrations. Some information on this aspect from other studies is, however, included below.

[5] Estimate based on data pooled from the fourth and fifth Total Diet Studies.

Estimated exposure in this assessment was based on preliminary data from the first three years of the fifth Total Diet Study (2000–2002) conducted in Ottawa (2000), Saint John (2001) and Vancouver (2002) (Dabeka 2007).

Mean aluminum concentrations in Canadian foods

In Canada, some foods have naturally high total aluminum concentrations, including yeast, raisins, mollusks and shellfish as well as some spices and herbs, where concentrations greater than 400 mg/kg were found (e.g., black pepper and oregano) (Dabeka 1007). Although concentrations in some aromatic herbs and spices may be high, their overall contribution to the daily diet is very low as only small quantities are normally ingested.

Tea is frequently studied by researchers as the plant generally assimilates high concentrations of aluminum (Wu et al. 1997). The fifth Total Diet Study in Canada showed aluminum concentrations of about 4.3 mg/kg in infused tea. This can be compared to the concentrations in other beverages of 0.67 mg/kg in red wine, 0.51 mg/kg in beer and a much lower average concentration of 0.08 mg/kg in coffee (Dabeka 2007). For the Canadian data, all samples were analyzed as prepared for consumption (i.e., brewed tea and coffee).

In addition to natural aluminum in foods, aluminum-containing food additives are permitted for use as a colouring agent, firming agent, stabilizing agent, pH adjusting agent, anti-caking agent, dusting agent, emulsifier, and carrier. Specific maximum levels of use prescribed in the Canadian Food and Drugs Regulations range from 0.036% (or 360 mg/kg) for aluminum sulphate in some egg products to 3.5% (or 35,000 mg/kg) for sodium aluminum phosphate in creamed and processed cheese products (Health Canada 2004).

Table 2.5 summarizes mean total aluminum concentrations found in various food groups in Canada based on the fifth Total Diet Study performed between 2000 and 2002. Certain food groups include diverse items, such that aluminum concentrations may vary considerably within a food group. More detailed information on the concentrations in specific items is presented below.

Cereal products are generally the primary source of dietary exposure to aluminum, followed by sugar-containing foods and dairy products. Other food categories account for less than 10% of the total aluminum dietary exposure. The mean total aluminum concentration in cereal products is a result of higher levels found in retail (ready-to-eat or mix) cakes, pancakes, muffins, Danish pastries, donuts, and cookies (concentrations ranging between 11 and 250 mg/kg). Such levels likely result from the direct addition of aluminum-based food additives, or from the use of baking powder in which aluminum-base food additves are also permitted (baking powder that is purchased in stores and used in home-cooking does not generally contain added aluminum salts.). Lower levels of aluminum are found in pasta, rice, bread, and cooked wheat, oatmeal and corn-based cereals, which are also included in the cereal products category.

Similarly, the mean aluminum concentration in the “Foods, primarily sugar” category is attributed to the level of aluminum found in chewing gum. Most food items included in that

particular category such as candy, gelatine desserts, honey, jams, pudding, and syrup, contain very low levels of aluminum.

Table 2.5 Mean total aluminum concentrations in various food groups based on the fifth Canadian Total Diet Study (2000–2002)

Food groups	Mean total aluminum concentration (mg/kg)
Dairy products	0.45
Fats	0.38
Fruits and fruit products	1.35
Vegetables	1.21
Cereal products*	28.8
Meat and poultry	1.42
Fish	2.16
Eggs	0.17
Foods, primarily sugar*	9.36
Mixed dishes and soups	0.49
Nuts and seeds	2.65
Soft drinks and alcohol	1.13

* see text for details on specific food items in this category

Total Diet Studies in Canada have also examined various fast food products, where mean aluminum concentrations exceeding 1 mg/kg were found in french fries and pizza, and up to approximately 50 mg/kg in chicken burger (Dabeka 2007).

Two of the three salts specifically named on the PSL (chloride and nitrate) are not used as food additives. Aluminum sulphate (including its potassium and sodium salts) may be used as a food additive, but other aluminum-containing additives (basic and acidic sodium aluminum phosphate, sodium aluminosilicate) are much more widely used[6]. This was confirmed through recent information gathered by Health Canada's Food Directorate from those members of the food industry who manufacture products in which aluminum-based food additives are permitted. This information indicates that aluminum sulphate (and its salts) are used as food additives in a limited number of food items, such as muffins, pizza, tortilla, burritos, egg products and some dry bakery mixes, and in quantities less than 0.5% of the final product weight.

Mean aluminum concentrations in Canadian infant formulas and in breast milk

Health Canada regularly tests infant formulas for metal concentrations as well as the water added to certain formulas as a point of comparison. Available data from the most recent

[6] Refer to www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/legislation/e_c-tables.pdf for food-additive uses.

Canada Total Diet Study as well as information from studies conducted by the Health Products and Food Branch are evaluated to estimate aluminum levels in bovine protein and soy-based infant formulas.

According to the fifth Canadian Total Diet Study conducted in 2000–2002, aluminum concentrations of 0.20 and 0.79 mg/kg were measured in the bovine protein and soy-based infant formulas, respectively. These concentrations were measured in the reconstituted infant formulas prepared for consumption.

Aluminum concentrations in several types of bovine protein and soy-based infant formulas were also measured in another Canadian study undertaken between 1999 and 2001 (Health Canada 2003). The mean concentrations in bovine protein formulas were about 0.13 mg/kg in liquid concentrates, 0.18 mg/kg in powdered formula to which a specified quantity of water was added and approximately 0.40 mg/kg in ready-to-use concentrates with iron added. Soy-based infant formulas had mean aluminum concentrations of approximately 0.73 mg/kg in the case of both ready-to-use concentrates and powdered formulas. Again, these concentrations were all measured in the reconstituted infant formulas prepared for consumption.

Two studies were undertaken in Canada to measure levels of aluminum in breast milk. They indicated that mean concentrations of aluminum in breast milk were of the same order of magnitude as elsewhere in the world. In one study in Quebec, which involved only five women, a mean concentration of aluminum in breast milk of 0.34 mg/kg was measured (Bergerioux and Boisvert 1979). In a second study, a median aluminum concentration of 0.014 mg/kg in 12 Albertan women was measured (Koo et al. 1988). Thus, the average concentration of aluminum in breast milk is considered to be approximately 0.11 mg/kg.[7]

Migration of aluminum from materials in contact with food

Aluminum concentrations in food generally increase when there is direct contact with aluminum packaging material or aluminum utensils, pots and pans, especially when food is cooked. Researchers have demonstrated that the migration of aluminum to food could depend on pH, container type, cooking time, purity of the aluminum used in the coating of utensils or aluminum pots, or salt addition to boiling water (Muller et al. 1993; Abercrombie and Fowler 1997; Gramiccioni et al. 1996; Gourrier-Fréry and Fréry 2004; Pennington 1988; InVS-Afssa-Afssaps 2003). For example, aluminum concentrations in coffee, soft drinks and beer increased from 0.02 mg/L to more than 0.25 mg/L when an aluminum percolator was used to brew coffee, or when soft drinks and beer were kept in aluminum cans for more than six months. A level up to 0.87 mg/L in drinks was also observed after 12 months of storage in cans (Muller et al. 1993; Abercrombie and Fowler 1997). Concentrations of up to 35 mg/L

[7] Weighted mean from the two Canadian studies (Bergerioux and Boisvert 1979; Koo et al. 1988). Human milk density = 1,030 g/L (Health Canada 1998a).

were found in acidified fruit juices after boiling in an aluminum pot (Liukkonen-Lilja and Piepponen 1992).

With respect to the uses of the three salts—aluminum chloride, aluminum nitrate and aluminum sulphate—in food packaging, aluminum sulphate is used as a component in metalized films and aluminum chloride is used as a component in a wax product that is applied as a coating on plastic films. While both of these products may be used in food packaging, the estimated amount of aluminum migrating from these films into the food would be negligible (Health Canada 2008b).

2.3.2.7 Consumer products

2.3.2.7.1 Prescription and Non-prescription drugs

The major pharmaceutical uses of aluminum are: as an antacid and as phosphate binder for patients with chronic kidney failure (aluminum hydroxide); as a component of the prescription antiulcer medication, sucralfate (sucrose sulfate-aluminum complex), as a component in some vaccines and injections (e.g., alum precipitated allergen extracts, MMR vaccine) (see section 2.3.2.8), as a hemostatic agent to control bleeding from minor cuts (aluminum potassium sulfate (alum), aluminum chloride or aluminum sulfate), as a component in hydrated magnesium aluminum silicate in the antidiarrheal, attapulgite, and as astringents (there are numerous aluminum derivatives in antiperspirants and in some deodorants). Aluminum containing antacids, represent, by far, the largest potential exposure to aluminum in individuals consuming these drug products on a regular, prolonged, basis.

Concentrations of aluminum compounds in over-the-counter products sold in Canada were obtained from the Health Canada Drug Product Database[8]. The Drug Product Database contains brand name, Drug Identification Number (DIN), ingredient and other information for approximately 23,000 drugs approved for use in Canada. Based on the concentrations of specific aluminum compounds, the elemental aluminum contents of orally administered over-the-counter products marketed in Canada are estimated to be 8,700 to 60,000 mg/kg product for antacids (heartburn medication), 30,000 to 50,000 mg/kg product for dental agents, and 3,500 mg/kg product for attapulgite.[9]

2.3.2.7.2 Cosmetics

Compounds such as aluminum chlorohydrate, ammonium aluminum sulphate, aluminum hydroxide, aluminum starch octenylsuccinate, aluminum-based dyes and aluminum silicate are used in deodorants, antiwrinkle preparations, toothpastes, eye and face makeup,

[8] Note that aluminum containing antacids are now classified as Natural Health Products (NHPs) in Canada. Aluminum-based antiperspirant preparations intended for the reduction of normal underarm perspiration are classified as cosmetics. Antiperspirants indicated for hyperhydrosis, or otherwise providing a more permanent effect than the aforementioned, are classified as NHPs. For more information please refer to the document at http://www.hc-sc.gc.ca/cps-spc/pubs/indust/cosmet-antiperspir-sudorif/index-eng.php

[9] www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php

shampoo, lipstick, moisturizers and other cosmetic products sold in Canada. Data on concentrations of aluminum compounds in these products are available through Health Canada's Cosmetic Notification System, a mandatory system under which manufacturers must submit information including composition data on cosmetics prior to first sale in Canada.

Table 2.6 presents reported ranges of aluminum concentrations that may be contained in a wide variety of cosmetic products sold in Canada. However, it should be noted that the data on concentrations are available with respect to reporting categories (< 0.1%, 0.1% to 0.3%, 0.3% to 1.0%, 1% to 3%, 3% to 10%, 10% to 30% and 30% to 100%). Thus the maximum concentration represents an upper limit of a reporting category, and is therefore very likely an overestimate, by a factor of up to 3.3, of the actual maximum concentration in the product category.

Table 2.6 Range of total aluminum concentrations in various categories of cosmetic products sold in Canada

Product Category	**Range of total aluminum concentration (mg/kg)***	**Product Category**	**Range of total aluminum concentration (mg/kg)**
Hair dye	442–300,000	Lipstick	44–300,000
Antiwrinkle preparation	171–333,000	Manicure preparation	44–300,000
Barrier cream	78–10,377	Baby Product	78–2,349
Dentifrice	1,588–52,930	Skin cleaner	57–529,300
Deodorant and antiperspirant	171–529,300	Skin moisturizer	42–158,790
Eye makeup	42–NA**	Tanning Preparation	5,293–15,879
Face makeup	44–NA**	Bath Product	346–10,000
Fragrance	206–30,000	Shaving Preparation	57–157,700
Hair conditioner	78–15,879	Hair Shampoo	309–1,588

* Note that the maximum concentration corresponds to an upper limit for a reporting category (see text) and may thereby overestimate the maximum concentration by up to a factor of 3.3)

** Maximum upper bound not available, as the upper limit of reporting category is 100%

2.3.2.8 Vaccines

Most of the vaccines authorized in Canada contain an aluminum salt adjuvant, according to the systematic vaccination schedule used for infants, young children, adolescents and adults (Canada Public Health Agency 2006). Various types of vaccine adjuvants are used by pharmaceutical companies, such as aluminum hydroxide, aluminum phosphate, aluminum sulphate and aluminum potassium sulphate. The quantity of aluminum ranges between 125 µg and 1,000 µg (aluminum hydroxide) per dose, depending on the vaccine. There is no standard or recommendation available in Canada with respect to the maximum quantity of aluminum or aluminum compound that may be used as an adjuvant in vaccines.

2.3.3 Toxicokinetics: human and experimental animals

An overview of the toxicokinetic processes of aluminum was carried out with the goal of highlighting the various factors influencing its pathway from the environment to target organs. Each toxicokinetic process is described below (absorption, distribution and elimination). Aluminum does not undergo phase I and II biotransformation reactions, occurring only in the +3 oxidation state. The metabolism of aluminum is therefore described in relation to its speciation, in the context of the distribution and elimination processes.

2.3.3.1 Absorption

Even at moderately elevated levels in the environment, exposure of aluminum leads to only small increases of aluminum in human tissues due to its low bioavailability through all routes of exposure. Bioavailability refers to the fraction of the total amount of the substance ingested, inhaled or in contact with the skin that reaches the systemic circulation. In this assessment, emphasis is placed on oral bioavailability, as the estimated daily intake (EDI) of the Canadian population shows that ingestion is the major route of exposure (see section 3.2.1); the bioavailability of aluminum with respect to other exposure routes (inhalation and dermal) is also reviewed. Bioavailability estimates for all exposure routes have been summarized in Table 2.7.

2.3.3.1.1 Oral absorption

The interpretation of aluminum oral bioavailability estimates requires the understanding of: (a) the methods used to calculate oral bioavailability, and (b) the physiological and biochemical factors that influence oral absorption. The ingested matrix to which aluminum is bound likely influences its potential absorption, therefore, the oral bioavailabilities of aluminum from drinking water, food and soil are distinguished.

Methods to calculate oral bioavailability

The methods to calculate the oral bioavailability in experimental studies are: (a) mass balance based on intake, and fecal and urinary excretion; (b) comparison of intake with urinary excretion; (c) concentration in a single blood sample and a calculated volume of distribution; (d) aluminum concentration in tissue; and (e) comparison of areas under the plasma concentration-time curve after oral and intravenous administration (Yokel and McNamara 2000). The most common method is comparison of intake with urinary excretion. This method is the simplest and least invasive, and is relatively reliable provided that the collection period is long enough to measure nearly all the aluminum excreted in the urine.

Prior to 1990, aluminum analyses were based on the quantification of the common isotope ^{27}Al ($\approx$ 100% of the natural isotopes). As ^{27}Al in the environment is ubiquitous, contamination during sampling and analysis may easily occur, leading to overestimation of the tissue concentrations, particularly when the administered amounts of aluminum are near the baseline exposure. The relative contribution from endogenous ^{27}Al is minimized by administering doses that are much higher than the levels encountered in the environment. However, oral absorption may depend on dose. Thus, this approach increases the uncertainty in the estimation of bioavailability of environmental concentrations of aluminum. On this point, the observed relationship between dose and bioavailability is inconsistent: increased

dose of aluminum decreased its bioavailability in the experimental studies of Greger and Baier (1983), Weberg and Berstad (1986), and Cunat et al. (2000) while opposite results were observed in other animal studies (Yokel and McNamara 1985; Ittel et al. 1993).

In recent years accelerator mass spectrometry (AMS) has been used to quantify the isotope ^{26}Al, administered as a tracer (Priest 2004). This analytical technique has allowed researchers to more accurately measure bioavailability of aluminum at levels comparable to the levels to which the general population is actually exposed, since it is possible to distinguish the aluminum in the administered dose (^{26}Al) from the aluminum already in the body (^{27}Al). However the cost and small number of facilities limit the sample analyses, which can result in the diminishing of the precision of the estimation and the information concerning the intra-individual variability (Yokel and McNamara 2000).

Factors influencing oral absorption

The principal mechanism of absorption of ingested aluminum seems to be a passive diffusion through the paracellular pathway (Zhou and Yokel 2005). This diffusion occurs predominantly in the small intestine (duodenum and jejunum) and, to a lesser extent, through the gastric mucosa in stomach (Powell and Thompson 1993; Walton et al. 1994). In addition to passive diffusion, Cunat et al. (2000) suggested that absorption of aluminum may occur by a transcellular and saturable route, which may explain the possible dependency of absorption on the dose level.

The rate of uptake, and consequently the cumulative absorption of aluminum, has been shown to vary depending on physiological and chemical factors. Krewski et al. (2007) summarized factors based on findings in both human and animal studies, including:

- Solubility: absorption is greater with more soluble aluminum compounds;
- Gastric pH: absorption is greater at pH 4 compared to pH 7, probably due to the generation of more soluble aluminum compounds;
- Carboxylic acids: increased absorption in the presence of carboxylic acids, particularly citrate that is naturally present in many foods and fruit juices;
- Silicon compounds: decreased absorption in the presence of silicon-containing compounds in the dietary intake, due to a possible formation of hydroxyaluminosilicate.

Among the factors cited above, particular attention has been given to the significant impact of citrate during the ingestion of aluminum. Oral bioavailability has been found to increase by a factor of 5 to 150 when aluminum is ingested with citrate solution, as verified with studies employing the same aluminum complex and under the same experimental conditions (Weberg and Berstad 1986; Yokel and McNamara 1988; Froment et al. 1989; Priest et al. 1996; Drueke et al. 1997; Schönholzer et al. 1997). Citrate probably facilitates the absorption by opening the tight junction between intestinal cells (Froment et al. 1989; Zhou and Yokel 2005). Zhou et al. (2008) recently explored the influence of citrate in drinking water at a similar molar concentration to aluminum. The researchers did not observe a

significant enhancement of aluminum absorption for an Al:citrate molar ratio of 1:1, and suggested that aluminum absorption may depend on citrate dose.

The principal biochemical explanation for how the factors listed above influence absorption is the nature of the ligand to which the ion Al^{3+} is associated in the gastrointestinal fluid. In vitro studies using Caco-2 cells derived from the human lower intestine show differences between ligands in the uptake rate of aluminum; aluminum citrate and aluminum nitrilotriacetate were absorbed more rapidly than aluminum lactate (Alvarez-Hernandez et al. 1994) and the uptake rate of aluminum fluoride was higher than that of, in decreasing order, Al^{3+}, aluminum maltolate, aluminum citrate and aluminum hydroxide (Zhou and Yokel 2005). Results from in vivo studies provided evidence for significant differences in the oral bioavailability calculated for different ingested aluminum complexes (Yokel and McNamara 1988; Froment et al. 1989). Cunat et al. (2000) concluded that the organic ligands enhance aluminum absorption, in comparison to the inorganic ligands (citrate > tartrate, gluconate, lactate > glutamate, chloride, sulphate, nitrate), based on the results of a study in which rat intestines were locally perfused with aluminum.

The pH of the exposure media may play an important role in the absorption of aluminum, as it affects aluminum speciation. In aluminum sulphate-treated water with low pH, the aluminum sulphate and Al^{3+} (very soluble) are the predominant forms while, when increasing the pH from 6.3 to 7.8, the predominant complex is aluminum hydroxide (likely insoluble). At pH above 7.8, the solubility in water increased due to the presence of the negative ions of aluminum hydroxyl (Walton et al. 1994). As mentioned in section 2.3.2.2.2, while treatment with aluminum sulphate may reduce the total aluminum concentration in finished water as compared to the untreated water source, through the removal of suspended solids containing aluminum, there is evidence that treatment with aluminum salts also increases the concentration of low-molecular-weight, dissolved aluminum species (Health Canada 1998b).

The low pH of the gastric fluid creates a high potential for transformation of the ingested aluminum complex. This led Reiber et al. (1995) to argue that the aluminum in drinking water would not be more readily assimilated than other forms of aluminum, and that regardless of the form in which the aluminum is consumed, a substantial portion of it will likely be solubilized to monomolecular aluminum in the stomach. Other researchers, however, consider this to be an oversimplication, in light of the observed differences in the oral absorption of different aluminum compounds (Krewski et al. 2007).

Concurrent absorption of aluminum with other dietary nutrients has been shown to influence the intestinal absorption of this metal. For example, the presence of vitamin D likely favours the absorption of aluminum (Adler and Berlyne 1985; Ittel et al. 1988; Long et al. 1991; Long et al. 1994) and the consumption of folic acid supplementation is expected to diminish aluminum absorption and/or its accumulation in various organs (bone, kidney and brain) by a possible formation of folate-Al complex (Baydar et al. 2005). Domingo et al. (1993) investigated the effects of various dietary constituents, such as lactic, malic and succinic acids, on the levels of absorption and distribution of aluminum in drinking water and in the diet of mice, where they observed an enhanced absorption with these concurrent ingestions.

A few studies have been conducted to examine whether food composition or the presence of food in the stomach affect oral aluminum bioavailability, and the results have been mixed. The nature of the contents in the stomach influenced the absorption of aluminum in the study of Walton et al. (1994) in which adult Wistar rats were exposed to water treated with aluminum sulphate along with various beverages and foods. The aluminum concentrations in serum increased when the aluminum sulphate treated drinking water was taken with orange juice; the same phenomenon was observed, but to a lesser extent, with coffee. The authors note that the low levels of aluminum in these two beverages would not have contributed to this increase in aluminum levels. In comparison, when aluminum sulphate treated water was given with beer, tea or cola (beverages that may contain appreciable levels of aluminum) the serum concentration did not markedly rise. Meat and carbohydrate/cereal products decreased aluminum absorption. Drüeke et al. (1997) performed a study in rats using ^{26}Al to examine the effect of silicon contained in drinking water as well as solid food, on the absorption of aluminum. In their study, high Si concentrations in the drinking water failed to depress the ^{26}Al fraction absorbed, as estimated on the basis of skeletal accumulation and urinary excretion. In addition, absorption of ^{26}Al was approximately 15 times higher in the fasted state than in the non-fasted state. As part of a study conducted in rats with ^{26}Al, Yokel et al. (2001a) tested the hypothesis that the stomach contents affect aluminum absorption. According to the authors, although stomach contents delayed aluminum absorption, it did not significantly alter the extent of ^{26}Al absorption.

Estimation of the oral bioavailability of aluminum in drinking water

Experimental data for oral bioavailability of aluminum from drinking water, obtained in studies conducted in humans and animals, and based on varying calculation and quantification methods, were evaluated.

The compilation of central values (mean or median) of the results of different studies in humans results in a range of 0.010% to 0.52% for oral bioavailability of aluminum in drinking water, based on experiments involving more than one volunteer. The lower value is the mean value obtained from the data of two volunteers exposed to ^{26}Al-hydroxide in Priest et al. (1998). This experimental study observed the higher value of 0.52% as well when these two volunteers were exposed to ^{26}Al-citrate. In a much larger study with 29 subjects consuming an aluminum-controlled diet, the oral bioavailability from aluminum sulphate-treated municipal drinking water was estimated at 0.36% to 0.39% (Stauber et al. 1999).

As for the central values for the oral bioavailability for experimental animals, a range of 0.04% to 5.1% is reported in experimental studies with the isotope ^{26}Al, whereas the range based on ^{27}Al is 0.01% to 4.56%. The maximum central value of 5.1% for the animal experiments using ^{26}Al was obtained following ingestion of a concentrated solution of citrate (Schönholzer et al. 1997). The second highest value is 0.97%, based on the exposure to aluminum chloride (Zafar et al. 1997). The maximum central value of 4.56% for ^{27}Al was obtained for aluminum citrate ingested by rats with renal failure (Yokel and McNamara 1988). If only healthy animals had been considered, the maximum value would have been 2.18% for ^{27}Al-citrate.

Krewski et al. (2007) proposed a range for the oral bioavailability of aluminum in drinking water of 0.05% to 0.4% for rats and rabbits, and 0.1% to 0.5% for humans, with a most likely value of 0.3%. The approximate correspondence between the ranges and the most likely estimates in humans and animals for bioavailability from drinking water suggests that there is little interspecies difference in this respect.

Estimation of the oral bioavailability of aluminum in food

In spite of the important contribution of food in the total exposure to aluminum, the database for oral bioavailability of aluminum in food is limited. In an early investigation into the potential for the absorption of aluminum accumulated in food, Jones (1938) demonstrated that a large percentage of aluminum in bread made with aluminum-based baking powder was soluble in the gastric juice of dogs. Several decades later, Yokel and Florence (2006) confirmed that some aluminum from biscuits made with baking powder containing acidic ^{26}Al-sodium aluminum phosphate (SALP) reaches the systemic circulation. In this study, about 0.12% of the ingested aluminum crossed the gastrointestinal tract of exposed rats. Using the same experimental method,[10] Yokel et al. (2008) estimated oral bioavailabilities of ~ 0.1% and ~ 0.3% for basic ^{26}Al-SALP incorporated into cheese at concentrations of 1.5% and 3%, respectively.

The oral bioaccessibility[11] of aluminum encountered in different foods was measured by Lopez et al. (2002) and Owen et al. (1994). It is not possible, however, to directly compare their results, since their methodologies differed. Moreover, the bioaccessibility estimates, ranging from 0.3% to 0.9% by Owen et al. (1994) and 0.85 to 2.15% by Lopez et al (2002), cannot be directly used to estimate the oral bioavailability of aluminum, as the in vitro-in vivo relationship has not been established (Ruby et al. 1999). Nonetheless these bioaccessibility studies do provide evidence that oral bioavailability is low and may change according to the nature of consumed foods. For example, the aluminum in bread, jam and tea appeared to be about 2.7 times more soluble than the aluminum in sponge cake (Owen et al. 1994). It is expected that the actual oral bioavailability of aluminum in food is lower than these bioaccessibility values, as solubility in the intestinal tract would not be the only factor limiting absorption.

The oral bioavailability of aluminum in food has also been estimated based on the comparison of aluminum intake in the general population with the urinary excretion and/or the body burden of aluminum (Ganrot 1986; Priest 1993, 2004; Powell and Thompson 1993; Nieboer et al. 1995). These estimates range from 0.1% to 0.8%. Note that the oral bioavailability estimate of 0.12% of Yokel (2006) for rats fed aluminum-containing biscuits

[10] Bioavailability is determined by comparing the areas under the serum concentration x time curve (AUC) for the ^{26}Al given orally and the ^{27}Al administered intravenously (Yokel et al. 2008).

[11] The oral bioaccessibility is the soluble fraction of the substance in the gastrointestinal system that is available for absorption (Ruby et al. 1999).

falls in this range, as does the estimate of 0.53% by Stauber et al. (1999), based on a controlled diet in humans.

Bioavailability of aluminum in antacids (aluminum hydroxide) has been estimated in three studies in humans, measured alone or in combination with citrate, orange juice, bicarbonate, or calcium acetate (Mauro et al. 2001; Haram et al. 1987; Weberg and Berstad 1986). These measured bioavailabilities, ranging from 0.001% to 0.2% were generally comparable to the bioavailabilities measured in food.

The limited data concerning the oral bioavailability of aluminum from foods do not allow for the determination, with good predictive value, of the potential absorption of aluminum in food. For the purpose of comparison with other media (Table 2.7), the interval of 0.1% to 0.8% is retained, with a most likely range of 0.1% to 0.3%, based on the recent work of Yokel and Florence (2006) and Yokel et al. (2008).

Estimation of the oral bioavailability of aluminum in soils

Another factor of importance in the human exposure assessment for aluminum is the oral bioavailability of aluminum in ingested soil, as soil ingestion is a significant exposure pathway for the toddler group (see section 3.2.1). No bioavailability data on soil were identified. Limited data, however, were found for the bioaccessibility of aluminum in soil, which, as noted above, is an in vitro measure of the soluble fraction of the substance available for absorption.

Shock et al. (2007) estimated the bioaccessibility of aluminum in different tundra soil samples contaminated by mining waste dust, by simulating gastric fluid in an in vitro experiment. The estimated values varied from 0.31% to 4.0%, according to the grain size and to the solid:fluid ratios used in the experiment. As expected, aluminum in the soil with small sized grains size had the greatest absorption.

As is the case for the bioaccessibility data of aluminum in food, these bioaccessibility estimates for aluminum in soil need to be tied to the *in vivo* bioavailability estimates from appropriate *in vivo* models (Ruby et al. 1999). Even if the experimental protocols used to measure food and soil aluminum bioaccessibility differed slightly, the data of Shock et al. (2007) suggest that the bioaccessibility of aluminum in soil is similar to that in food. In the absence of more relevant data, the range for the oral bioavailability of aluminum in soil is therefore assumed to be similar or less than that of food. The relative oral bioavailability of aluminum in soil is considered to be a major source of uncertainty for this exposure pathway; however, bioavailability from soil is expected to be low.

2.3.3.1.2 Dermal absorption

Utilization of antiperspirant with aluminum would contribute to the body burden if aluminum passes through the skin barrier. There is some evidence from case studies, described below, that small amounts of aluminum do reach the systemic circulation. However, to date, no data for dermal bioavailability are available from controlled studies of more than one or two individuals.

In the study of Flarend et al. (2001), ^{26}Al-chlorohydrate (aluminum complex in antiperspirant) was applied to a single underarm of one man and one woman. The cumulative urinary excretion after 43 days following the application accounted for 0.0082% (male) and for 0.016% (female) of the applied dose. After correcting this fraction for the aluminum not excreted in urine (15% of the absorbed dose), this application was estimated to result in a dermal bioavailability of about 0.012%. On the basis of these data, the authors estimated that the amount of aluminum absorbed from regular use would be 0.25 μg/d.

Guillard et al. (2004) reported on one clinical case in which a woman who used an antiperspirant cream with aluminum chlorohydrate over four years showed elevated levels of aluminum in plasma and urine (10.47 μg/dL in plasma[12]). When the woman discontinued use, concentrations in her urine and plasma dropped to reported normal values after the third and eighth months, respectively.

2.3.3.1.3 Inhalation absorption

The ambient air of multiple occupational environments, such as the aluminum production industry and welders' factory (Priest 2004), may have high levels of aluminum. The higher urinary excretion of aluminum in exposed workers, compared to the general population, demonstrates that some inhaled aluminum can reach the systemic circulation (Sjogren et al. 1985; Sjogren et al. 1988; Pierre et al. 1995). This absorption depends on the form of aluminum in the ambient air (adsorbed to PM, vapour condensation fumes and flakes) and, in the case of particulate matter, also depends on the distribution of the sizes of the aerodynamic diameter of PM ($PM_{2.5}$ versus PM_{10}).

Priest (2004) estimated a deposited pulmonary fraction of 1.9% in a study of two volunteers who inhaled ^{26}Al-oxide adsorbed to particles with a mass median aerodynamic diameter (MMAD) of 1.2 μm. The last value is supported by animal studies showing a deposition of fly ash of aluminum into the lungs from 2% to 12% (Krewski et al. 2007). As well, Yokel and McNamara (2001) have proposed an absorption fraction of about 1.5% to 2%, on the basis of the relationship between the urinary excretion of aluminum-exposed workers and the concentrations of airborne soluble aluminum measured in their environment.

An investigation in New Zealand rabbits exposed via the nasal-olfactory pathway (sponge soaked in aluminum solutions inserted into nasal recess for four weeks) provided evidence that inhaled aluminum in the olfactory tract can cross the nasal epithelium to reach the brain directly through axonal transport (Perl and Good 1987). While an analytical protocol for quantifying the amount of aluminum transported along this pathway under environmental exposure conditions has been described (Divine et al. 1999), further experimental work is required to document transport of aluminum via this pathway to the olfactory bulb, and subsequently to other regions of the brain.

[12] Guillard et al. (2004) indicated that the normal range of aluminum in blood plasma would be < 1.0 μg/dL.

2.3.3.1.4 Parenteral administration

Intravenous injection of aluminum-containing products (e.g., intravenous feeding solutions) results in complete availability of the aluminum to the systemic circulation (Yokel and McNamara 2001; Priest 2004). In the case of intramuscular injection of aluminum species (e.g., via vaccination), potentially all of the aluminum injected may be absorbed into the bloodstream. However, the uptake rate from the muscle to blood circulation differs according to the aluminum complex. Evidence of this was provided in an experimental study, in which rabbits were injected with ^{26}Al-hydroxide and ^{26}Al-phosphate, two common vaccine adjuvants, at standard dose levels. After 28 days, 17 % of the aluminum hydroxide and 51% of the aluminum phosphate were absorbed (Flarend et al. 1997). The authors estimate that this dose, when administered in humans, would represent an increase of 0.4 μg/dL in plasma (see section 2.3.3.2 on distribution, for estimates of normal plasma concentrations).

2.3.3.1.5 Summary of estimates of aluminum bioavailability

The estimates of aluminum bioavailability presented for the different exposure routes in sections 2.3.3.1.1 to 2.3.3.1.4 are summarized in Table 2.7. The information available to generate these estimates varies considerably depending on the exposure route, and should be considered in any application of these estimates in risk assessment.

Table 2.7 Ranges of estimated aluminum bioavailability for various routes of exposure in humans and/or animals

Route of exposure		Bioavailability (%)
Oral	Drinking water (a)	0.0086 to 0.65 (H) 0.01 to 5.1 (A) Proposed likely estimate: 0.3
	Food (b)	0.10 to 0.80 (H) 0.02 to 0.3 (A) Proposed likely range: 0.1 to 0.3
	Antacids (c)	0.001 to 0.20 (H)
	Soil ingestion (d)	Equal or less than food (default assumption)
Dermal (e)		0.012 (H)
Pulmonary (f)		1.5 to 2.0 (H)
Parenteral (g)		100.0

(H) = data from experimental studies conducted in humans
(A) = data from experimental studies conducted in animals

(a) Ranges based on a compilation of the central values of estimates of the oral bioavailability of aluminum from drinking water, obtained in numerous experimental studies conducted in humans and animals. Proposed likely estimate based on experimental work of Stauber et al. (1999) in humans and the critical review of experimental animal data in Krewski et al. (2007).

(b) Based on comparisons of estimates of aluminum intake and urinary excretion in humans and experimental animal data. The estimate of bioavailablility of aluminum in food is associated with greater uncertainty than

that of drinking water, because of the limitations of the database. Proposed likely range based on Yokel and Florence (2006) and Yokel et al. (2008).
(c) Based on human data reported in three studies for the bioavailability of aluminum in antacids alone or in combination with citrate, orange juice, bicarbonate, or calcium acetate.
(d) Assumed to be similar to that in food as a default value in the absence of bioavailability data from soil ingestion; considered to be of low predictive value.
(e) Based on experimental results reported in one study following a dermal exposure in two individuals.
(f) Proposed absorption fraction by Yokel and McNamara (2001) on the basis of the results from two studies in aluminum-exposed workers.
(g) Includes both intravenous (IV) and intramuscular (IM) injection.

2.3.3.1.6 Integrating bioavailability in human health risk assessment

As discussed in previous sections, the generally low oral absorption of aluminum (< 1%) is well recognized. Nonetheless, there is considerable uncertainty associated with differences in oral bioavailability, in relation to:

- the bioavailability of aluminum in different environmental media (soil, different types of food, drinking water, air, dermal application);
- the bioavailability of aluminum in humans versus experimental animal species;
- the influence of dose and dosing regime (bolus dose versus repeated exposure via drinking water or food).

In the characterization of human health risks, relative bioavailability rather than absolute bioavailability is the parameter of greatest interest. Relative bioavailability for a substance may, for example, refer to the ratio of absorbed fractions via two different exposure pathways, or it may refer to the ratio of total absorption by humans (all pathways considered) as compared to the total absorption in experimental animals in the critical study or studies.

Relative bioavailability can be established by directly measuring two absorption fractions and taking the ratio of the two, or potentially indirectly through the measurement of in vitro bioaccessibility and then by comparing in vitro bioaccessibilities (e.g., the fraction of a substance that is extracted through a weak acid solution simulating gastric fluid). In the case of aluminum, bioaccessibility would considerably overestimate bioavailability, as the available evidence indicates that only a fraction of the species dissolved in the stomach is eventually absorbed. However, to the extent that bioaccessibility is proportional to bioavailability, relative bioaccessibility will be approximately equivalent to relative bioavailability.

In the previous sections, experimental data were reviewed with respect to both bioavailability and bioaccessibility of aluminum salts in various media, in humans, and experimental animals. The discussion that follows reconsiders these data from the perspective of relative bioavailability.

The most comprehensive data concerns the bioavailability of aluminum dissolved in drinking water, as measured in both human and animal studies. In humans, measurements of oral absorption of aluminum (citrate, chloride, hydroxide or lactate complexes) generally

varies between 0.01% and 0.65%, while in experimental animals the range of reported values is 0.01% to 5.1%. The ranges largely overlap and do not provide evidence for differences between humans and animals in the bioavailability of aluminum in drinking water. The proposed likely estimate for aluminum bioavailability in both humans and animals is 0.3% (see Table 2.7).

The data on bioavailability of aluminum in food are much more limited, both for humans and animals. Section 2.3.3.1.1 proposes a range of 0.1% to 0.8% for the bioavailability of aluminum salts in food (humans) and 0.02 to 0.3 in animals. These ranges have a high level of uncertainty because of the limited database, but do not provide evidence for differences between humans and animals in the bioavailability of aluminum in food.

The bioaccessibilities of aluminum in soil and food were also compared in section 2.3.3.1.1. These very limited data do not provide evidence for a difference in the amount of aluminum available for absorption of aluminum from these two media, and hence do provide a basis for concluding that there are differences in bioavailability between soil and food.

In comparing the bioavailability of aluminum in drinking water and food, in both animals and humans, the ranges of experimental values largely overlap, and the proposed likely value for drinking water is at the upper end of the proposed likely range for food. Thus the available data are insufficient for identifying a difference in bioavailability of aluminum in drinking water and food.

With regard to inhalation absorption of aluminum, there is again significant variability in the available data. These data do indicate that the bioavailability of aluminum from inhalation may be higher than from the oral route; however, since the concentrations of aluminum in ambient and indoor air are low, the absorption factor for the inhalation route would not significantly influence the evaluation of cumulative exposure from soil, air, drinking water, and food.

Although dermal absorption of aluminum salts is thought to be very low, the data is extremely limited (confined to two studies), each involving one or two individuals (see section 2.3.3.1.2). Therefore, no definitive conclusions can be drawn with respect to its relative bioavailability, although the information available suggests that it is lower than for other routes of exposure.

Consideration of bioavailability may considerably influence the conclusions of human health risk characterization if relative bioavailabilities for different salts, different exposure media and different species are greater than or less than one. In this assessment, however, the limited available data did not provide evidence for relative oral bioavailabilities significantly different from one, either with respect to comparisons of humans and experimental animals, or with respect to comparisons of water, food and soil. The bioavailability via inhalation, which is higher than oral bioavailability, would not significantly influence the estimated absorbed dose, because of the low estimated concentrations of aluminum in ambient and indoor air. Dermal exposure, which appears to be associated with a very low absorption, was considered only qualitatively in this assessment. For these reasons, the estimated values of bioavailability

for different media were not explicitly integrated into the estimation of population exposure or the characterization of relative contribution of the three salts to overall exposure.

2.3.3.2 Distribution

Once absorbed into the systemic circulation, much of Al^{3+} is readily associated at the binding sites of transferrin (Tf), the plasma protein for iron transport. Since, under normal conditions, Tf in blood is only one-third saturated with iron, binding sites for the absorbed aluminum are available (Harris et al. 1996). Consequently, the Al-Tf complex is the predominant aluminum species in plasma, accounting for approximately 91% of the total aluminum in plasma (7% to 8% of aluminum is associated with citrate and less than 1% with phosphate and hydroxide) (Martin 1996). As well, Day et al. (1994) reported that, one hour after the ingestion of ^{26}Al-citrate, 99% of the ^{26}Al in blood was measured in plasma of which 80% was bounded to Tf, 10% to albumin and 5% to proteins having low molecular weight; after 880 days, 86% of aluminum in blood was bounded to plasma proteins (mostly to Tf) and the rest was associated with erythrocytes.

The major physiological compartment of aluminum is the skeleton. Krewski et al. (2007) suggest that approximately 58%, 26%, 11%, 3%, 0.95%, 0.3%, 0.25% and 0.2% of the aluminum body burden would be in the bone, lung, muscle, liver, brain, heart, kidney and spleen, respectively. Aluminum measured in the lungs may reflect deposition of airborne particles. In addition, a significant amount of aluminum analyzed in skin may result from unabsorbed aluminum deposited on skin surface (Priest 2004).

The transport of aluminum into the body and its deposition into the tissues and organs have been shown to vary widely (Priest 2004). This variability, yielding different aluminum concentrations in tissues and organs, can be explained by some of the same factors influencing aluminum absorption. For example, the presence of citrate seems to enhance the distribution of aluminum into the tissue before being associated with Tf (Quartley et al. 1993; Maitani et al. 1994). According to Jouhanneau et al. (1997), the concomitant ingestion of citrate increases aluminum absorption, but does not appear to modify the relative distribution of ^{26}Al in bone, brain and liver in comparison with ingestion without citrate.

Experimental studies have reported volumes of distribution (V_d) for aluminum, describing its potential to be distributed in tissues and organs. Most of these studies suggested that the initial V_d is approximately the blood volume (Krewski et al. 2007). However, longer collection periods lead to higher V_d, indicating a possible dependency between elimination rate and blood concentrations of aluminum (Krewski et al. 2007) (see section 2.3.3.3). Calculating the oral bioavailability of aluminum using blood volume, instead of V_d, may consequently lead to an underestimation (see section 2.3.3.1).

As neurological and reproductive/developmental endpoints are of greatest concern with respect to the environmental exposures evaluated in this assessment (see section 3.2.3.2), particular attention is paid to the distribution processes leading to accumulation in the brain and in the foetus. As well, aluminum retention in bone was investigated, as it plays an important role in the kinetics of aluminum. The principal observations with regard to retention

in these tissues as well as measurements of plasma aluminum levels are briefly described below.

Plasma

In a review of blood aluminum concentrations for healthy individuals, plasma or serum measurements varying between 0.19 and 1.02 μg/dL in 11 studies were reported (Nieboer et al. 1995). However, according to the authors, potential problems of controlling contamination and analytical sensitivity influenced the estimates of earlier reports such that the true value more likely lies in the range of 0.11 to 0.32 μg/dL (0.04 to 0.12 μmol/L).Valkonen and Aitio (1997) reported a mean aluminum concentration of 0.16 μg/dL (0.06 μmol/L) in the serum of a healthy, non-exposed population (n = 44) who did not use antacid drugs. In another study, the mean level of aluminum in serum in 18 healthy subjects not using aluminum-containing medicines was 0.099 μg/dL (Razniewska and Trzcinka-Ochocka 2003). Liao et al. (2004) reported blood aluminum levels in workers from three optoelectronic companies in Taiwan, China. The median aluminum concentration measured was 0.36 μg/dL in the exposed workers (n = 103) and 0.32 μg/dL in the non-exposed office workers (n = 67). Higher levels of aluminum were found in aluminum welders, with mean plasma aluminum levels of 1.25 to 1.39 μg/dL (pre-shift) and 1.48 to 1.86 μg/dL plasma (post-shift) (Kiesswetter et al. 2007).

Some data on measured serum aluminum levels in animals exposed only through the normal laboratory diet were identified. Kohila et al. (2004), Johnson et al. (1992), Gonzalez-Munoz et al. (2008) and Kaneko et al. (2004) reported values ranging from approximately 0.15 to 0.66 μg/dL in different strains of rats and mice. Note that some variation in serum levels would be due to the high variability in aluminum concentration in different brands and lots of laboratory chow.

No studies were identified in which both animal and human serum levels were compared within a single study, using the same analytical methodology. The aluminum content of the standard laboratory animal diet is significantly higher than that of the typical human diet, however, so it would not be unexpected that serum aluminum concentrations observed in laboratory animals would be generally higher than reported levels in humans.

Bone

Bone exhibits more affinity to aluminum than does the brain; for example the aluminum concentrations in bone are about five-fold greater than those in the brain after repeated exposure in rats and rabbits (DuVal et al. 1986; Fiejka et al. 1996; Garbossa et al. 1998). However, the slower elimination of aluminum from the brain, as compared to bone, may be attributed in part to the bone-cell turnover and the lack of neuron turnover (Krewski et al. 2007).

In general, aluminum in bone is principally captured in the mineralization front and in the osteoid (Boyce et al. 1981; Cournot-Witmer et al. 1981; Ott et al. 1982; Schmidt et al. 1984). There are three probable mechanisms of aluminum deposition in bone that govern the elimination rate of aluminum in this matrix (Priest 2004). First, aluminum can be attached to the bone surface by heterionic exchange with calcium; this aluminum can be easily released to

the fluids close to the bone surface, and then bound to Tf. Second, aluminum can be incorporated into the structure of the developing hydroxyapatite crystal during the formation of the mineral lattice; this strongly binds the molecule to bone cells and there is little subsequent release of aluminum from the bone matrix. Third, aluminum can be complexed to organic components at the surface of bone; in this case, the migration of aluminum through its deposition at the mineralization front can occur, leading to a slow turnover.

Brain

The concentrations measured in the brains of exposed rats ranged from 0.0006% to 0.009% of aluminum administered dose per gram of brain, after intravenous or intraperitoneal injection (Krewski et al. 2007). It was suggested that 90% of the aluminum in brain is associated with citrate, 5% with hydroxide, 4% with Tf and 1% with phosphate (Yokel 2001). In humans, the aluminum accumulation is higher in the cerebral cortex and hippocampus than in other brain structures (Gupta et al. 2005).

There are two ways by which aluminum can reach the central nervous system, either through the blood-brain barrier or through the choroid plexus in the cerebrospinal fluid of the cerebral ventricles. Although there is some evidence that aluminum crosses the blood-brain barrier by Tf-receptor mediated endocytosis of the Al-Tf complexes (Roskams and Connor 1990), other mechanisms of uptake, independent of Tf, may be involved as well (Yokel and McNamara 1988; Allen et al. 1995; Radunovic et al. 1997), such as diffusion of the low molecular weight aluminum species or other carrier-mediated processes. In addition, aluminum may reach the brain through the nasal epithelium by axonal transport (Perl and Good 1987; Zatta et al. 1993), although the potential magnitude of this pathway has not been quantified. Axonal transport, however, would not be expected to contribute significantly to exposure in the general population due to the low concentration of aluminum in ambient air, outside of particular occupational settings (see section 2.3.2.1).

The transport of aluminum out of the brain seems to occur by its association with citrate (Yokel 2000). The ability to remove aluminum from the brain is low (Krewski et al. 2007). For instance, in a study in which ^{26}Al-Tf was administered intravenously in rats, Yokel et al. (2001b) reported that brain concentrations of aluminum did not significantly decrease 128 days after administration.

Placenta and foetus

Aluminum distributes to the placenta and foetus, as has been demonstrated by experimental studies in which aluminum was administered by different routes to rabbits, mice and guinea pigs during gestation (Yokel 1985; Cranmer et al. 1986; Golub et al. 1996b; Yumoto et al. 2000). Yumoto et al. (2000) estimated that approximately 0.2% of the subcutaneous injected dose of ^{26}Al-chloride was transferred to the foetus as well as to the placenta. In the study of Cranmer et al. (1986), fetal aluminum content was significantly increased following both intraperitoneal and oral administration, although the increase was greater with intraperitoneal dosing. No study investigating the level of aluminum in the human placenta was identified.

Milk

Aluminum is efficiently transferred from blood to milk in exposed lactating animals (Yokel and McNamara 1985; Muller et al. 1992; Yumoto et al. 2000) as well as in human lactating mothers (see section 2.3.2.5). According to the calculations of Findlow et al. (1990), almost all the aluminum in milk (human and bovine) should be associated with citrate, with approximately 88% as $Al(citrate)(OH)_2^{-2}$ and approximately 11% as $Al(citrate)(OH)^{-1}$.

2.3.3.3 Elimination

The principal organ of aluminum excretion is the kidney, accounting for more than 95% of the total excretion (Exley et al. 1996; Krewski et al. 2007). The urinary excretion is believed to occur by passive filtration through the glomerulus, instead of active secretion by the proximal tubules. This hypothesis is based on the results of animal studies demonstrating that when only the free fraction of aluminum was assumed to be removed from blood, the elimination rate of aluminum is approximately the same as the glomerular filtration rate (Henry et al. 1984; Yokel and McNamara 1985, 1988). If this hypothesis is true, then the factors influencing glomerular filtration rates (such as kidney disease, pregnancy and age) should also influence the rate of elimination of aluminum (Guyton 1991). Indeed, it has been observed that individuals with renal failure have lower capacity of elimination (Nieboer et al. 1995; Krewski et al. 2007).

A small portion of the absorbed aluminum appears to be eliminated through other excretion routes. The second most important route would likely be biliary excretion. Most of the experimental studies with animals have demonstrated that less than 1.5% of the total eliminated aluminum occurred by biliary excretion (Krewski et al. 2007). As well, sweat, saliva and seminal fluid can contribute, to a much lesser extent, to the elimination of aluminum from the body (Krewski et al. 2007).

The elimination rate of aluminum appears to be regulated by the presence of various aluminum complexes in the body's systemic circulation. aluminum citrate complexes are eliminated more easily than Al-Tf (Maitani et al. 1994), most likely because the lower molecular weight of the aluminum citrate complex would facilitate glomerular filtration. This may explain why the presence of citrate can enhance renal elimination (Van Ginkel et al. 1993; Cochran et al. 1994). Also, the concomitant presence of aluminum and silicon yields a filterable complex (probably the same observed in the gastrointestinal tract); this complex seems to favour renal excretion by limiting the renal reabsorption of aluminum (Bellia et al. 1996; Birchall et al. 1996). As well, fluoride is a natural element which contributes to the rapid elimination of aluminum (Chiba et al. 2002).

Some animal studies have shown lower clearances of aluminum from the body, and consequently higher elimination half-lives ($t_{½}$), after increasing the aluminum dosages (Höhr et al. 1989; Pai and Melethil 1989; Xu et al. 1991). This observation is probably explained by the fact that the fraction of ultrafilterable aluminum complexes decreased when the aluminum concentrations in blood increased (Xu et al. 1991; Yokel and McNamara 1988). Also, Greger and Radzanowski (1995) obtained a positive correlation between the $t_{½}$ of aluminum in tibia and kidneys and the age of exposed rats, indicating that the ability to remove aluminum may diminish with time.

Priest et al. (1995) and Talbot et al. (1995) investigated the elimination rates of aluminum in humans, on the basis of the time-profiles of aluminum in blood and urine of seven volunteers who had received intravenous injection of ^{26}Al-citrate. Blood, urine and feces were collected during the five days following injection, except for the volunteer in Priest et al. (1995) for which the follow-up was at 13 days. Around 59.1% (46.4% to 74.42% range) of the uptake was excreted in the cumulative urine collected during 24 hours following injection whereas after five days, around 71.8% of the dose was recovered in urine (62.3% to 82.9% range). These results are considerably different than those reported in a study by Steinhausen et al. (2004), in which two volunteers received an IV injection of ^{26}Al-chloride, where the five-day urinary excretion accounted only for 25% of the dose.

Priest et al. (1995) and Talbot et al. (1995) described the whole-body retention of aluminum, blood concentration and urinary excretion, after the first day of injection, by a power function (e.g., $C_b(t) = 0.37t^{-0.9}$, expressed as a percent of injection/L). However, in a study with a follow-up period of 11 years, Priest (2004) demonstrated that the pattern of the whole-body retention of aluminum must be represented by a multiple-exponential equation.[13] Numerous studies have actually shown that the rate of aluminum clearance in blood diminishes with time following aluminum administration, and thus a single elimination half-life ($t_{½}$) cannot describe the whole-body elimination of aluminum (Priest 2004). Some authors have attempted to calculate specific $t_{½}$ of aluminum for the tissues and organs of rats (Greger et al. 1994; Greger and Radzanowski 1995; Rahnema and Jennings 1999). In general, it was shown that aluminum deposited in well-perfused tissues/organs (e.g., kidneys and lungs) is released more rapidly than aluminum in slowly-perfused tissues (e.g., bone and spleen). These $t_{½}$ values varied from 2.3 to 113 days. However, even if the brain is well-perfused, the retention of aluminum appears to be strong (see section 2.4.2.2). According to the experimental data in animals, Krewski et al. (2007) estimated that the $t_{½}$ of aluminum deposited in brain is from 13 to 1,635 days.

A multicompartmental model was developed to describe the kinetics of aluminum in humans, based on the retention of ^{26}Al in the volunteer of the Priest et al. (1995) study, who was followed over more than ten years (Priest 2004). Five compartments are used to describe aluminum accumulation in the different organs and tissues; for each compartment, specific tissues or organs are indicated with a specific elimination half-life. These compartments are fed by the compartment of blood and extracellular fluids. As well, Nolte et al. (2001) proposed an open compartmental model to describe the kinetics of aluminum in humans based on the binding of aluminum with transferrin and citrate; this model was used by Steinhausen et al. (2004).

[13] The equation of the retention is $R(t) = 29.3e^{-0.595 \cdot t} + 11.4e^{-0.172 \cdot t} + 6.5e^{-0.000401 \cdot t}$; the corresponding elimination half-lives are 1.4, 40 and 1,727 days.

2.4 Effects characterization

2.4.1 Ecotoxicology

Below, a brief summary of effects data for the most sensitive aquatic and terrestrial organisms is presented. More extensive descriptions of environmental effects are provided in several reviews (e.g., ATSDR 2006; Bélanger et al. 1999; Roy 1999a).

When aluminum salts are added to water, they hydrolyse, and monomeric aluminum can be formed in the dissolved fraction. It is the monomeric aluminum, and not the salts, that can adversely affect organisms (Driscoll et al. 1980; Parker et al. 1989; Baker et al. 1990). The following summary focuses, therefore, on the effects of the dissolved (particularly monomeric) forms of aluminum that are produced when aluminum salts dissociate.

2.4.1.1 Aquatic organisms

Most of the research on the impact of aluminum on aquatic life has been related to the impacts of acid rain. In this report, emphasis was placed on the potential toxic impacts of aluminum in waters of neutral or near-neutral pH as the available information suggests that releases associated with the three aluminum salts being assessed occur primarily into waters of circumneutral pH (Roy 1999b; Germain et al., 2000). As described below, because of this consideration, the most relevant effects data identified were for fish. This assessment report does not provide a detailed examination of potential effects from exposure to polymeric aluminum, as polymeric aluminum is most likely to form, and to cause toxicity, during the neutralization of acidic aluminum-rich waters and this is unlikely to occur in the release scenarios considered in this assessment (Roy 1999b).

The gills are the primary target organ for aluminum in fish (Dussault et al. 2001). Aluminum binds to the gill surface, causing swelling and fusion of the lamellae and increased diffusion distance for gas exchange (Karlsson-Norrgren et al. 1986; Tietge et al. 1988). The resulting damage leads to loss of membrane permeability, reduced ion uptake, loss of plasma ions, and changes in blood parameters relating to respiration. Fish death may result from ionoregulatory or respiratory failure, or a combination of both, depending upon the pH of the water and concentration of waterborne aluminum (Neville 1985; Booth et al. 1988; Gensemer and Playle 1999). Ionoregulatory disturbances prevail at lower pH (e.g., below 4.5) and relate to decreased levels of plasma Na^+ and Cl^- ions (Neville 1985; Gensemer and Playle 1999). At pH levels above 5.5, binding of the positively charged aluminum species to negatively charged sites on the gill surface, with subsequent aluminum polymerization, leads to mucous secretion, clogging of the interlamellar spaces and hypoxia (Neville 1985; Poléo 1995; Poléo et al. 1995; Gensemer and Playle 1999).

Aluminum exposure may also disrupt ionic balance and osmoregulation in aquatic invertebrates (Otto and Svensson 1983). Reduced Na^+ and/or Ca^{2+} uptake in response to aluminum exposure have been documented in crayfish (Appleberg 1985; Malley and Chang 1985), mayfly nymphs (Herrmann 1987) and the water boatman, *Corixa* sp. (Witters et al. 1984). Aluminum reduced Na^+ influx and, to a lesser extent, increased outflux, in *Daphnia magna*, thereby impairing osmoregulation (Havas and Likens 1985). Aluminum may disrupt the respiratory organs of some invertebrates, such as the anal papillae of the phantom midge,

Chaoborus sp. (Havas 1986). Respiratory effects can occur when acidic waters are rapidly neutralized, such as when an acidic tributary enters a larger, neutral receiving stream, leading to the formation of mononuclear and polynuclear aluminum species from the dissolved ion (Gensemer and Playle 1999). These species may bind to or precipitate onto the bodies of invertebrates, creating a physical barrier to respiration. Aluminum has been reported to impair reproduction in *Daphnia magna* (Beisinger and Christensen 1972), although recent work with *Daphnia pulex* suggests that adaptive strategies which heighten survivorship and fecundity may occur following long-term exposure to sublethal levels (Wold et al. 2005). Hall et al. (1985) reported that aluminum may reduce the surface tension of water, affecting egg deposition, emergence, feeding and mating behaviour of some stream invertebrates.

2.4.1.1.1 Pelagic

Water pH is known to have a significant effect on the toxicity of dissolved aluminum. Under acidic conditions, aluminum is most toxic in the pH range 5.0–5.5. At more acidic pH, its toxicity decreases, while at still lower pH, aluminum can offer transitory protection against the toxicity of H^+ (Muniz and Leivestad 1980; Baker 1982; van Coillie et al. 1983; Roy and Campbell 1995). Elevated concentrations of the cations Ca^{2+} and Mg^{2+} reduce the toxicity of metals (Pagenkopf 1983; Campbell 1995), yet there are relatively few results examining the effects of elevated calcium on aluminum toxicity. In fish exposed to aluminum at low pH, elevated calcium has been shown to improve survival (Booth et al. 1988; Mount et al. 1988; Sadler and Lynam 1988), reduce losses of plasma ions (Brown 1981; Sadler and Lynam 1988; McDonald et al. 1989) and reduce accumulation of aluminum on gills (Wood et al. 1988a,b). However, Duis and Oberemm (2001) reported low hatching success and high embryo mortality in vendace, *Coregonus albula,* exposed to high aluminum concentrations of 2.1 and 2.4 mg/L at low pH (4.75, 5.00) and in the presence of 111 to 117 mg/L calcium. Increasing calcium concentrations to 233 to 256 mg/L had no influence on hatching and survival percentages, suggesting that the toxic effect of high aluminum levels can exceed the protective effect of high calcium.

The toxicity of dissolved aluminum is reduced in the presence of inorganic ligands, such as fluorides, sulphates and silicates, as well as organic ligands, such as fulvic and humic acids (Roy 1999a). It is well established that DOM in particular influences the speciation and absorption of aluminum. In laboratory studies with fish, the toxicity of aluminum was reduced in the presence of organic acids, such as citric acid (Driscoll et al. 1980; Baker 1982), salicylic or oxalic acid (Peterson et al. 1989), humic acid (van Coillie et al. 1983; Parkhurst et al. 1990; Peuranen et al. 2002) and fulvic acid (Neville 1985; Lydersen et al. 1990a; Witters et al. 1990; Roy and Campbell 1997). In laboratory studies with amphibians (frog eggs and tadpoles), LC_{50}s for aluminum increased (i.e., toxicity was reduced) in the presence of DOM. However, in the field, the effects of DOM in attenuating aluminum toxicity are difficult to separate from the influences of pH and aluminum concentration (Clark and Hall 1985; Freda 1991).

Most aquatic toxicity studies involving aluminum have been conducted under conditions of low pH, and a number of these accounted for the solubility of the metal in the experimental design. The general conclusion of these studies is that aluminum toxicity is related to the concentration of dissolved inorganic monomeric aluminum (Roy 1999a).

At pH < 6.0, fish, the salmonids in particular, are among the most sensitive organisms to dissolved aluminum. In soft acidic waters, the LC_{50} can be as low as 54 µg/L (for Atlantic salmon at pH 5.2), while in chronic studies, a Lowest-Observed-Effect Concentration (LOEC) of 27 µg/L was determined for growth (for brown trout [*Salmo trutta*] at pH 5.0). Some species of algae show a comparable sensitivity. Parent and Campbell (1994) determined a LOEC of 150 µg/L (as inorganic monomeric aluminum) at pH 5.0 with the alga *Chlorella pyrenoidosa*. While many invertebrates tolerate elevated levels of aluminum, Havens (1990) found that exposures to 200 µg Al/L at pH 5.0 were extremely toxic to *Daphnia galeata mendotae* and *Daphnia retrocurva*. France and Stokes (1987) concluded that stress from aluminum exposure was secondary to the stress of low-pH exposure for survival of *Hyalella azteca*. Results of other studies also suggest that invertebrates are more sensitive to low pH than to aluminum. Amphibians show a similar sensitivity. Freda (1991) summarized her work by concluding that aluminum can be lethal to amphibians that inhabit soft acidic (pH 4 to 5) waters if concentrations exceed 200 µg inorganic Al/L.

At pH 6.0 to 6.5, there are few studies that provide effects estimates in terms of inorganic monomeric aluminum. At pH 6.0, a LOEC of 8 µg/L (inorganic monomeric aluminum) for growth of the alga *C. pyrenoidosa* can be estimated from the data of Parent and Campbell (1994). Growth of the alga was reduced at this single exposure concentration in media without phosphate. This LOEC is, however, well within the likely range of natural concentrations of inorganic monomeric aluminum in surface water. In comparison, Neville (1985) observed that 75 µg Al/L (as inorganic monomeric aluminum) caused physiological distress to rainbow trout (*Oncorhynchus mykiss*) at pH 6.1 but not at pH 6.5.

At pH 6.5 to 8.0, there are few effects data available. At neutral or near-neutral pH, aluminum has a tendency to precipitate, and the chemistry of these solutions is difficult to control. While the toxicity of alum in neutral-pH waters has been the subject of many studies, the results are unreliable, due to extreme variation between replicates of the same exposure concentration and between duplicate experiments (Lamb and Bailey 1981; Dave 1985; George et al. 1995; Mackie and Kilgour 1995). However, a No-Observed-Effect Concentration (NOEC) for respiratory activity at pH 6.5 is provided by the results of the study by Neville (1985), who found that rainbow trout tolerated 75 µg Al/L (as inorganic monomeric aluminum) during exposures at this pH. Wold et al. (2005) reported a LOEC of 0.05 mg/L Al for reduced survival and reproduction in *Daphnia pulex* exposed for 21 days to concentrations ranging from 0.05 to 0.50 mg Al/L (nominal) as aluminum sulphate. The test water was maintained at a pH of 7 ± 1, suggesting that the observed effects were due to the presence of aluminum hydroxide rather than the dissolved inorganic monomeric aluminum that is usually associated with toxicity. In addition, the study reported that clonal populations of *D. pulex* derived from a lake with ongoing alum treatment showed higher age-specific survivorship, higher fecundity and faster growth rates than those collected from waters having less recent or no prior alum exposure. The researchers hypothesized that *Daphnia* may be capable of exhibiting adaptive strategies that heighten survivorship and fecundity when exposed to sublethal chemical stresses.

Gopalakrishnan et al. (2007) reported a lowest 24-hour EC_{50} value of 0.210 mg/L for development of the trochophore larva in the marine polychaete, *Hydroides elegans*. The study was conducted at a pH of 8.1 and aluminum concentrations (measured using atomic absorption

spectrophotometry) were well maintained within 2% to 15% of nominal values. Differential sensitivities were observed during embryogenesis and larval development, with lowest toxicity evident at the stage of the fertilization membrane and successively higher toxicity at the blastula and trochophore stages, respectively.

At pH > 8.0, LOECs for survival of rainbow trout are ≥ 1.5 mg/L as total aluminum (Freeman and Everhart 1971). In a more recent study, Gundersen et al. (1994) reported LC_{50}s for exposures of rainbow trout in the pH range 8.0–8.6. The LC_{50}s at all pHs were approximately the same value, ~ 0.6 mg/L (range: 0.36–0.79 mg/L) as dissolved aluminum (i.e., filterable through a 0.4-µm filter), and were similar in both acute (96-hour) and longer-term (16-day) exposures at hardness levels ranging from 20 to 100 mg/L (as calcium carbonate). A NOEC for mortality of 0.06 mg dissolved Al/L can be derived from data given for one of the 16-day exposures conducted at 20 mg/L hardness and pH 8.0. Although these concentrations were measured as dissolved aluminum, it is probable that the monomeric aluminate ion, $AlOH_4^-$, predominated at this pH.

In contrast, Poléo and Hytterød (2003) reported that juvenile Atlantic salmon, *Salmo salar*, exposed under alkaline (pH 9.5) conditions to concentrations of around 0.35 mg/L (predominantly aluminate ion) showed no acute toxicity effects. The researchers noted that the aluminum concentrations used in their study were lower than those of Freeman and Everhart (1971) and Gundersen et al. (1994), and hypothesized that more environmentally relevant concentrations of aluminum do not have any acute effect on salmonids under alkaline conditions, while very high concentrations of aluminum might have. While no acute effects were observed, physiological responses in the form of elevated blood glucose and hematocrit levels and a decrease in plasma Cl^-, were evident after a three-week exposure period and were considered indicative of a stress response in the fish. The authors concluded that the combination of high pH and aluminum may impose some stress but this is unlikely to represent a serious problem unless the exposure continues for a long period of time. High alkalinity conditions such as those used in the study can occur in water bodies during periods of intense photosynthetic activity in the summer months. At these times, concentrations of aluminum present in the water would also be expected to rise as the solubility of the substance increases over that at lower pH.

While toxicity is most commonly associated with inorganic monomeric aluminum species, there is evidence that aluminum undergoing transition from one species to another is also bioavailable and can exert adverse effects on organisms. Such transition conditions can occur in mixing zones, for example, when acidic waters enter a larger, more neutral receiving system or during the liming of acidic waters. Berkowitz et al. (2005) found that the addition of alum to lake water samples (pH 8.22 to 9.08) resulted in a rapid initial decrease in pH and alkalinity followed by a gradual recovery in pH over several weeks. Dissolved Al concentrations increased following treatment, and then decreased after 150 days. Soucek (2006) determined that freshly neutralized aluminum (i.e., aluminum in transition from ionic species in acidic waters to polymers or precipitating hydroxides after a rapid pH increase) impaired oxygen consumption in *Daphnia magna* and the perlid stoneflies, *Perlesta lagoi* and *Acroneuria abnormis* (lowest LOEC for the study 0.5 mg/L, which was also the lowest concentration tested). Alexopoulos et al. (2003) reported that freshly neutralized aluminum at a concentration of 0.5 mg/L associated specifically with the gills of the freshwater crayfish,

Pacifastacus leniusculus, creating a physical barrier during precipitation that resulted in impaired respiration and asphyxiation. Particulate aluminum has been shown to decrease filter feeding in the freshwater bivalve, *Anodonta cygnea*, presumably as an avoidance response to the toxicant (Kádár et al. 2002). Poléo and Hytterød (2003) examined toxicity under steady-state (pH retained at 9.5) and non-steady state (pH lowered from 9.5 to 7.5) conditions in order to evaluate the possible impact of transient aluminum chemistry on Atlantic salmon, *Salmo salar*. No increase in toxicity occurred under the non-steady state conditions (i.e., where aluminum solubility was lowered as the pH decreased) and the physiological disturbances observed at high pH were mitigated. The results contrasted with those obtained in studies where aluminum solubility was lowered by raising the pH of aluminum-rich water. In these cases, toxicity to fish increased as the solubility of aluminum was decreased and aluminum precipitated onto the gills (e.g., Poléo et al. 1994; Poléo and Bjerkely 2000).

Verbost et al. (1995) reported enhanced toxicity in a mixing zone of acid river water containing aluminum (pH 5.1, aluminum 345 µg/L) with neutral lake water (pH 7.0, aluminum 73 µg/L). The resulting water (pH of 6.4, aluminum 235 µg/L) was expected to have low toxicity; however, the freshly mixed water was highly toxic to brown trout, *Salmo trutta*, with necrosis and apoptosis of the gills evident in exposed fish. A clear gradient in the deleterious effects occurred with increasing distance from the mixing area, with fish furthest from the mixing zone exhibiting only mild effects. The researchers concluded that freshly mixed acid and neutral water contains toxic components during the first seconds to minutes after mixing, and that even short exposure to this toxic mixing zone is detrimental to migrating trout. Farag et al. (2007) hypothesized that colloids formed in mixing zones may contribute to aluminum toxicity in fish by providing a direct route of the metal to the gills.

Finally, in a study done with DWTP sludge from Calgary and Edmonton, Alberta, AEC (1987) concluded that all sludges tested were non-toxic using a microbial test and acutely and subacutely non-toxic to rainbow trout. However, delayed release of first broods and significantly reduced reproduction were reported in the freshwater cladoceran, *Ceriodaphnia dubia*, exposed for 7 days to 100% aluminum sludge effluent collected from a DWTP in the U.S. (Hall and Hall 1989). The researchers considered that the effects were likely due to the combined effects of reductions in pH and dissolved oxygen concentrations, physical stress due to high levels of suspended solids, and possibly the presence of aqueous aluminum. Aqueous aluminum alone was probably not the factor exerting sub-lethal toxicity in 100% effluent since similar aqueous aluminum concentrations were observed in the 50% effluent where delays and significant reductions in reproduction were not observed. The same study observed significant mortality in fathead minnow, *Pimephales promelas*, exposed to the 100% effluent, as well as a lowest test concentration of 6.3%. Mortality in the intervening concentrations of 12.5, 25 and 50% were not statistically different from that in the controls. Mortality at 100% effluent was attributed to physical stress resulting from high levels of suspended solids. While a causative agent for the observed mortality at 6.3% could not be identified, the researchers noted that this test concentration had the highest concentration of aqueous aluminum, with measured levels up to 0.43 mg/L as compared with 0.05 to 0.31 mg/L at the other test concentrations. No sublethal impacts were evident in the fish testing.

2.4.1.1.2 Benthic

Alum can be used to treat eutrophic lakes to reduce the amount of phosphorus present in water or prevent its release from sediment. Lamb and Bailey (1981) concluded that a well-planned and controlled alum treatment would not result in significant mortality in benthic insect populations. Connor and Martin (1989) measured no detrimental effects on midge or alderly larvae following treatment of Kezar Lake, New Hampshire, sediment, and long-term effects on benthic invertebrates were minimal. Narf (1990) reported that benthic population diversities and numbers increased or remained the same following lake treatment with alum. Smeltzer (1990) observed a temporary impact on benthos after treatment of Lake Morey, Vermont, with an alum/sodium aluminate mixture. Benthos density, already low in the year prior to treatment, and richness were lower following treatment. However, changes were not significant, the benthic community recovered, and two new chironomids appeared the following year.

The Sludge Disposal Committee examined the impact of alum sludge discharge in aquatic environments and concluded that residue will tend to deposit near the point of discharge if the water velocity is low (Cornwell et al. 1987) and that it could have adverse effects, including development of anaerobic conditions. Roberts and Diaz (1985) related the reduction in phytoplanktonic productivity observed during alum discharge in a tidal stream in Newport News, Virginia, to the reduction in light intensity. Lin et al. (1984) and Lin (1989) found no buildup of sludge in pooled waters in the Vermillion and Mississippi rivers following sedimentation basin cleaning of DWTPs in St. Louis, Missouri. There were no significant differences in types and densities of macroinvertebrates in bottom sediments, and even higher density and diversity were found in some sites.

George et al. (1991; 1995) reported that macroinvertebrates located downstream of four DWTPs appeared to be stressed by alum discharges. In the Ohio River, effects seemed temporary and were limited in space. In addition, organisms collected from upstream locations indicated that environmental factors other than the aluminum sludge discharge may also have been affecting the system. A water–sediment microcosm study done with bottom sediment from the receiving rivers over a 72-day period showed significantly lower oligochaete content in bottom sediment treated with alum sludge. Testing with bentonite gave the same results, and the authors concluded that aluminum sludge deposits on sediment may have the potential to detrimentally affect benthic macroinvertebrate populations by limiting their access to oxygen or food and, therefore, the smothering effect from sludge may prove to be more important to aquatic organisms than aluminum content. However, in laboratory testing, filtrates obtained from aluminum sludge were toxic to the freshwater alga, *Selenastrum capricornutum*, in waters with low pH or a hardness of less than 35 mg/L $CaCO_3$, suggesting that water-soluble constituents from the aluminum sludge may be capable of affecting algal growth. The study recommended that further toxicity testing be conducted to more fully ascertain potential toxic effects, and that aluminum sludge not be discharged into soft surface waters (i.e., hardness < 50 mg $CaCO_3$/L) or those with a pH of less than 6.

A study has been undertaken to examine the environmental impact of filter backwash and basin cleaning effluents to the Ottawa River from the Britannia and Lemieux Island DWTPs in Ottawa (RMOC 2000; City of Ottawa 2002). In this study, riverine characteristics

downstream of the Britannia site were reported to be beneficial for the sampling of benthic invertebrates due to the slow water velocities of a bay environment. Unlike the Britannia site, the Ottawa River in the vicinity of the Lemieux Island DWTP was characterized by strong currents and an absence of natual benthic habitat. To examine the impact of effluents from the Lemieux Island facility, artificial habitat was installed for benthic organisms at both upstream and downstream locations from the discharge site. The results of the sampling showed that species abundance and diversity was depressed at both sites downstream from the effluent discharges in comparison to sampling sites located upstream. At sites located 150 and 6,000 m upstream from the Britannia DWTP outfall, approximately 160 and 250 organisms were counted, whereas downstream sites located at 0, 300, 500 and 1,500 m (furthest sampling location) had between 3 (at 0 m) and approximately 100 organisms (at 1,500 m) (diversity of organisms not provided for Britannia site). At the artificial sampling sites 30 and 110 m downsteam of the Lemieux Island DWTP, approximately 250 and 1,000 organisms were counted representing 17 and 21 taxa, respectively. The site located 90 m upstream from the Lemiux discharge had approximately 1,800 organisms representing 24 taxa.

Toxicity of basin sediment from each of the Britannia and Lemieux Island DWTPs was also examined. The studies showed complete mortality of midge larvae (*Chironomus riparius*) within the 10 day test exposure, while survival of *Hyalella azteca* (14 day exposure) was not significantly different from that of the control animals. The study could not determine whether the mortality was attributable to the physical characteristics of the sludge (e.g., particle size) or the presence of chemical contaninants. The sludge from the Lemieux Island DWTP was shown to inhibit growth of *Hyalella azteca* over the 14 day exposure period, but the Britannia DWTP sludge resulted in no observed effect. The study did not suggest why one sludge demonstrated growth effects, but not the other (methodology and experimental conditions were not provided).

Ultimately, the cause of the the depressed levels of organisms downstream in the Ottawa River from Britannia and Lemieux DWTPs was not due to one causal factor, rather may have resulted from a number of attributes including: physical composition of the sediment and its ability to support life; ongoing blanketing of the area due to new discharges; and toxicity of dissolved aluminum leaching out of the sediment into the water column (City of Ottawa 2002).

In studies related to wastewater releases by DWTPs, AEC (1984) reported there is potential for smothering effects on benthic organisms related to settled sludge on sediments following their release to rivers in Alberta. A number of other possible adverse impacts resulting from the discharge of aluminum sludge to receiving waters were identified, including: formation of sludge deposits in quiescent areas of streams; toxic effects on aquatic organisms from other contaminants present in the sludge; periodic high oxygen demand if water treatment plant sludge is discharged in large slugs or if previously deposited sludge is periodically re-suspended due to increased stream velocity; increased aluminum concentrations of downstream water supplies; and aesthetic problems where stream flow, stream turbidity, and/or sludge dilution are low. The researchers concluded that aluminum sludge exhibits a wide range of characteristics which depend on the raw water characteristics (turbidity, etc.) and other factors and, therefore, while numerous suspicions have been expressed regarding the potential for adverse effects resulting from the discharge of alum

sludges to receiving waters, there appeared to be a lack of good scientific evidence to substantiate these concerns. Recommendations of the report included the acquisition of baseline data through bioassay testing and other studies, as well as consideration of alternatives to direct stream disposal practices such as reduction of the quantities of alum sludge produced through substitution with other coagulants, discharge at controlled rates to a sanitary sewer, lagooning with natural freeze-thaw dewatering, thickening and dewatering followed by landfilling, and land application.

A subsequent study examining the binding, uptake and toxicity of aluminum sludges from three water treatment systems in Edmonton and Calgary determined that aluminum was effectively bound to sludges within the pH range 4.5 to 10.0, with more than 99.98% of the total aluminum being in the form of sludge (AEC 1987). Sludge collected from the three plants was found to be non-toxic to rainbow trout, Long Evans rats, and the microbial toxicity test system, Microtox.

2.4.1.2 Terrestrial organisms

Research on the effects of aluminum to soil organisms has concentrated largely on screening for aluminum-tolerant strains of root nodulating bacteria and mycorrhizal fungi, due to the importance of these species in improving crop production (Bélanger et al. 1999). In general, toxicity threshold values for bacterial species fall in the range of 0.01 to 0.05 mM (pH 4.5 to 5.5), while those of mycorrhizal fungi range from 0.1 to 20 mM (pH 3.4 to 4.5) when based on hyphal growth inhibition and 30 to 157 mg/kg soil (pH 4.5 to 5.0) when based on reduced spore germination. For soil macroinvertebrates, growth of newly hatched earthworm, *Dendrodrilus rubidus*, was significantly reduced at 10 mg Al/kg soil (soil pH 4.2 to 4.9; Rundgren and Nilsson 1997), while significantly inhibited growth and cocoon production were reported for the earthworm, *Eisenia andrei*, at concentrations ranging from 320 to 1000 mg/kg dry soil, with toxicity decreasing as soil pH increased from 3.4 to 7.3 (van Gestel and Hoogerwerf 2001). A more complete examination of potential impacts to soil-dwelling microorganisms, fungi and invertebrates can be found in Bélanger et al. (1999).

The remainder of this section focuses on the effects of aluminum on sensitive plant species. It should be noted, however, that the problem with alum sludge may be associated not only with the direct toxic effects of aluminum on plants, but also with indirect effects related to phosphorus deficiencies (Jonasson 1996; Cox et al. 1997; Quartin et al. 2001). Aluminum's capacity to fix labile phosphorus by forming stable aluminum-phosphorus complexes and hence make it unavailable to plants can be responsible for the observed effects. In addition, toxic substances captured by the floc during water treatment may be available for uptake by soil species and exert adverse effects.

The presence of aluminum in solution, soil solution or soil resulted in a decrease in seedling growth, elongation or branching of roots of hardwood and coniferous species at varying levels (Horst et al. 1990; Bertrand et al. 1995; McCanny et al. 1995; Schier 1996). The most sensitive species was honeylocust (*Gleditsia triacanthos*) (Thornton et al. 1986a, 1986b). All measures of growth, except root elongation, consistently declined as solution aluminum increased, 0.05 mM or 1.35 mg/L being the critical value for a 50% general decrease (pH = 4.0). Since honeylocust is not an important species in Canadian forests and since the

results obtained by Thornton et al. (1986b) contradict the results obtained for this species by other researchers, it was decided that the two next Lowest-Observed-Adverse-Effect Concentrations (LOAECs) are more relevant. Hybrid poplar (*Populus* hybrid) (Steiner et al. 1984) and red oak (*Quercus rubra*) (DeWald et al. 1990) showed a 50% decline in root elongation at an aluminum solution level of 0.11 mM (2.97 mg/L). The most sensitive coniferous species is pitch pine (*Pinus rigida*) (Cumming and Weinstein 1990). Seedlings inoculated with mycorrhizal fungus, *Pisolithus tinctorius*, showed increased tolerance to aluminum, whereas non-mycorrhizal seedlings exposed to 0.1 mM (2.7 mg/L) (pH 4.0) aluminum exhibited decreased root and shoot growth.

In an experiment done with scots pine (*Pinus sylvestris*), Ilvesniemi (1992) found that when nutrition was optimal, pines tolerated high levels of aluminum, but in nutrient-poor solution, their tolerance to aluminum was reduced tenfold. Hutchinson et al. (1986) and McCormick and Steiner (1978) also observed that pines were tolerant of high levels of aluminum in optimal nutrient solution.

Grain crop and forage crop species were also affected by different levels of aluminum (Bélanger et al. 1999). Wheeler et al. (1992) found that two barley (*Hordeum vulgare*) cultivars and eight common wheat (*Triticum aestivum*) cultivars were particularly sensitive, growth being decreased by more than 50% at aluminum levels as low as 0.005 mM (0.135 mg/L) (pH 4.5). Wheeler and Dodd (1995) also showed a 50% decline in growth of clover species, *Trifolium repens*, *Trifolium subterraneum* and *Trifolium pratense*, at 0.005 mM (0.135 mg/L) aluminum (pH 4.7). In a solution culture study, Pintro et al. (1996) found that the root elongation rate of maize (*Zea maize* HS777 genotype) was also negatively affected at an aluminum level of 0.005 mM (0.135 mg/L) (pH 4.4). In a study done on barley, Hammond et al. (1995) found significant amelioration of the toxic effects of aluminum on root and shoot growth when silicon was added to the solution medium. Silicon amelioration of aluminum toxicity in maize has also been reported (Barcelo et al. 1993; Corrales et al. 1997). In the presence of silicon, aluminum uptake seems to be decreased because of the formation of aluminum-silicon complexes, thus leading to a decrease in absorption of aluminum. In addition, complexes formed with organic anions, sulphate and phosphate appear to be non-toxic to plants (Kinraide 1997; Takita et al. 1999; Matsumoto 2000), while the aluminum-hydroxy species was reported to be phytotoxic in early studies (Alva et al. 1986; Wright et al. 1987; Noble et al. 1988a) but not in more recent ones (Kinraide 1997). Complexation with fluoride has been shown to ameliorate the phytoxic effects of aluminum in nutrient solutions (Cameron et al. 1986; Tanaka et al. 1987; MacLean et al. 1992); however, the aluminum-fluoride complex may also become toxic at high concentrations, with toxicity linked to the proportion and concentration of the different types of aluminum-fluoride species present in solution (Kinraide 1997; Stevens et al. 1997). Manoharan et al. (2007) reported severely restricted root growth in barley exposed to fluoride and aluminum in acidic soils (pH 4.25 to 5.48). Toxicity was attributed the activities of AlF_2^+ and AlF^{2+} complexes formed in the soil. Fluoride may enter soil through the application of phosphate fertilizers, which usually contain 1% to 4% fluoride as an impurity (Loganathan et al. 2003). Calcium supplementation has also been reported to alleviate aluminum toxicity in barley, possibly by reducing cellular absorption of the metal and enhancing protection through increased activity of antioxidant enzymes (Guo et al. 2006).

Wheeler and Dodd (1995) investigated the effect of aluminum on yield and nutrient uptake of some temperate legumes and forage crops using a low ionic strength solution. The solution aluminum levels at which top yield and root yield of 58 white clover cultivars were reduced by 50% ranged from approximately 0.005 to 0.02 mM (0.135 to 0.540 mg/L) (pH 4.5 to 4.7).

Although inorganic monomeric forms of dissolved aluminum (Al^{3+}, $Al(OH)^{2+}$ and $Al(OH)_2^{+}$) are believed to be the most bioavailable and responsible for most toxic effects (Alva et al. 1986; Noble et al. 1988b), information on the concentrations of different dissolved aluminum complexes was not reported in many of the effects studies reviewed. For studies indicating particular sensitivity that were carried out in the laboratory in artificial solutions, it is likely that the majority of the aluminum present in these key studies was in inorganic monomeric forms. Considering that solution culture experiments gave lower LOEC values than did sand culture experiments in forest species studies, the effects data reviewed are considered to be conservative estimates of the effects levels for vegetation grown in natural soils.

2.4.2 Experimental mammal studies

The scientific literature concerning the effects of aluminum exposure in experimental mammals is large, including studies with a variety of administration routes (ingestion, inhalation, dermal, intraperitoneal, intravenous, intracisternal). The characterization of effects presented below includes studies of oral, inhalation and dermal administration, with emphasis on the oral exposure studies. This reflects the importance of the oral route in environmental exposures within the general Canadian population, as compared to dermal and inhalation as well as the research emphasis on oral studies within the scientific community. For more detailed discussion of other routes of exposure, the reader may consult the comprehensive reviews cited, in particular Krewski et al. (2007).

Health Canada considers neurotoxicity and reproductive/developmental toxicity as the categories of effects of greatest potential concern for the general population, in light of the evidence from case studies and epidemiological investigations, discussed in section 2.4.3. Recent comprehensive reviews also collectively support this conclusion (InVS-Afssa-Afssaps 2003; ATSDR 2006; JECFA 2006; Krewski et al. 2007; EFSA 2008). Thus, most of the studies presented in this section focus on neurotoxicity or reproductive/developmental toxicity in which aluminum is administered to the experimental animals through diet, drinking water or gavage.

Various aluminum salts, including chloride, nitrate, sulphate, lactate, citrate, maltolate, fluoride and hydroxide have been used in experimental animal studies to investigate the effects of Al^{3+} absorbed in the bloodstream and distributed to target organs. Aluminum speciation (i.e., the ligands associated with aluminum) and the overall composition of the diet may influence toxicokinetics and consequently the subsequent toxicity of Al^{3+} (see section 2.3.3.1.1). With respect to absorption, however, no one aluminum salt is representative of the mix of aluminum compounds in the human diet that contribute to the Al^{3+} reaching the bloodstream. Therefore, for the purpose of characterizing effects of total aluminum, all oral studies were examined, regardless of the aluminum salt administered. Relative bioavailability of particular salts is then considered in the exposure-response analysis of section 3.2.3.

A number of the experimental animal studies are designed to explore the influence of factors that may potentially exacerbate the toxic effects of aluminum (e.g., restraint) or provide protection (e.g., therapeutic substances such as Gingko). The results reported in this section, however, focus on the differences between aluminum-treated animals and controls, rather than the influence of these other factors.

In most of the studies consulted, there is a lack of data on the aluminum concentration in the base diet. Studies on different brands of commercial laboratory animal chow show that aluminum levels in the chow can be significant relative to the administered doses, and also highly variable between brands and even between different lots of the same brand (ATSDR 2006). Typical levels of 250 to 350 ppm of aluminum in rodent chow (ATSDR 2006) would contribute approximately 13 to 18 mg Al/kg/d in rats and 33 to 46 mg Al/kg/d in mice, on the basis of default reference values for animal intake and body weight proposed in Health Canada (1994). While it may be hypothesized that the absorption of the base diet aluminum may differ from (and be significantly less) than the absorption of the administered aluminum, there are little relevant experimental data on this question (see section 2.3.3). Therefore the lack of data on base diet aluminum in many of the toxicity studies must be considered as a major uncertainty in the overall database, when considering these studies in the exposure-response analysis and risk characterization.

Notwithstanding the importance of quantifying total aluminum exposure in animal studies, in order to provide a qualitative summary of the literature for the purpose of hazard identification, all studies have been evaluated, regardless of whether the base diet aluminum concentration is reported. In the exposure-response analysis (section 3.2.3), however, administered and combined doses are distinguished and the influence of this factor is considered.

The description of the studies in this section is focused on the nature of the effects investigated and observed, rather than the exposure-response relationship. The database is large (138 studies) and the experimental conditions (e.g., administered salts and dosing regimen) vary, and in the majority of the studies only one dose was tested. Thus direct comparisons of the dose-effect data may be misleading. While some information on the lowest observed dose at which effects occurred is provided[14] as well as the highest dose at which no effects were observed, a more detailed discussion of the exposure-response analysis is presented in section 3.2.3. The details of the studies considered in that analysis are summarized in Tables C1 and C2 (Appendix C). Tables summarizing the full dataset are available in the Health Canada Supporting Document, prepared for this assessment (Health Canada 2008a).

[14] The LOELs and NOELs reported in this section may correspond to the doses reported by the researchers, or may be calculated based on reported concentrations in food or drinking water, assuming default values for animal body weight, and food and drinking water consumption rates drawn from Health Canada (1994).

2.4.2.1 Acute toxicity

Oral exposure

The oral LD_{50} (lethal dose, 50% kill, single administration) for different aluminum salts, as measured in different strains of mice, rats, guinea pigs and rabbits, varies according to the aluminum salt administered as well as according to the experimental animal species. In an early review an LD_{50} of apparently 6,200 mg Al/kg bw was reported for $Al_2(SO_4)_3$ and of 3,850 mg Al/kg bw for $Al(Cl)_3$ administered to mice (Sorenson et al. 1974), although it is unclear from the review article if these values refer to the dose in terms of aluminum or the dose in terms of the salts. Sorenson et al. (1974) also reported LD_{50} values from 260 to 4,280 mg/kg bw for $Al(NO_3)_3 \bullet 9H_2O$ in two separate studies on rats. The lower value of 260 mg/kg $Al(NO_3)_3 \bullet 9H_2O$ clearly underestimates the LD_{50} (i.e., overestimates the toxicity), as Colomina et al. (2002), Colomina et al. (2005) and Domingo et al. (1996) have shown. These research groups tested administered doses of 50 to 100 mg Al/kg bw/d, equivalent to approximately 700 to 1,400 mg $Al(NO_3)_3 \bullet 9H_2O$/kg bw/d, and the effects were limited to alterations in weight gain and subtle neurological effects (see sections 2.4.2.2 to 2.4.2.4 and section 3.3 for more detailed discussion of these studies).

In a study of oral and intraperitoneal administration during 14 days, Llobet et al. (1987) estimated the acute oral toxicity of aluminum chloride, nitrate and sulphate in Sprague-Dawley rats and Swiss mice. Aluminum chloride and nitrate produced acute toxicities of similar magnitude (LD_{50} of 222 to 370 mg Al/kg) in the mice and rats, whereas the toxicity of aluminum sulphate was considerably lower (LD_{50} > 730 mg Al/kg in both species).

Inhalation exposure

In Golden Syrian hamsters and New Zealand rabbits exposed over a short duration (four to six hours per day for three to five days at levels of 7 to 200 mg/m^3) to aluminum chlorohydrate through inhalation, the effects observed are those typically associated with inhalation of particulate matter, including alveolar wall thickening, increased number of macrophages and increased lung weight (ATSDR 2006). A more detailed discussion of the pulmonary effects in experimental animals of inhalation exposure to aluminum oxide dust and refractory alumina fibres, and aluminum hydroxide is provided by Krewski et al. (2007). The observed responses to various species of aluminum are described as "typical of foreign body reaction", including alveolar proteinosis and wall thickening, and some nodule formation.

Dermal exposure

Dermal effects of aluminum compounds (10% w/v chloride, nitrate, chlorohydrate, sulphate, hydroxide) applied to skin of mice, rabbits and pigs over five-day periods (once per day) include epidermal damage, hyperkeratosis, acanthosis and microabscesses (ATSDR 2006; Krewski et al. 2007).

2.4.2.2 Short-term toxicity (duration of exposure less than 90 days)

Oral exposure

The results of 40 short-term studies in adult mice, rats and rabbits (exposure duration between 3 and 13 weeks) are summarized below. In all the studies considered, aluminum was administered orally in drinking water, in the diet or by gavage. The aluminum salts include lactate, chloride, sulphate, nitrate and hydroxide. In some studies citrate was administered with the aluminum salt in order to enhance absorption.

As discussed in section 2.4.2, many of the short-term studies did not quantify the concentration of aluminum in the base diet. In these cases the value of the actual combined dose is highly uncertain, particularly in the studies where the administered dose was significantly less than the possible baseline dose in the diet (e.g., Basu et al. 2000; El-Demerdash 2004; Kaizer et al. 2005; Kaur and Gill 2005, 2006; Jyoti and Sharma 2006; Sparks et al. 2006; Kaur et al. 2006). In three studies (Thorne et al. 1986; Shakoor et al. 2003; Campbell et al. 2004), ambiguities in the reporting of the doses precluded consideration of the dose-response relationship; however the qualitative observations from these studies are included in the following summary of effects.

Neurobehavioural effects in adult rats and mice following oral administration from 21 to 90 days included decreased performance in the rotarod test (Bowdler et al. 1979; Shakoor et al. 2003; Kaur et al. 2006), decreased performance in passive and active avoidance tests (Commissaris et al. 1982; Connor et al. 1988; Connor et al. 1989; Kaur et al. 2006), reduced motor activity (Commissaris et al. 1982; Golub et al. 1989; Shakoor et al. 2003), decreased forelimb and hindlimb grip strength (Oteiza et al. 1993), increased sensitivity to flicker (Bowdler et al. 1979) and air puff startle response (Oteiza et al. 1993), and reduced recovery in neurological function following spinal cord injury (Al Moutaery et al. 2000).

Of the above studies, the lowest administered dose at which effects occurred was observed by Kaur et al. (2006), in which male Wistar rats were administered 10 mg Al/kg bw/d as aluminum lactate for up to 12 weeks, with testing at 0, 4, 8 and 12 weeks. A significant decrease in performance between exposed and control groups was observed at four weeks and became more pronounced following eight weeks of exposure. Decreased performance in memory function tests (passive and active avoidance responses) was also observed in the exposed animals tested at 12 weeks.

In contrast, no alterations in passive or active avoidance test results were reported in aluminum-exposed animals, at doses of 67 mg Al/kg bw/d of aluminum chloride administered by gavage to male Sprague-Dawley rats for 28 days (Bowdler et al. 1979) and 600 mg Al/kg bw/d of aluminum nitrate administered in drinking water for 14 days to male CD mice (Colomina 1999).

Reduced body weight among aluminum-exposed animals was observed by Bataineh et al. (1998), at a dose of 15 mg Al/kg bw/d of aluminum chloride administered to male Sprague-Dawley rats in drinking water for 12 weeks. On the other hand, Colomina et al. (1999) observed a reduction in body weight only at 600 mg Al/kg bw/d of aluminum nitrate, and no effect at 300 mg Al/kg bw/d, in mice administered aluminum via drinking water for 14 days. In other short-term studies, the authors either did not observe this effect, at a dose of100 mg Al/kg bw/d administered in the diet of Swiss Webster mice (Donald et al. 1989;

Golub and Germann 1998), or did not report differences in body weight between exposed and control groups.

The most extensive histopathological changes in the short-term studies were reported by Roy et al. (1991a) in which male rats were given doses of 17 to 172 mg Al/kg bw/d as aluminum sulphate via gavage. The concentration of aluminum in the base diet was not quantified. Multifocal neuronal degeneration, abnormal and damaged neurons, and reduced neuronal density were identified in specific brain regions (e.g., cerebral cortex, subcortical region and base of brain) at 29 mg Al/kg bw/d. In the liver, Roy et al. (1991a) observed cytoplasmic degeneration in the periphery of the hepatic lobule at all doses. With increasing doses, multifocal degeneration of the entire liver tissue was observed, followed by fibrous tissue proliferation. Kidney effects observed in this study at 22 mg Al/kg bw/d included increased swelling and degeneration of the cortical tubules.

Other histopathological effects reported in different strains of rats include necrosis-like changes in hippocampal CA1 cells and accumulation of synaptic vesicles in presynaptic terminals (Jyoti and Sharma 2006), congestion of cerebral and meningeal blood vessels, multifocal neuronal degeneration, neurofibrillary degeneration and foci of demyelination (El-Rahman 2003), increased membrane fluidity and decreased cholesterol/phospholipid ratio in synaptosomes (Silva et al. 2002), increased number of vacuolated spaces in the matrix of the cerebral cortex (Basu et al. 2000), decreased NADPH-diaphorase positive neurons in the cerebral cortex (Rodella et al. 2001) and increased hippocampal muscarinic receptors (Connor et al. 1988). The lowest administered doses at which such changes occurred were in the studies of Jyoti and Sharma (2006) in which exposed male Wistar rats received a dose of 10 mg Al/kg bw/d of aluminum chloride in drinking water for five weeks, and of Basu et al. (2000), in which male Sprague-Dawley rats received 10 mg Al/kg bw/d of aluminum chloride via gavage for 40 days.

The biochemical changes to the brains of adult rodents resulting from oral administration of aluminum salts for periods of less than 90 days included effects on cholinergic neurotransmission (Kumar 1998; Shakoor et al. 2003; El-Demerdash 2004; Kaizer et al. 2005; Kaur and Gill 2006) as well as changes in the levels of other neurotransmitters and signalling proteins (Flora et al. 1991; Tsunoda and Sharma 1999b; Kumar 2002; El-Rahman 2003; Becaria et al. 2006), alterations in calcium transfer, binding and signalling in the brain (Kaur et al. 2006; Kaur and Gill 2005), evidence of oxidative stress in different regions of the brain (Fraga et al. 1990; Katyal et al. 1997; Abd el-Fattah et al. 1998; El-Demerdash 2004; Nehru and Anand 2005; Becaria et al. 2006; Jyoti and Sharma 2006), changes in ATPase activity (Katyal et al. 1997), alterations to cyclic AMP second messenger systems (Johnson and Jope 1987), increased levels of amyloid precursor protein (Becaria et al. 2006) and increased TNF-∝ (alpha tumour necrosis factor) mRNA expression in the brain (Tsunoda and Sharma 1999a; Campbell et al. 2004). The lowest administered dose at which such effects were observed was 10 mg Al/kg bw/d administered to rats as aluminum lactate via gavage or as aluminum chloride via drinking water in Kaur and Gill (2006) and Basu et al. (2000).

Inhalation exposure

The toxicological literature for short-term inhalation exposure studies is limited compared to that for oral exposure. The most recent comprehensive reviews of this literature can be found in ATSDR (2006) and Krewski et al. (2007). The most sensitive and best documented endpoints concern the respiratory system. The observed effects were those commonly associated with particle inhalation exposure (> 7 mg/m^3), including a thickening of the alveolar walls, an increase in alveolar macrophages and heterophils, granulomatous nodules and lesions, and increased lung weight (ATSDR 2006).

2.4.2.3 Subchronic and chronic toxicity (exposure duration greater than 90 days, non-cancer endpoints)

Oral exposure

The results of 49 subchronic and chronic toxicity studies (exposure greater than 90 days) in adult mice, rats, rabbits, monkeys and dogs are summarized below. In all the studies considered, aluminum was administered orally in drinking water, in the diet or by gavage. The aluminum salts include lactate, chloride, sulphate, nitrate, hydroxide, citrate, maltolate, fluoride and KASAL (basic sodium aluminum phosphate).

As in the case of the short-term studies, many of the subchronic and chronic toxicity studies did not quantify the concentration of aluminum in the base diet. In those studies where the administered dose was substantially less than the possible baseline dose in the diet, the uncertainty associated with the actual combined dose was increased (see, for example, Krasovskii et al. (1979); Fleming and Joshi (1987); Bilkei-Gorzo (1993); Varner et al. (1993); Varner et al. (1994); Varner et al. (1998); Sahin et al. (1995); Somova et al. (1997); Jia et al. (2001a); Pratico et al. (2002); Abd-Elghaffar et al. (2005); Hu et al. (2005); Becaria et al. (2006); and Li et al. (2006)).

Neurobehavioural effects in adult mice and rats, following oral exposure for 90 days or more, included decreased spontaneous motor activity (Commissaris et al. 1982; Lal et al. 1993; Jia et al. 2001a; Jia et al. 2001b; Hu et al. 2005). The lowest administered dose associated with this effect was 1 mg Al/kg bw/d as observed by Huh et al. (2005) in male Sprague-Dawley rats who received aluminum maltolate at this dose in drinking water over a period of one year[15]. In contrast Domingo et al. (1996) and Colomina et al. (2002) found no differences in field activity of Sprague-Dawley rats, where animals received an administered dose of 100 mg Al/kg bw/d of aluminum nitrate (with citrate) in drinking water for periods of four to six months. Decreased motor coordination as measured by performance in the rotarod test (Sahin et al. 1995), decreased grip strength, and effects on temperature sensitivity and negative geotaxis (Golub et al. 1992a) were also observed.

Other observed neurobehavioural effects included learning and memory deficits (maze performance, passive avoidance tests) reported by Bilkei-Gorzo (1993), Lal et al. (1993),

[15] The methodological limitations and uncertainties associated with this study are discussed in section 3.2.3.

Gong et al. (2005), Gong et al. (2006) and Li et al.(2006). The lowest administered dose associated with such effects was 6 mg Al/kg bw/d, observed by Bilkei-Gorzo (1993) in Long Evans rats exposed for 90 days to aluminum chloride (plus citrate) via gavage, although there was some ambiguity in the reporting of doses in this study. In contrast, no effects on similar learning or memory tests were observed by Varner et al. (1994), Domingo et al. (1996), Colomina et al. (2002) and von Linstow Roloff et al. (2002). In the study of von Linstow Rolloff et al. (2002) an administered dose of 140 mg Al/kg bw/d was administered to male Lister hooded rats as aluminum sulphate in drinking water.

With respect to body weight, Pettersen et al. (1990), Gupta and Shukla (1995), Colomina et al. (2002) and Kaneko et al. (2004) observed reductions in body weight in aluminum-exposed animals (rodents and dogs) at doses ranging from 25 mg Al/kg bw/d of aluminum maltolate administered in drinking water to mice for up to 120 days (Kaneko et al. 2004) to 94 mg Al/kg bw/d of aluminum nitrate administered in drinking water to rats for 114 days (Colomina et al. 2002). In the Kaneko et al (2004) study, aluminum chloride was administered to another exposure group at the same dose as aluminum maltolate, and no difference in body weight between aluminum-exposed animals and controls was observed. The authors attributed the contrasting observations to the greater bioavailability of aluminum maltolate as compared to chloride, documented as well by the greater accumulation of aluminum in the brain, liver, kidney and spleen in mice exposed to aluminum maltolate.

Histopathological effects reported in rats and mice included increased damaged or abnormal neurons in specific brain regions (e.g., cerebral cortex and hippocampus) (Varner et al. 1993; Varner et al. 1998; Abd-Elghaffar et al. 2005), neurofibrillary degeneration and vacuolization of nuclei (Somova et al. 1997), and vacuolated astrocytes and vacuolization of neuronal cytoplasm (Florence et al. 1994). The lowest administered dose in which these effects were observed was less than 1 mg Al/kg bw/d in the Varner et al. (1998) and Varner et al. (1993) studies in which aluminum nitrate and sodium fluoride (to form aluminum fluoride) was administered in drinking water to male Long Evans rats for periods of 45 to 52 weeks.[16]

Petterson et al. (1990) observed mild to moderate histopathological effects in testes, liver and kidney, including hepatocyte vacuolization, seminiferous tubule germinal epithelial cell degeneration and tubular-glomerularnephritis in beagle dogs receiving a dose of 75 mg Al/kg bw/d of sodium aluminum phosphate. In this same study, no significant differences between exposure groups and controls were observed at the lower doses of 4 to 27 mg Al/kg bw/d.

The biochemical endpoints examined in subchronic and chronic experimental studies are considerably varied, as are the methodologies used to investigate these endpoints. The observed effects included a decrease in nitrergic neurons in the somatosensory cortex (Rodella

[16] The methodological limitations and uncertainties of the Varner et al. (1993) and Varner et al. (1998) studies are discussed in section 3.2.3.

et al. 2006), perturbations in ATPase activity in the brain (Lal et al. 1993; Sarin et al. 1997; Swegert et al. 1999; Silva and Goncalves 2003; Kohila et al. 2004; Silva et al. 2005), induced apoptosis in the brain (Huh et al. 2005), effects on cholinergic enzyme activities (Bilkei-Gorzo 1993; Zheng and Liang 1998; Dave et al. 2002; Zatta et al. 2002; Kohila et al. 2004), increased cytokine levels (Becaria et al. 2006), increased catalytic efficiency of monoamine oxidases A and B (Huh et al. 2005), increased caspase 3 and 12 (Gong et al. 2005; Huh et al. 2005), increased staining for amyloid precursor protein levels (Gong et al. 2005) and amyloid beta (Aβ) levels (Pratico et al. 2002), decrease in long-term potentiation in hippocampal slices (Shi-Lei et al. 2005), and alterations in phospholipid and cholesterol levels in the myelin membrane, synaptosomes or the brain (Sarin et al. 1997; Swegert et al. 1999; Pandya et al. 2001; Silva et al. 2002; Pandya et al. 2004). The lowest administered dose associated with significant effects on biochemical endpoints was 1 mg Al/kg bw/d as administered as aluminum maltolate in drinking water for one year (Huh et al. 2005)[17].

Other biochemical and biophysical effects observed in the brains of aluminum-exposed rodents included alterations in trace metal (Cu, Zn and Mn) metabolism in the brain (Sanchez et al. 1997; Yang and Wong 2001; Jia et al. 2001a; Fattoretti et al. 2003; Fattoretti et al. 2004), altered synapses in the hippocampus and frontal cortex (Jing et al. 2004), increase in area occupied by mossy fibres in the hippocampal CA3 subfield (Fattoretti et al. 2003; Fattoretti et al. 2004), increase (Flora et al. 2003) and decrease (Jia et al. 2001a) in glutathione peroxidase activity, and increase in catalase activity (Flora et al. 2003). Increased lipid peroxidation was reported by Lal et al. (1993), Gupta and Shukla (1995), Sarin et al. (1997), Pratico et al. (2002), Flora et al. (2003) and Kaneko et al. (2004). Jia (2001a), Gupta and Shukla (1995) and Abd-Elghaffar (2005) reported decreased levels of superoxide dismutase, and Jia et al. (2001a) observed increased levels in malondialdehyde. Johnson et al. (1992) observed decreased levels of cytoskeletal proteins (microtubule associated protein-2, spectrin) in the hippocampus and brain stem.

Inhalation exposure

The toxicological literature for subchronic and chronic inhalation exposure studies is limited. ATSDR (2006) and Krewski et al. (2007) report on several studies of durations of six months (six hours a day, five days a week). The most sensitive and best documented endpoints concerned the respiratory system. The observed effects are those commonly associated with particle inhalation exposure (> 600 $\mu g/m^3$), including a thickening of the alveolar walls, and an increase in alveolar macrophages, granulomatous lesions and relative lung weight (ATSDR 2006).

[17] The methodological limitations and uncertainties associated with the study by Huh et al. (2005) are discussed in section 3.2.3.

2.4.2.4 Reproductive and developmental toxicity

Oral exposure

The results of 49 studies investigating gestational, lactational and/or post-weaning exposure of rats, mice and guinea pigs to aluminum salts through diet, through drinking water or by gavage are summarized below. The aluminum salts administered in these studies included chloride, nitrate, sulphate, lactate and hydroxide. In a few studies citrate or ascorbic acid was added to enhance absorption of aluminum.

As discussed in sections 2.4.2.2 and 2.4.2.3, the lack of information on base diet for some studies is a major source of uncertainty with respect to the potential combined dose, particularly when the administered dose was low in comparison to the possible base diet dose (e.g., Clayton et al. 1992; Ravi et al. 2000). There is also uncertainty associated with reported LOELs that are of the same magnitude as the reported LD_{50} for the administered salt (Johnson et al. 1992; Misawa and Shigeta 1993; Poulos et al. 1996; Llansola et al. 1999).

The most commonly observed neurobehavioural effects in developmental studies included decreased grip strength (Golub et al. 1992b; Golub et al. 1995; Colomina et al. 2005), reduced temperature sensitivity (Donald et al. 1989; Golub et al. 1992b), reduced or delayed auditory startle responsiveness (Misawa and Shigeta 1993; Golub et al. 1994), and impaired negative geotaxis response (Bernuzzi et al. 1986; Bernuzzi et al. 1989a; Muller et al. 1990; Golub et al. 1992b). Decreased activity levels (Cherroret et al. 1992; Misawa and Shigeta 1993), locomotor coordination (Golub et al. 1987; Bernuzzi et al. 1989a; Bernuzzi et al. 1989b; Muller et al. 1990; Golub and Germann 2001b) as well as impaired righting reflex (Bernuzzi et al. 1986; Bernuzzi et al. 1989b) were also observed, although not consistently—refer to Thorne et al. (1987), Golub et al. (1992b), and Misawa and Shigeta (1993). The lowest administered dose at which effects on these endpoints were observed was 100 mg Al/kg bw/d, observed in Wistar rats administered aluminum lactate in the maternal diet during gestation (Bernuzzi et al. 1989b) as well as in Swiss Webster mice administered aluminum lactate in the maternal diet during gestation, lactation and then in the diet of offspring throughout the lifespan (Golub et al. 2000).

The observations on the effects on learning and memory of developmental exposure to aluminum salts also varied considerably. For example, in some studies improved performance in the maze tasks was observed (Golub et al. 2000; Golub and Germann 2001a; Colomina et al. 2005) while in others impaired performance (Golub and Germann 2001b; Jing et al. 2004) or no change (Thorne et al. 1987) was found. Golub and Germann (2001b) observed diminished maze learning in Swiss Webster mice pups when dams were exposed to aluminum lactate in the diet at a combined dose of 50 mg Al/kg bw/d, but not at 10 mg Al/kg bw/d, during gestation and lactation, and pups were exposed via diet for two weeks following weaning. In this experiment, animals (controls and aluminum-exposed) were fed a sub-optimal diet, designed to simulate the usual diet of U.S. women with regard to recommended dietary amounts of trace elements.

The observations of Roig et al. (2006) suggested a biphasic effect on learning in rats exposed to aluminum nitrate during gestation, lactation and post-weaning; in a two-dose study,

the low-dose group (50 mg Al/kg bw/d of aluminum nitrate plus citrate in drinking water) performed significantly better in the water maze test than the high-dose group (100 mg Al/kg bw/d), but there was no significant difference between the high-dose group and the controls. With respect to passive avoidance tests, the same group of researchers also reported improved performance in aluminum exposed animals at an administered dose of 100 mg Al/kg bw/d (Colomina et al. 2005).

Developmental exposure of mice and rats to aluminum salts also produced some evidence of disturbances in brain biochemistry, such as alterations in brain lipid contents and increased lipid peroxidation (Verstraeten et al. 1998; Verstraeten et al. 2002; Nehru and Anand 2005; Sharma and Mishra 2006) or decreased lipid peroxidation (Golub and Germann 2000), decreased levels in superoxide dismutase (Nehru and Anand 2005), delayed expression of a phosphorylated neurofilament protein (Poulos et al. 1996), differential effects on choline acetyltransferase activity in various brain regions (Clayton et al. 1992; Rajasekaran 2000; Ravi et al. 2000), decreased serotonin and noradrenaline levels in specific brain regions (Ravi et al. 2000), decreased concentrations of manganese in brain (Golub et al. 1992b; Golub et al. 1993), alterations to signal transduction pathways associated with glutamate receptors and decreased expression of proteins of the neuronal glutamate-nitric oxide-cGMP pathway (Llansola et al. 1999; Kim 2003), and alterations in secondary messenger systems (Johnson et al. 1992). With respect to biochemical endpoints, the lowest administered dose at which effects were measured was approximately 20 mg Al/kg bw/d, observed by Kim (2003) in which male and female Fisher rats received this dose of aluminum chloride in drinking water for 12 weeks prior to mating, after which treatment at this dose continued in dams during gestation and lactation.

Chen et al. (2002), Wang et al. (2002a) and Wang et al. (2002b) reported impairment of synaptic plasticity, as measured by field potentials in the dentate gyrus of the hippocampus. Johnson et al. (1992) reported decreased levels of microtubule associated protein-2 in the brains of rat pups exposed eight weeks following weaning, although no changes in other cytoskeletal proteins were observed. A significant decrease in myelin sheath width was observed in mice pups exposed during gestation, lactation and then through the diet following weaning (Golub and Tarara 1999), and in guinea pig pups exposed prenatally from GD30 to birth (Golub et al. 2002). These effects were observed at administered doses above 85 mg Al/kg bw/d as aluminum chloride in drinking water of Wistar rat dams (Wang et al. 2002a; Wang et al. 2002b; Chen et al. 2002) and 100 mg Al/kg bw/d in the diet of Swiss Webster mice dams (Golub and Tarara 1999).

Although the focus of the majority of the investigations of prenatal exposure was neurodevelopmental toxicity, effects on some reproductive endpoints were reported as well. Golub et al. (1987), Bernuzzi et al. (1989b), Gomez et al. (1991), Colomina et al. (1992), Belles et al. (1999), Sharma and Mishra (2006) and Paternain et al. (1988) reported reduced maternal weight gain, although no change in this parameter was observed by Donald et al. (1989), Golub et al. (1993), Golub et al. (1995) and Golub et al. (1996a), nor was it reported in the other studies. In regard to pup body weight, Sharma and Mishra (2006), Wang et al. (2002a), Llansola et al. (1999), Cherroret et al. (1995), Misawa and Shigeta (1993), Gomez et al. (1991), Paternain et al. (1988), Domingo et al. (1987), Thorne et al. (1987), Golub and Germann (2001a), Colomina et al. (1992), and Bernuzzi et al. (1989a), Bernuzzi et al. (1989b)

reported decreases in aluminum-exposed groups, while other studies reported no effects (Donald et al. 1989; Clayton et al. 1992; Golub et al. 1992b; Golub et al. 1993; Golub et al. 1995; Golub et al. 1996a; Colomina et al. 1994; Verstraeten et al. 1998). The lowest administered dose at which effects on reproductive parameters, including fetal growth, were observed was 13 mg Al/kg bw/d (Paternain et al. 1988; Domingo et al. 1987a), in which Sprague-Dawley rat dams received this dose via gavage as aluminum nitrate.

Cherroret et al. (1995) reported decreased plasma concentrations of total proteins and albumin and increased plasma $\alpha 1$ globulins, which the authors attributed to an inflammation process in young rats exposed postnatally by gavage at doses of 100 to 200 mg Al/kg bw/d. The same research group also observed effects on duodenal enterocytes, with a decrease in microvilli width and significant variation in K, Ca, S and Fe concentrations (Durand et al. 1993).

Other observed reproductive/developmental effects included a decrease in the number of corpora lutea and number of implantation sites (Sharma and Mishra 2006) as well as skeletal malformations (Paternain et al. 1988; Colomina et al. 1992; Sharma and Mishra 2006). Colomina et al. (2005) reported a delay in sexual maturation in both males and females, although this effect was produced at different dose levels in the two sexes (at 50 mg Al/kg bw/d in females and at 100 mg Al/kg bw/d in males). Misawa and Shigeta (1993) observed delayed pinna detachment and eye opening in female pups.

No significant maternal or developmental toxicity, as measured by fetal weight gain, reproductive parameters or fetal malformations, was observed by McCormack et al. (1979) at a combined dietary dose of aluminum chloride of 50 mg Al/kg bw/d, nor by Gomez et al. (1990) where 265 mg Al/kg bw/d of aluminum hydroxide was administered to dams via gavage during gestation.

Inhalation and dermal exposure

No studies were identified concerning the reproductive effects of inhalation or dermal exposure to aluminum salts.

2.4.2.5 Carcinogenicity

The literature concerning oral exposure bioassays is very limited. An increase in gross tumours was reported in male rats and female mice in a one-dose study but few study details were reported (Schroeder and Mitchener 1975a, 1975b, as reported in ATSDR 2006). Two other studies reported no increased incidence of tumours in rats and mice exposed orally to aluminum compounds (Hackenberg 1972; Oneda et al. 1994).

No increased tumour incidence was observed in rats following inhalation of alumina fibres at concentrations of up to 2.45 mg/m^3 (Krewski et al. 2007).

The International Agency for Research on Cancer did not classify specific aluminum compounds for carcinogenicity, but classified the exposure circumstances of aluminum production as carcinogenic to humans (Group 1) (IARC 1987).

2.4.2.6 Genotoxicity

The genotoxicity of various aluminum compounds is described in detail by Krewski et al. (2007) and ATSDR (2006). Briefly, aluminum compounds have produced negative results in most short-term in vitro mutagenic assays, including the Rec-assay using *Bacillus subtilis*, in *Salmonella typhimurium* TA92, TA 98, TA102, TA104 and TA1000 strains (with and without S9 metabolic activation), and in *Escherichia coli* (see Krewski et al. 2007).

In vitro studies of rat ascites hepatoma cells reported that aluminum chloride could serve as a stimulator for the crosslinking of chromosomal proteins (Wedrychowski et al 1986a, 1986b, as reported in Krewski et al. 2007, ATSDR 2006). Studies on human blood lymphocytes showed that aluminum chloride could induce positive responses for both micronuclei formation and sister chromatid exchange (see Krewski et al. 2007).

More recently Lima et al. (2007) investigated the genotoxic effects of aluminum chloride in cultured human lymphocytes. Comet assay and chromosome aberrations analysis were used to evaluate DNA-damaging and clastogenic effects of aluminum chloride at different phases of the cell cycle. All tested concentrations (5 to 25 μM aluminum chloride) were cytotoxic, reduced the mitotic index, induced DNA damage and were clastogenic in all phases.

Roy et al. (1991) administered doses of aluminum sulphate and potassium aluminum sulphate in drinking water to male rats at doses ranging from 17 to 171 mg Al/kg bw/d for up to 21 days. The frequency of abnormal cells increased in direct proportion to both the dose and the duration of exposure to the aluminum salts. Most aberrations were chromatid breaks, with translocations recorded at higher doses.

In a recent review of the safety of aluminum from dietary intake, EFSA (2008) summarized indirect mechanisms that might explain the genotoxic effects observed in experimental systems. The proposed mechanisms included cross-linking of DNA with chromosomal proteins, interaction with microtubule assembly and mitotic spindle functioning, induction of oxidative damage, and damage of lysosomal membranes with liberation of DNAase to explain the induction of structural chromosomal aberrations, sister chromatid exchanges, chromosome loss and formation of oxidized bases in experimental systems. EFSA (2008) suggested that these indirect mechanisms of genotoxicity, occurring at relatively high levels of exposure, would not likely be of relevance for humans exposed to aluminum via the diet.

2.4.3 Human studies

In this section, information on the potential human health effects associated with aluminum exposure is briefly summarized with the goal of describing the range of potential effects. As such, various exposure routes are considered in order to identify the possible target organs. This information includes data from case studies, epidemiological investigations into the potential health effects of exposure to aluminum in drinking water, occupational investigations of exposure to aluminum dust and welding fumes, and exposure to aluminum via vaccines and of dermal application of aluminum-containing antiperspirants.

In section 3.2.2 an evaluation of these health effects is presented, in order to: (a) identify critical effects; and (b) determine which, if any, of the human studies may be used to estimate the dose-response relationship. The latter determination is based on the strength of the available evidence and the relevance of the studies to environmental exposure in the general Canadian population.

2.4.3.1 Human case studies of exposure to aluminum

Human cases studies of aluminum toxicity have been well documented for specific medical conditions, most frequently in patients with renal impairment undergoing dialysis with aluminum-contaminated dialysate or receiving medications with elevated aluminum concentration. A small number of case studies or investigations have focused on children and pre-term infants receiving parenteral nutrition. Although the effects in particular sub-groups of susceptible individuals are not representative of exposure conditions for the general population, they are presented in order to identify the target organs of aluminum exposure. A more detailed discussion of these human case studies is presented in the comprehensive reviews InVS-Afssa-Afssaps (2003) and Krewski et al. (2007). As well, a case study is described below in which exposure to aluminum was associated with the accidental discharge of aluminum into the municipal water supply.

Aluminum toxicity in patients with renal impairment

Historically, patients undergoing dialysis treatment were exposed to aluminum through the water used to prepare dialysis solutions and from aluminum compounds prescribed as phosphate binders (Krewski et al. 2007). Today, this exposure is strictly controlled.[18] However, in the past, many cases of aluminum-induced encephalopathy, resulting in alterations in behaviour and memory, speech disorders, convulsions and muscle-twitching occurred in dialysis patients (Foley et al. 1981; Alfrey 1993). In cases of intoxication, the aluminum was introduced into the systemic circulation through the dialyzing membrane (in hemodialysis) or abdomen (in peritoneal dialysis) thus bypassing the gastrointestinal barrier, and was therefore completely available at the cellular level. The effects of elevated aluminum exposure in dialysis patients has provided clear evidence for the neurotoxicity of aluminum in humans.

Researchers have also identified cases of individuals with impaired renal function who, because of their reduced capacity to eliminate aluminum and chronic high exposure to aluminum-containing medications, also developed encephalopathy, even though they were not undergoing dialysis (Foley et al. 1981; Sedman et al. 1984; Sherrard et al. 1988; Moreno et al. 1991). A fatal case of aluminum-induced encephalopathy occurred in a patient with chronic renal failure who did not have dialysis treatment, but who consumed large doses of aluminum-containing antacids (Zatta et al. 2004).

[18] Cases of elevated aluminum exposure in dyalisis patients are rare, but are still occasionally reported. See www.cdc.gov/mmwr/preview/mmwrhtml/mm5725a4.htm for a recent example.

Other toxic effects of aluminum observed in dialysis-exposed patients include haematological effects such as anaemia (Bia et al. 1989; Yuan et al. 1989; Shah et al. 1990; Caramelo et al. 1995) and skeletal toxicity (osteomalacia and osteitis fibrosis) (Mathias et al. 1993; Jeffery et al. 1996; Ng et al. 2004).

Aluminum exposure via intravenous nutritional support

Klein (2005) reviewed the human evidence regarding the effects of aluminum exposure via solutions used for intravenous nutritional support with regard to effects on bone (osteomalacia) and the central nervous system. With respect to parenteral nutrition, infants may be a particularly sensitive sub-group because of the immaturity of the blood-brain barrier and renal excretory mechanisms. Bishop et al. (1997) investigated cognitive impairment in pre-term infants in relation to parenteral nutrition. In a randomized trial the researchers found that performance in neurodevelopmental testing conducted at 18 months was significantly better in 92 pre-term infants who had received a low-aluminum nutritional solution as compared to 90 pre-term infants receiving a standard solution with higher aluminum content. No follow-up testing that evaluated cognitive performance in the children of this cohort as they aged was identified.

Investigation of aluminum exposure associated with contamination event in Camelford, UK

Exley and Esiri (2006) reported an unusual case of fatal dementing illness in a 58-year-old woman, resident of Camelford, Cornwall, in the United Kingdom. Fifteen years earlier, at the age of 44 years, this person was exposed to high concentrations of aluminum sulphate in drinking water, which had been accidentally discharged in the drinking water supply of the region. During this event, up to 20,000 people were exposed to aluminum concentrations in drinking water varying from 100 to 600 mg/L. At the autopsy of the woman, a rare form of sporadic early-onset b-amyloid angiopathy in the cerebral cortical and leptomeningeal vessels, and in leptomeningeal vessels over the cerebellum was identified. Coincident high concentrations of aluminum were also found in the severely affected regions of the cortex. To date, this remains the only documented case. Exley and Esiri (2006), who reported this case, state that the role of aluminum is uncertain but may be clarified through future research in similarly exposed and unexposed populations (controls).

2.4.3.2 Epidemiological studies of aluminum exposure via drinking water

By the end of the 1980s, four epidemiological studies with an ecological design (i.e., using group rates of exposure and disease) had reported positive associations between the concentration of aluminum in drinking water and the occurrence of Alzheimer's disease (AD) or of dementia (Vogt 1986; Martyn et al. 1989; Flaten 1990; Frecker 1991). These observations resulted in further research into the relationship of aluminum in drinking water and various dementia syndromes, particularly AD.

Epidemiological studies based on observations of individuals were conducted in the 1990s with the aim of investigating the association between AD or other cognitive dysfunctions and exposure to aluminum in drinking water. Health Canada published a comprehensive review of epidemiological studies in Guidelines for Canadian Drinking Water

Quality - Technical Documents: Aluminum (Health Canada 1998b) and in the SOS report of 2000. The discussion presented below summarizes the information presented in the previous reviews and presents more recently published findings of the eight-year follow-up analysis of a large cohort in southwestern France (Rondeau et al. 2000; Rondeau et al. 2001). The study designs and findings of the relevant epidemiological studies are presented in Table B1 (Appendix B). These data have also been described in detail in Krewski et al. (2007) and InVS-Afssa-Afssaps (2003). Analysis of the epidemiological database and its applicability in a quantitative risk assessment is presented in the Hazard Characterization of this assessment (section 3.2.2.1).

Twelve studies are presented in Table B1, based on case-control, cross-sectional, or longitudinal designs. The observations from two Ontario case-control studies are drawn from the same study population—the Ontario Longitudinal study of Aging (LSA)—and all the French studies were based on observations from the "Principal lifetime occupation and cognitive impairment in a French elderly cohort" or PAQUID cohort. However, the LSA and PAQUID study populations differ with respect to the case definition and the manner of diagnosis of disease. In the PAQUID investigations, the earlier studies used a case-control design whereas the more recent studies by Rondeau et al. (2000) and Rondeau et al. (2001) used a cohort incidence analysis.

Positive findings for an association between aluminum exposure and AD or other neurological dysfunctions were found to be statistically significant ($p < 0.05$) in seven of the twelve studies, although the strength and significance of these associations depended on how the data were analysed (see Appendix B) These seven studies were carried out in Ontario (Neri and Hewitt 1991; Forbes et al. 1992; Forbes et al. 1994; Forbes et al. 1995a; Forbes et al. 1995b; Neri et al. 1992; Forbes and Agwani 1994; Forbes and McLachlan 1996; McLachlan et al. 1996), in Quebec (Gauthier et al. 2000) and in France (Michel et al. 1991; Jacqmin et al. 1994; Jacqmin-Gadda et al. 1996; Rondeau et al. 2000; Rondeau et al. 2001).

In Ontario, a series of analyses was conducted on the LSA cohort to investigate the relationship between the concentration of aluminum in drinking water and cognitive impairment, as established by interviews and questionnaires (Forbes et al. 1992; Forbes et al. 1994; Forbes et al. 1995a; Forbes and Agwani 1994). These authors observed statistically significant associations only when they controlled their analyses according to certain physical-chemical parameters of water, such as fluoride, pH, and silica. Since the methods of interviews and questionnaires for characterizing cognitive functions were deemed to be insufficiently specific for accurately detecting neurological impairments, Forbes et al. (1995b) and Forbes and McLachlan (1996) consulted death certificates from individuals on the LSA cohort and examined the association between aluminum in drinking water and AD or presenile dementia as categorized by the corresponding ICD[19] codes. Positive relationships between aluminum and AD and presenile dementia were reported with and without adjustments with different

[19] International Classification of Disease (World Health Organization).

water quality parameters. For instance, some of the highest risks for AD were observed when high concentrations of aluminum (≥ 336 µg Al/L) were combined with high pH (≥ 7.95), low levels of fluoride (< 300 µg/L) or low levels of silica (< 1.5 mg/L).

Neri and Hewitt (1991) and Neri et al. (1992) reported a significant dose-response relationship between AD or presenile dementia and aluminum using hospital discharge records from Ontario, and by matching cases and controls according to age and sex. Another study from Ontario was a case-control analysis from the Canadian Brain Tissue Bank cohort in which AD was confirmed by histopathological criteria (McLachlan et al. 1996).

Although all studies from Ontario assessed the exposure of aluminum based on the data of the water quality surveillance program of the Ontario Ministry of the Environment, only McLachlan et al. (1996) evaluated the past exposure to aluminum.[20] However, in the McLachlan et al. (1996) study, the analysis was not controlled for potential confounders and modifying factors (e.g., age, sex, education and occupation), and the significant positive associations were not adjusted for other chemical or physical parameters in water.

The single study from Quebec was a case-control analysis of AD and exposure to various aluminum species in residential drinking water (Gauthier et al. 2000). The diagnosis of AD was based on a three-step procedure to discriminate between AD and other neurological disorders. In addition to controlling for a number of confounding factors as well as the aluminum speciation, these authors took into account historical exposure to aluminum in drinking water. Gauthier et al. (2000) reported 16 odds ratios (OR) but observed only one significant positive association (i.e., OR > 1), which was related to the concentration of monomeric organic aluminum in drinking water. This significant association was found, however, when only current exposure was considered, and not for long-term exposure, which would be expected to be more biologically-relevant.

The three studies conducted on populations from the United Kingdom showed no significant association between aluminum concentration in drinking water and neurological dysfunction, following adjustment for sex and age (Wood et al. 1988; Forster et al. 1995; Martyn et al. 1997), but none of these authors adjusted their statistical tests according to the physical-chemical properties of the drinking water. The health outcome in the two case-control studies was AD, diagnosed by a three-step procedure for including cases of presenile dementia (Forster et al. 1995) or by a clinical diagnosis using unspecified criteria (Martyn et al. 1997). This latter study, which took into account past exposure, also did not observe differences between cases and controls when the analyses were restricted to subjects exposed to low levels of silica in drinking water (< 6 mg/L). The cross-sectional study of Wood et al.

[20] Present exposure (i.e., exposure based on residence at the time of the study or at the time of diagnosis) may poorly characterize the exposure relevant to development of the disease, if the subject has moved frequently in the past, or in the case of a historical change in the water supply (i.e., change in water supply or treatment process).

(1988) was based on data collected from patients from northern England with hip fractures, for whom dementia was evaluated (no information about the diagnostic tests).

The study from Switzerland (Wettstein et al. 1991), which was a cross-sectional examination of mnestic skills in octogenarians from Zurich and aluminum in drinking water, also reported no significant associations when controlling for socio-economic status, age, and education. It should be noted that the high-exposure district in this study had drinking water with a mean aluminum concentration of 98 μg/L. Thus the analysis was carried out for a drinking water supply that was generally lower in aluminum than the drinking water supplies considered in the other investigations.

All the studies from France were based on the PAQUID cohort. The studies of Michel et al. (1991) and Rondeau et al. (2001), reported significant positive associations between the exposure to aluminum in drinking water and the occurrence of AD or dementia diagnosed by a two-step procedure, whereas the positive associations reported by Jacqmin et al. (1994) and by Jacqmin-Gadda et al. (1996) were based on the scores of the Mini-Mental State Examination (MMSE). The results of Michel et al. (1991) have been discounted, however, because of a reliance on potentially unreliable historical information on drinking water concentrations (Jacqmin et al. 1994; Smith 1995; WHO 1997).

Jacqmin et al. (1994) and Jacqmin-Gadda et al. (1996) analysed the same database collected from the PAQUID cohort in different ways, with inconclusive results. The first study included an initial report of the effect of pH on the association between aluminum and cognitive impairment (Jacqmin et al. 1994). Without considering the effect of the pH-aluminum interaction, these authors reported a positive association between aluminum and cognitive impairment, whereas consideration of this interaction resulted in a negative association. These results remained statistically significant only if occupation was included in the logistic regressions. Jacqmin-Gadda et al. (1996) expanded their analyses to include the levels of silica in drinking water. While their results indicate a protective effect of aluminum against cognitive impairment with high level of silica (≥ 10.4 mg/L) and high pH (≥ 7.5), the consideration of the interaction of aluminum and silica in their logistic regression suggests an adverse effect of aluminum on neurological functions.

Rondeau et al. (2000) retained the unimpaired subjects in the studies of Jacqmin et al. (1994) and Jacqmin-Gadda et al. (1996), and evaluated the incidence of dementia and AD one, three, five and eight years after the initial MMSE. This follow-up analysis reported a positive association between aluminum and AD or dementia, after adjustment for age, sex, education and place of residence as well as for consumption of wine and bottled mineral water. This study addressed some of the limitations of previous epidemiological investigations by adjusting for the potential confounders, and while exposure levels were not weighted according to residential history, residential history was considered. At baseline, 91% of the subjects had lived more than ten years in the same parish, with a mean length of residence of 41 years. A total of 3,401 participants were included in the study at baseline, although only 2.6% of the subjects were exposed to an aluminum concentration greater than 100 μg/L. Nonetheless, the associations between aluminum in drinking water and dementia, and aluminum in drinking water and AD, were highly significant. Only two exposure groups

(< 100 μg/L or > 100 μg/L) were defined in the principal analysis and no dose-response relationship was found when exposure categories were more finely divided.

Many of the epidemiological studies investigating the association between aluminum in drinking water and the development of cognitive impairment or AD did not control for important potential confounders or modifying factors, or did not adequately characterize past exposure. The Rondeau (2000) study addressed some of these limitations. However, the subjects in the cohort were not generally exposed to high levels of aluminum (97% of subjects exposed to less than 100 μg/L), and within the limited exposure range, no dose-response relationship was observed.

2.4.3.3 Epidemiological investigations of exposure to aluminum in antacids, antiperspirants or food

Only very weak or no associations have been found between repeated exposures to aluminum in antacids and AD in a number of analytical epidemiological studies (Heyman et al. 1984; Graves et al. 1990; Flaten et al. 1991; CSHA 1994; Forster et al. 1995; Lindsay et al. 2002). Positive associations between AD and the use of aluminum containing antiperspirants were reported in two case-control studies, but the interpretation of the results is difficult due to methodological limitations of the studies (e.g., missing data, and misclassification due to varying brands and subtypes of antiperspirant with varying aluminum contents) (Graves et al. 1990; CSHA 1994). This positive observation, however, was not supported by a follow-up study on the CSHA[21] cohort (Lindsay et al. 2002); the results show that regular use of antiperspirant did not increase the risk of AD.

Rogers and Simon (1999) conducted a pilot study to examine dietary differences in individuals with AD and matched controls (n = 46: 23 subjects, 23 controls). The exposure assessment was based on questionnaires to determine past dietary habits. According to the authors, there may be an association between AD and the consumption of foods containing high levels of aluminum food additives. However, the sample size was very small and the association was statistically significant only for one category of food (pancake, waffle and biscuit).

2.4.3.4 Epidemiological investigations of exposure to aluminum in vaccines

Aluminum adjuvants are included in some vaccines to enhance and extend the immune response of some antigens. Aluminum hydroxide and phosphate salts as well as aluminum sulphate can be used as an adjuvant (Eickhoff and Myers 2002).

Possible associations between AD and historical exposure to vaccines have been investigated in the CSHA cohort (Verreault et al. 2001). Exposure to conventional vaccines appears to lower the risk of developing AD. After adjustments for age, sex and education, the ORs were 0.41 (95% CI 0.27–0.62) for the diphtheria or tetanus vaccines, 0.60 (95% CI 0.37–

[21] Canadian Study of Health and Aging.

0.99) for the poliomyelitis vaccines and 0.75 (95% CI 0.54–1.04) for the influenza vaccine. Except for the influenza vaccine, all others contain aluminum-adjuvants (Eickhoff and Myers 2002).

The possible links between the hepatitis B vaccine, which contains aluminum-adjuvants, and the risk of demyelinating diseases such as multiple sclerosis (MS) have been investigated in France (Touze et al. 2000; Touze et al. 2002), England (Sturkenboom et al. 2000; Hernan et al. 2004), the U.S. (Zipp et al. 1999; Ascherio et al. 2001), Canada (Sadovnick and Scheifele 2000) and Europe (Confavreux et al. 2001). Only the study of Hernan et al. (2004) observed a significant positive association between MS and the hepatitis B vaccine, but no association between MS and the tetanus or influenza vaccines, which also contain aluminum adjuvants.

2.4.3.5 Epidemiological investigations of occupational exposure to aluminum

Subclinical neurological effects have been observed in a number of studies of workers chronically exposed to aluminum (aluminum potroom and foundry workers, welders, and miners). Many of these studies involved small numbers of workers and involved the assessment of exposure based on occupation rather than measured airborne aluminum concentrations, and most involved mixed exposures to various dusts and chemicals. Endpoints examined in different studies varied and for those that were similar, results were not always consistent. The types of neurological effects observed included impaired motor function (Hosovski et al. 1990; Sjogren et al. 1996; Kilburn 1998), decreased performance on cognitive tests (attention, memory, visuospatial function) (Hosovski et al. 1990; Rifat et al. 1990; Bast-Pettersen et al. 1994; Kilburn 1998; Akila et al. 1999), subjective neuropsychiatric symptoms (Sjogren et al. 1990; White et al. 1992; Sim et al. 1997) and quantitative electroencephalographic changes (Hanninen et al. 1994).

In one case-control study from England (Salib and Hillier 1996) and two from the U.S. (Gun et al. 1997; Graves et al. 1998), the relationship between the occurrence of AD and occupational exposure to aluminum was investigated. In each study, disease status was defined by standard criteria (e.g., NINCDS-ADRDA and/or DSM),[22] and exposure to airborne aluminum (e.g., welding fumes, dusts and flakes) was assessed through occupational history questionnaires administered to informants. In none of these studies was there a significant association between occupational exposure to airborne aluminum and AD.

A four-year longitudinal study investigated neurobehavioural performance in 47 aluminum welders in the train and truck construction industry, with a control group drawn from assembly workers in the same industry (Kieswetter et al. 2007). Exposure to aluminum in dust was assessed through total dust collected on filter samples attached to the welders'

[22] NINCDS is the National Institute of Neurological and Communicative Disorders and Stroke; ADRDA is the Alzheimer's Disease and Related Disorders Association; DSM is the Diagnostic and Statistical Manual of Mental Disorders (published by American Psychiatric Association).

helmets as well as through biomonitoring (aluminum in plasma and urine) at the time of neurobehavioural testing (start of investigation, after two years, after four years). The battery of neurobehavioural tests included an evaluation of cognitive abilities, psychomotor performance, attention and memory. This study used a small number of participants to explore the potential use of different biomonitoring measures, dust levels and exposure duration to predict performance in neurobehavioural tests. The study was not designed to find a relationship if one existed, but rather to explore the use of different exposure measures. Although exposure to aluminum among the welders was considered to be high in comparison to other occupational studies of aluminum (88 to 140 μg Al/g creatinine in urine, or approximately 103 to 164 μg Al/L),[23] no association between exposure and neurobehavioural performances was found.

A meta-analysis was conducted for nine investigations of occupational aluminum exposure and neurobehavioural performance, with a total of 449 exposed subjects with mean urinary aluminum concentrations of 13 to 133 μg Al/L (Meyer-Baron et al. 2007). Even if almost all effect sizes indicated an inferior neurobehavioural performance of the exposed group to aluminum, only one out of ten performance variables (the digit symbol test) was statistically significant. However, the statistical significance of the digit symbol results relationship to aluminum exposure was reduced when one study, in which the biomonitoring measure was estimated on the basis of an uncertain conversion factor, was excluded from the analysis. The authors concluded that with respect to occupational exposure, as indicated by urinary concentrations of less than 135 μg Al/L, there is concurring evidence of an impact on cognitive performance and acknowledge that international standardization for exposure is needed.

2.4.4 Mode of action of toxic effects of aluminum

Information related to possible modes of action by which aluminum affects the nervous system, as explored in animal and human studies, has been discussed in a number of recent reviews (Strong et al. 1996; Savory 2000; Kawahara 2005; ATSDR 2006; Savory et al. 2006; Krewski et al. 2007; Shcherbatykh and Carpenter 2007; Goncalves and Silva 2007). In addition, Jeffery et al. (1996) and Krewski et al. (2007) consider the mode of action in relation to bone and hematopoietic tissue.

The mechanism of aluminum neurotoxicity is an area of active research, with multiple lines of investigation. The purpose of the present discussion is to briefly summarize the areas of investigation relating to mode of action of aluminum toxicity, as mostly tested in laboratory rodents or in vitro studies, and present the range of views regarding the relevance of these data to human neurodegeneration, and particularly the development of AD.

[23] Meyer-Baron et al. (2007) propose a conversion factor of 1.17 to obtain μg Al/L from μg Al/g creatinine, determined as the mean of reported conversion factors between 0.71 and 1.61.

Neurotoxic effects

There is evidence from studies in both laboratory animals and humans that absorbed aluminum is distributed to the brain, particularly the cerebral cortex and hippocampus. For example, the accumulation of aluminum in the brains of adult mice, rats and monkeys from the exposed groups was reported in 23 studies of neurological effects of orally administered aluminum (described in section 2.4.2).[24] Increased aluminum in the brains of pups exposed only during pregnancy was observed by Sharma and Mishra (2006), but not by others (Colomina et al. 2005; Golub et al. 1992b). Other studies of prenatal exposure in which exposure continued through lactation also reported increased aluminum in the brain (Wang et al. 2002a; Chen et al 2002; Golub et al. 1993). In contrast, Golub et al. (2000) observed decreased aluminum levels in the brains of mice exposed during gestation, lactation and through their lifespan.

Other research documenting the distribution of aluminum in the brain is described in section 2.3.3.2.

The research on aluminum neurotoxicity in laboratory animals has generally focused on the following interrelated categories of biochemical and cellular effects:

- peroxidation of membrane lipids and other sources of oxidative stress;
- increased inflammatory response;
- alterations in the lipid/phospholipid composition of myelin, with consequent effects on neurotransmission and synaptic function;
- impaired glucose metabolism;
- effects on neurotransmission, including cholinergic and glutamatergic systems;
- alterations to second messenger systems (e.g., inositol triphosphate, cAMP and Ca^{2+});
- accumulation of intracellular calcium;
- accumulation of mitochondrial Ca^{2+}, resulting in release of cytochrome c and subsequent apoptosis;
- perturbation in the distribution and homeostasis of essential metals with potential adverse metabolic effects;
- alteration of phosphorylation level of neurofilaments, including phosphorylation of tau-protein, and resulting neurofibrillary tangle formation;
- inhibition of axonal transport;
- accumulation of amyloidβ peptide;

[24] Studies showing accumulation of aluminum in brain regions include Flora et al. (1991, 2003), Golub et al. (1992a), Lal et al. (1993), Varner et al. (1993, 1994, 1998), Florence et al. (1994), Gupta and Shukla (1995), Domingo et al. (1996), Sarin et al. (1997), Somova et al. (1997), Zheng and Liang (1998), Colomina et al. (1999), Kumar (1999), Swegert et al. (1999), Jia et al. (2001a), Baydar et al. (2003), Fattoretti et al. (2004), Jing et al. (2004), Abd-Elghaffar et al. (2005), Huh et al. (2005), Kaur et al. (2006) and Roig et al. (2006).

- alterations in gene expression and binding to DNA;
- alterations to the permeability of the blood-brain barrier.

There has been some effort to integrate the evidence for the above biochemical effects into a common mechanism, or at least a group of mechanisms of action for the neurotoxicity of aluminum (for example, see Kawahara (2005) and Shcherbatykh and Carpenter (2007)). Strong et al. (1996) argued that "a single unifying mechanism of aluminum neurotoxicity that will encompass all the potential means by which aluminum acts at the cellular level probably does not exist." These authors did, however, propose the following general categories by which aluminum neurotoxicity may be characterized, as a means for focusing future research on mechanisms of action:

- the induction of cytoskeletal pathology in the form of neurofilamentous aggregates: the mechanisms of this induction include those at the level of gene expression to altered post-translational processing (phosphorylation or proteolysis) of neurofilaments;

- alterations in cognition and behaviour in the absence of cytoskeletal pathology but with significant neurochemical and neurophysiological modifications: these include effects on cholinergic activity, signal transduction pathways and glucose metabolism;

- developmental neurotoxicity: research into this lifestage could focus on whether the mechanisms of action of aluminum that have led to neurobehavioural alterations in the developing fetus are similar to those responsible for toxicity in the adult as well as the nature of these alterations (permanent versus transient).

The relationship between the mechanism of aluminum neurotoxicity in animals and to the potential mechanism in AD remains an important topic of discussion. This is a complex debate as the basic cellular mechanism for AD is not clear. The presence of senile plaques composed of Aβ peptides in the brains of individuals with AD is well-documented, but the means by which these peptides produce neurotoxicity is not known (Marchesi 2005). Superimposed on the debate on the mechanisms for AD is the controversy as to whether environmental exposure to aluminum could contribute to the development of AD. The recent literature includes arguments across the spectrum, from the view that no compelling evidence for the "aluminum hypothesis" exists today (Becking and Priest 1997; Wisniewski and Lidsky 1997) to the view that the different animal and epidemiological evidence suggest that environmental aluminum may indeed be an important contributing factor for AD and that it is important not to prematurely reject this hypothesis (Yokel 2000; Gupta et al. 2005; Kawahara 2005; Exley 2006; Miu and Benga 2006; Savory et al. 2006). The proponents of further investigation into the role of aluminum in the development of AD cite the following lines of evidence, in addition to the epidemiological evidence described in section 2.4.3.2. For each of these points, the counter arguments that have been put forward are also noted:

- Increased aluminum in the whole brains of AD individuals at autopsy, as compared to age-matched non-AD brains, has been observed in some studies,

although not in others. Investigations focusing on the measurement of aluminum in the senile plaques and neurofibrillary tangles of AD brains have also produced variable results, possibly as a result of difficulties and differences of the analytical methods used (Environment Canada and Health Canada 2000; Yokel 2000).

- Aluminum injected into the brain or spinal cord of certain species (e.g., rabbit, cat, guinea pig and ferret) produce effects that have some similarities to AD pathology, although there are significant differences as well.

  For example, abnormally phosphorylated tau is the principal protein of the paired helical filaments that make up the neurofibrillary tangles that are characteristic of AD. Aluminum-induced phosphorylation of tau protein has been demonstrated in some in vitro and in vivo studies (Yokel 2000; Savory et al. 2006). Yet, although aluminum induces neurofilament aggregates in model species, these differ structurally from neurofibrillary tangles that are diagnostic of AD in humans.

  The deposition of senile plaques, a hallmark of AD, is not observed in animal models, but increased immunoreactivity to Aβ and its parent molecule, amyloid precursor protein, via aluminum has been demonstrated in both in vitro and in vivo studies (Environment Canada and Health Canada 2000).

- Dialysis encephalopathy (see section 2.4.3.1 for discussion) is clearly recognized as resulting from aluminum intoxication. This condition has provided clear evidence for the neurotoxicity of aluminum in humans. Nonetheless, the very different clinical symptoms and progression of the two diseases as well as their differing pathologies have been cited as evidence of a lack of causal relationship between aluminum and AD (Wisniewski and Lidsky 1997).

  In a study investigating the morphological alterations in the brains of 50 patients with a history of chronic renal failure and long-term hemodialysis, Reusche et al. (2001) evaluated the degree of changes generally associated with dialysis-associated encephalopathy (DAE) (Al-containing inclusions in glia and neurons) and those associated with AD (βA4 amyloid and AD-type neurofibrillary tangles), and compared to the brains of age-matched patients with a record of heart attacks or carcinomas, and without evdidence of neurological disease. Cumulative aluminum ingestion was estimated through records of prescription of aluminum-containing drugs (dialysis was not considered a significant source of aluminum exposure in these patients). A statistically significantly association between the degree of DAE-related morphological change and cumulative aluminum ingestion was observed, whereas no such association was observed with respect to the less frequently observed AD-type morphological change, and no significant difference between controls and patients was observed with respect to AD morphology. The authors concluded that exposure to aluminum through long-term ingestion of aluminum-containing drugs does not result in AD morphological changes.

Bone toxicity

In the case of osteomalacia associated with aluminum exposure, two distinct mechanisms of actions are recognized (ATSDR 2006). Firstly, the oral exposure to high levels of aluminum can produce a complex with dietary phosphorus, impairing gastrointestinal absorption of this element necessary for bone mineralization. Secondly, the osteomalacia associated with increased bone concentrations of aluminum, principally located at the mineralization front, is associated with increased mineralization lag time, increased osteoid surface area, low parathyroid hormone levels, and elevated serum calcium levels (ATSDR 2006).

Hematopoetic tissue

Among patients with chronic renal failure who receive dialysis treatment, some individuals will develop a hypochromic microcytic anemia, the severity of which correlates with the plasma and red blood cell aluminum levels and can be reversed by terminating exposure to aluminum or by aluminum chelation with desferrioxamine (Jeffery et al. 1996). While the mechanism for this effect in dialysis patients is not known, Jeffery et al. (1996) suggest that it may be aluminum interference with iron metabolism, possibly through disruption in cellular transfer of iron to ferritin to heme.

3 ASSESSMENT OF "TOXIC" UNDER CEPA 1999

3.1 CEPA 1999 64(a) and 64(b) Environment

3.1.1 Environmental risk characterization

The approach taken in the ecological component of this risk assessment was to review new information relevant to the three aluminum salts recommended for assessment by the Ministers' Expert Advisory Panel (i.e., aluminum chloride, aluminum nitrate, aluminum sulphate), and to evaluate this information with reference to the original characterization of potential risk presented in Environment Canada and Health Canada (2000).

Environment Canada and Health Canada (2000) identified the pelagic, benthic and soil compartments as primary media of potential exposure for aluminum derived from the three salts subject to assessment, and conducted an analysis of potential risk for each compartment. This analysis is provided in the sections below, along with additional information collected subsequent to the publication of the 2000 assessment and deemed relevant to the evaluation of potential risk.

3.1.1.1 Aquatic organisms

3.1.1.1.1 Pelagic

Environmental exposure in water to aluminum from the three aluminum salts is expected to be greatest in areas near direct releases of process wastewater to the aquatic environment. Unfortunately, few measured data are available for receiving environments following direct releases from water treatment facilities or pulp and paper mills. In addition, measurements of total concentrations of a metal can rarely be correlated directly with their biological effects. Metal in particulate form is generally considered to be less available for uptake by organisms, and the formation of complexes with inorganic (e.g., OH^-, SO_4^{2-}) or organic (e.g., fulvic acid) ligands can reduce the available fraction of the dissolved form of a metal. Speciation modelling using the estimation models MINEQL+ and WHAM was conducted in order to estimate the level of dissolved inorganic monomeric aluminum present in rivers following release of wastewater from eight DWTPs and two pulp and paper plants (Germain et al. 2000). The modelling provided results in the pH range of 6.56 to 8.38 and therefore the dissolved monomeric aluminate ion, $Al(OH)_4^-$, would be the predominant aluminum species present (see Figure 2.1). As indicated in Section 2.4.1, dissolved inorganic monomeric aluminum is considered to have the highest bioavailability to aquatic species and to present the greatest risk of adverse effects to pelagic organisms. The level of dissolved inorganic monomeric form of aluminum was calculated, using aluminum levels estimated in effluents (Fortin and Campbell 1999) and assuming a 1:10 dilution. For the DWTPs considered, average concentrations of dissolved inorganic monomeric forms of aluminum (which are assumed to be the bioavailable forms) at saturation varied from 0.027 to 0.348 mg/L during backwash events, assuming that microcrystalline gibbsite is controlling the aluminum solubility. According to Hem and Robertson (1967), microcrystalline gibbsite controls aluminum solubility at pH values of less than 7, while the precipitate formed when the pH of water is in the 7.5–9.5 range has a solubility similar to that of boehmite. This precipitate will evolve to bayerite, a more stable and insoluble form of aluminum hydroxide, within a week. If it

is assumed that boehmite is controlling the solubility, dissolved aluminum levels would be lower, ranging from 0.005 to 0.059 mg/L (Fortin and Campbell 1999). For the two pulp and paper mills considered, the dissolved aluminum values were among the lowest, whatever form is controlling the aluminum solubility.

The calculated dissolved aluminum concentration of 0.348 mg/L represents the saturation concentration, assuming that microcrystalline gibbsite controls solubility when aluminum salts are used to treat drinking water. This value was calculated for a location in the Canadian Prairies, where the pH of receiving waters (8.38) and solubility were the highest of all sites examined (Fortin and Campbell 1999). Backwash events can be considered to last for about 30 minutes and occur every 48 to 72 hours for each filter at a DWTP (Environment Canada and Health Canada 2000). If it is assumed that most DWTPs have about 20 filters (small DWTPs have fewer filters), it is estimated that concentrations in receiving waters near the point of discharge could be as high as 0.348 mg/L as much as 10% of the time. The rest of the time, aluminum concentrations would approach background values, which, for locations on the Prairies, are likely on average to be about 0.022 mg/L as monomeric inorganic aluminum (Environment Canada and Health Canada 2000). The temporally weighted concentration of dissolved monomeric aluminum at this location averaged over a period of several days would therefore be about 0.055 mg/L. This concentration was taken as a conservative (reasonable worst-case) Predicted Environmental Concentration (PEC) for waters close to discharge points.

Because aluminum releases reported by DWTPs occur in circumneutral to neutral waters, two Critical Toxicity Values (CTVs) corresponding to the pH of waters where releases occur could be chosen. The work of Neville (1985) provides a NOEC of 0.075 mg/L as inorganic monomeric aluminum, based on the absence of deleterious effects on ventilation and respiratory activity of rainbow trout at pH 6.5. This CTV is considered valid for the pH range 6.5–8.0. A second CTV for alkaline conditions (pH > 8.0) is based on the work of Gundersen et al. (1994), who determined similar LC_{50}s (~ 0.6 mg dissolved Al/L) during several experiments in the pH range 8.0–8.6 and water hardness range 20 to 100 mg/L (as calcium carbonate). A NOEC for mortality of 0.06 mg dissolved Al/L can be derived for rainbow trout from data given for one of the 16-day exposures at 20 mg/L hardness and pH 8.0. The chemical concentrations in Gundersen et al. (1994) are expressed as “total” and “dissolved” aluminum; there was, unfortunately, no attempt to identify the forms of dissolved aluminum present. At the experimental pH, it is probable that a good proportion of the dissolved aluminum was the monomeric aluminate ion as the predominant species.Since the pH in waters for which the PEC was estimated is 8.38, the corresponding CTV is 0.06 mg/L as dissolved inorganic monomeric aluminum.

It is possible that effects may be elicited at concentrations below that of the selected CTV of 0.06 mg/L. Wold et al. (2005) reported a 21-day LOEC for reduced survival and reproduction in *Daphnia pulex* at a lowest test concentration of 0.05 mg/L. Testing was conducted at a pH of 7 ± 1, suggesting that the observed effects were due to the presence of aluminum hydroxide rather than the dissolved inorganic monomeric aluminum that is usually associated with toxicity. Recent studies (e.g., Verbost et al. 1995; Kádár et al. 2002; Alexopoulos et al. 2003) provide evidence that the particulate and/or colloidal forms of aluminum, such as may be present under the transition conditions of mixing zones, are

bioavailable and can exert adverse effects on organisms. Impaired oxygen consumption, gill damage, and reduced feeding behaviour have been reported in aquatic invertebrates and fish present in waters containing freshly neutralized aluminum (i.e., aluminum in transition from ionic species to polymers or precipitating hydroxides), although it is not clear whether these effects result from physical damage to structures such as the gills, or from direct chemical toxicity. Therefore, while there may be circumstances or conditions under which particulate and colloidal forms of aluminum can exert adverse effects on aquatic organisms, these conditions are likely to be localized and/or transitory in nature, and the selected CTV of 0.06 mg/L, based on the inorganic monomeric form, is considered sufficiently representative of the overall potential for adverse impacts in aquatic species.

In determining Predicted No-Effect Concentrations (PNECs) for aluminum, the nature of the biological response was considered, since some organisms respond to a narrow aluminum concentration range. This results in an abrupt "threshold" where an evident biological response occurs, with no observable effects at slightly lower concentrations (Hutchinson et al. 1987; Roy and Campbell 1995). Consequently, since the CTV chosen is a NOEC, the application factor used to derive a PNEC from the CTV was 1. Aluminum being a natural element, it is also useful to consider whether the PNEC is within the range of natural background concentrations. Although based on limited data, on an overall basis, the 90th-percentile value for dissolved aluminum at sampling stations located upstream of points of discharge of aluminum salts is 0.06 mg/L (Germain et al. 2000). It should be noted that only a portion of this dissolved aluminum is in inorganic monomeric forms (corresponding to the PNEC). Thus, the 90th-percentile value for inorganic monomeric aluminum in uncontaminated water is expected to be less than 0.06 mg/L.

The reasonable worst-case quotient for receiving water can therefore be calculated as follows:

$$\text{Quotient} = \frac{\text{PEC}}{\text{PNEC}}$$

$$= \frac{0.055 \text{ mg/L}}{0.06 \text{ mg/L}}$$

$$= 0.92$$

Since this conservative quotient is relatively close to 1, it is helpful to consider further the likelihood of biota being exposed to such concentrations in Canada.

It is likely that chemical equilibrium modelling overestimates inorganic forms of aluminum in solution, since it appears to overestimate dissolved aluminum. One reason for the overestimate is that a very large fraction of the aluminum released from DWTPs during backwash events is most probably in solid form, while calculations used to estimate the PEC assumed that all of the aluminum was in dissolved form (Germain et al. 2000). Although the modelling assumed that saturation was achieved instantly, this "solid" aluminum may take a relatively long time to dissolve such that aluminum levels in receiving waters do achieve saturation. In fact most of the aluminum solids released are expected to settle relatively

quickly to bottom sediment. Dissolved concentrations may also be overestimated because of the assumption that the solubility of aluminum is controlled by microcrystalline gibbsite. Based on limited data on concentrations of dissolved aluminum at different treatment steps at one Canadian DWTP, solubility may be controlled by less soluble forms of aluminum hydroxide, such as boehmite (Fortin and Campbell 1999).

The possibility that modelled concentrations overestimate actual values is further supported by data for two sites on the North Saskatchewan River, where the dissolved inorganic aluminum concentrations predicted by modelling are 0.110 and 0.099 mg/L, while the measured concentrations at these sites are 0.005 and 0.010 mg/L (Roy 1999b).

Srinivasan et al. (1998) studied the speciation of aluminum at six different stages of water treatment at Calgary's DWTP. The total aluminum concentration ranged from 0.038 to 5.760 mg/L, and the dissolved inorganic aluminum concentration varied from 0.002 to 0.013 mg/L. George et al. (1991) measured < 0.06 mg monomeric Al/L in alum sludge from ten different DWTPs containing up to 2,900 mg total Al/L. These results show that the concentration of dissolved aluminum in process wastewaters is less than the PNEC.

Finally, while the potential for aluminum to influence the cycling and availability of phosphorus and other trace elements in aquatic systems is recognized (see Section 2.3.1; Environmental Fate), no empirical data were found to suggest the occurrence of this process in Canadian surface waters and, in particular, as a result of aluminum released from the three aluminum salts that are the subject of this assessment. For this reason, the potential for risk from this source will not be evaluated further here.

3.1.1.1.2 Benthic

Acute toxicity to benthic and pelagic organisms resulting from exposure to potentially high concentrations of aluminum in aluminum-based sludge is unlikely, because of the solubility constraints in receiving waters discussed above. Filtrates obtained from alum sludge were toxic to freshwater algae in waters with low pH (less than 6) or low hardness (less than 35 mg/L $CaCO_3$/L); however, the available information indicates these conditions are not prevalent in Canadian waters that receive large inputs of aluminum from the three aluminum salts being assessed. AEC (1987) determined that aluminum was effectively bound to sludge within the pH range of 4.5 to 10.0, with less than 0.02% of the total aluminum released in waterwaters dissolved in the liquid phase associated with the sludge.

Hall and Hall (1989) reported delayed and reduced reproduction in *Ceriodaphnia dubia* following exposure to undiluted alum sludge effluent, suggesting that sublethal effects may be possible in the environment. However, effluent dilution occurs immediately upon release into a receiving water body. In addition, any observed ecosystem impacts would be difficult to link directly to the presence of aluminum given the potentially large number of contaminants that may also be present in the sludge.

There is evidence that aluminum sludge released from DWTPs can deposit and form a blanket over sediments in rivers with slow water velocity, and macroinvertebrate populations may be stressed due to a lack of oxygen and carbon sources on which to feed. For this reason,

George et al. (1991) recommended that sludge be discharged during periods of fast water movement as this may be less detrimental to primary producers and benthic communities. AEC (1984) reported smothering effects related to settled sludge on sediments following disposal to rivers in Alberta may occur but concluded that while there is potential for adverse impacts resulting from the deposition of alum sludge in receiving waters, further research is needed. The study recommended alternative treatment and disposal methods for alum sludge be considered, including reduction in the quantities produced through substitution with alternative coagulants, routing of the sludge through sanitary sewer, lagooning, and landfilling or land application.

The City of Ottawa (2002) found depressed abundance of benthic organisms downstream from the Britannia DWTP up to 1,500 m from the discharge site compared to upstream sampling sites. Areas of sediment with an appearance similar to depositons at the outfall from the Britannia DWTP and with higher levels of aluminum were found 1,500 m downstream from the outfall while sampling sites closer to the discharge did not exhibit such strong similarities, and had lower concentrations of aluminum which approached aluminum concentrations found in the sediment 150 m upstream from the discharge. This study thus showed that sludge sediment from the the Britannia DWTP can travel to distant locations from the point of discharge where deposition may occur due to site specific hydrological characteristics. In this study, it was also unclear whether the identified impacts were a result of the physical composition of the sediments (e.g., grain size), on-going blanketing of the area, and/or toxicity of dissolved aluminum leaching out of sediment and into the water column.

In their environmental risk assessment guidance document for metals, ICMM (2007) indicate that trace metals discharged into aquatic ecosystems are most likely to be scavenged by particles and removed to sediments. Once associated with surface sediments, the metals are subjected to many types of transformation reactions, including formation of secondary minerals, and binding to various sediment fractions (e.g., sulphides, organic carbon, iron hydroxides). For this reason, it may be difficult to establish clear relationships between measured concentrations of a metal in sediment and the potential for impacts to benthic organisms.

Overall, the greatest potential for risk to the benthic environment resulting from the release of aluminum-based effluents and sludges likely relates to the physical effects of blanketing and smothering of benthic communities in the vicinity of the outfall. While this impact does not constitute direct aluminum toxicity, the presence of aluminum coagulants and flocculants in water treatment processes results in the formation of substantial quantities of sludge, which may then be released into the environment. It is reasonable to expect that physical impairment of bethic populations would not be limited to alumimum coagulants sludge, but could also result from any other chemical coagulant used for the treatment of drinking water. However although the potential for local impacts to benthic organisms exists, there are relatively few reports of such damage.

In recognition of the potential for adverse ecosystem effects, many Provinces have implemented strategies designed to reduce or eliminate the release of water treatment plant effluents and sludges to receiving water bodies (see Section 2.2.2). It is expected that addressing issues relating to overall effluent and sludge concerns, most notably the extremely

high levels of total suspended solids (TSS) should also effectively deal with physical and chemical aspects of aluminum sludge toxicity in the aquatic receiving environment.

3.1.1.2 Terrestrial organisms

Terrestrial organisms are exposed to added aluminum when alum sludge from water treatment facilities, primarily MWWTPs, is applied to agricultural soils.

The lowest level of dissolved aluminum reported to adversely affect terrestrial organisms is 0.135 mg/L, which can reduce root and seedling growth in sensitive grain and forage crops. This concentration was therefore selected as the CTV, assuming that most of the dissolved aluminum was in inorganic monomeric forms. Considering that this CTV was derived from experiments using solution cultures, the effects data on which the CTV is based could overestimate the sensitivity of crops grown in soils in the field. Because of that, the fact that many species were affected at the same low level and the fact that aluminum is naturally present in soil, an application factor of 1 was applied to the CTV to derive the PNEC. The conservative PNEC for soil-dwelling organisms is therefore 0.135 mg dissolved monomeric Al/L.

No data were identified on concentrations of dissolved aluminum in soils that have received applications of alum sludge. However, as was noted in section 2.2.2.2, spreading on agricultural land is permitted in Canada only when the pH is greater than 6.0 or when liming and fertilization (if necessary) are done. Thus, the pH of receiving soils will likely be in the circumneutral range, where the solubility of aluminum is at a minimum. Based on results of equilibrium modelling, with the total dissolved aluminum concentrations being controlled by the precipitation of microcrystalline gibbsite, total dissolved aluminum concentrations would not exceed the PNEC unless soil pHs were less than about 5.1 (Bélanger et al. 1999). Because it is very unlikely that the pH of soils receiving alum sludge applications will be this low, it is very unlikely that the PNEC of 0.135 mg/L is exceeded in Canadian soils receiving such applications. In addition, while a shift in soil pH at the site of sludge application could mobilize the aluminum present in the sludge, the events causing such a shift (e.g., storm events) and the resulting impacts are likely to be local and transitory in nature.

The expectation that the solubility and hence bioavailability of aluminum in sludges applied to agricultural soils will be extremely limited is supported by data on aluminum levels in plants growing on such soils. For example, aluminum in yellow mustard seed (*Sinapsis alba*) and Durum wheat seed (*Triticum turgidum* var. *durum*) collected from plants grown in soil amended with alum sludge from Regina's DWTP were found to be not statistically different from those of seeds collected in control plots (Bergman and Boots 1997).

Finally, although it has been noted that aluminum in the sludge can fix labile phosphorus by forming stable aluminum-phosphorus complexes and hence make it unavailable to plants, causing deficiencies (Jonasson 1996; Cox et al. 1997), this is unlikely to occur when soil receiving sludge is also fertilized as required in Canada.

3.1.2 Other lines of evidence relating to aluminum salts

Trends in production and use

An apparent increase in production and use of aluminum salts occurred over the period 1995 to 2000; however, from 2000 to 2006, user demand remained relatively constant and the total amount of aluminum contained in the salts (i.e., aluminum chloride, aluminum nitrate, aluminum sulphate, PAC, PASS, ACH and sodium aluminate), and therefore available for release to the Canadian environment, appeared stable at around 16,000 tonnes per year (Cheminfo Services Inc. 2008). Water treatment applications continued to be the primary consumer of sulphate and chloride salts in the years following publication of the original State of the Science report (Environment Canada and Health Canada 2000), with lesser quantities used in the pulp and paper sector.

Despite the proportionally higher demand for aluminum sulphate in comparison with the other aluminum salts (86% of the total demand in 2006), aluminum producers reported declining use of alum (and sodium aluminate) over the period 2000 to 2006, with increased use of other aluminum-based products, such as polyaluminum chloride (PAC), aluminum chlorohydrate (ACH) and polyaluminum silicate sulphate (PASS), as well as non-aluminum products such as iron salts. PAC and iron chlorides were increasingly used as substitute coagulants/flocculants for alum in drinking water treatment, the former substance for its superior settling properties in colder water temperatures and the latter due to awareness of residual aluminum issues and superior performance in floc settling and dewatering of sludge (Cheminfo Services Inc. 1008). PAC is also particularly effective at water treatment facilities experiencing large fluctuations in water temperature, turbidity, pH and alkalinity. ACH, which is a highly concentrated and highly charged type of PAC, is sometimes used preferentially over alum because of its better buffering capacity, and PASS is very effective at removing phosphorus in cold waters with lower dosing rates and less sensitivity to variable conditions of alkalinity, pH, temperature and suspended solids (Cheminfo Services Inc. 2008). Physical process changes, such as conversion from acid to alkaline paper-making, have also contributed to reduced demand for alum.

Trends in sources and releases to the environment

No evidence of significant new sources of aluminum derived from the three salts that are the subject of this assessment has been identified.

Data provided in the study by Cheminfo Services Inc. (2008) indicated that while a slight decrease in Canadian consumption of aluminum salts occurred over the period from 2000 to 2006, the total amount of aluminum contained in these salts remained virtually unchanged, and this suggests that overall concentrations and total entry of aluminum into the environment have remained relatively constant.

Information collected since the publication of Environment Canada and Health Canada (2000) indicates that primary exposure routes for aluminum derived from the three salts have also remained unchanged. For drinking water treatment, releases are primarily to surface

waters, with lesser proportions of aluminum released to sewer for subsequent wastewater treatment or present in sludge that is directed to landfill. While low levels of aluminum have been measured in final effluents leaving municipal wastewater treatment plants, the majority of the metal appears to remain within sludge which is then transferred to landfill or processed for landfarming. Releases related to industrial applications have decreased in recent years, largely due to lower aluminum use in the pulp and paper sector and therefore lower quantities entering receiving waters from industrial treatment plants and reduced quantities sent to landfill in paper products (Cheminfo Services Inc. 2008).

3.1.3 Sources of uncertainty

There are a number of uncertainties in this risk characterization. Regarding effects of aluminum on pelagic organisms, there are only a few acceptable studies conducted at circumneutral pH (6.5–8.0), conditions similar to those of aquatic environments receiving releases from DWTPs. There are also uncertainties associated with the decision to use an application factor of 1 to derive a PNEC for pelagic organisms, a choice that was made considering concentrations of aluminum in uncontaminated waters and the biological response of organisms to a narrow concentration range, resulting in an abrupt "threshold" where biological response occurs.

There are uncertainties associated with levels of aluminum released by DWTPs and with the levels and form of aluminum present in the aquatic environment. The use of the MINEQL+ and WHAM models provided aluminum results higher than those measured in the receiving environments when calculations were done assuming that aluminum solubility is controlled by microcrystalline gibbsite. When calculations were done with the boehmite form of aluminum hydroxide, levels were much lower than what was calculated with the microcrystalline gibbsite form (Fortin and Campbell 1999). Direct measurement and determination of aluminum speciation in final effluents from water treatment plants would confirm the estimated levels and forms provided by MINEQL+ and WHAM models.

Other uncertainties exist relating to the impact of aluminum sludge releases on benthic organisms. There are some indications that sludge releases, whatever the coagulant or flocculant used, may have a smothering effect on benthos. In recognition of the potential for adverse ecosystem effects, many Provinces have implemented strategies designed to reduce or eliminate the release of water treatment plant effluents and sludges to receiving water bodies (see Section 2.2.2). It is expected that addressing issues relating to overall effluent and sludge concerns, most notably the extremely high levels of total suspended solids (TSS) should also effectively deal with physical and chemical aspects of aluminum sludge toxicity in the aquatic receiving environment.

In relation to terrestrial organisms, there are uncertainties associated with the limited data available for effects on soil-dwelling organisms other than plants. The lack of information on aluminum levels in pore waters of soils receiving applications of alum sludge is not considered critical, since these levels are constrained by theoretical limits on solubility that are below the PNEC for sensitive vegetation.

3.2 CEPA 1999 64(c): Human health

3.2.1 Estimated population exposure

The average daily intake of aluminum in six age groups in Canada is estimated on the basis of concentrations measured in: (a) indoor and outdoor air (section 2.3.2.1); (b) drinking water (section 2.3.2.2.2); (c) soil (section 2.3.2.4); and (d) food (section 2.3.2.6). Table 3.1 shows the overall estimate of average daily intakes by age group and different environmental media (water, indoor air, outdoor (ambient) air, soil, and food and beverages) for total aluminum. Total aluminum was considered, instead of the three specified salts, as concentrations of aluminum in foods, soil, drinking water, and air are generally reported as total aluminum, and not in terms of specific salts.

The average daily intake values were derived using a deterministic exposure assessment, which provides a single point estimate of intake (in this case and estimate of the mean). Probabilistic exposure assessments, on the other hand, provide information on the full range of possible intakes in the study population, and may, as well, give a more accurate estimate of mean exposure. The potential influence of a probabilistic analysis on the current assessment, with regard to the daily total aluminum intake in food, is discussed in more detail in section 3.2.1.4.

Consideration of the environmental media—drinking water, air, soil and food—in the derivation of the average daily intake is consistent with other assessments of priority substances. Daily intake of other sources of aluminum (e.g., antacids, vaccines and cosmetics) is difficult to quantify for the general Canadian population, both because of the limited data on exposure and absorption, and the variability in usage within the population. Therefore, these sources were not included in the estimation of the average daily intake. All of these additional sources may however, constitute non-negligible exposures to aluminum, and should be considered in the qualitative evaluation of uncertainty associated with the estimate of the average daily intake.

3.2.1.1 Air

3.2.1.1.1 Estimated average daily intake of total aluminum in outdoor air

The estimated average daily intake of total aluminum in airborne particles in outdoor air was determined using more than 10,000 measurements taken over the past ten years at some 50 sites in Canada. The average provincial/territorital total aluminum concentration of 0.17 μg/m^3 in PM_{10} in Canada was used in the daily intake estimate (section 2.3.2.1.1). By age group, average daily intakes for PM_{10} were very low, ranging from 0.03 μg/kg bw/d for seniors to 0.1 μg/kg bw/d for young children aged six months to four years old.

3.2.1.1.2 Estimated average daily intake of total aluminum in indoor air

In the case of indoor air, only measurements conducted on PM_{10} samples were evaluated to estimate intake since the concentration of aluminum in $PM_{2.5}$ was often below the detection limit. The concentration based on the average daytime and nighttime concentrations of total aluminum is estimated to be 1.49 μg/m^3 (section 2.3.2.1.2). The estimated average daily intake from indoor air is therefore higher than that from outdoor air, ranging from

0.3 μg/kg bw/d in adults and seniors to 0.8 μg/kg bw/d in young children aged six months to four years old.

3.2.1.2 Water

On the basis of data provided by municipal drinking water treatment plants from across Canada (section 2.3.2.2.2), the mean total aluminum concentration was estimated to be 101 μg/L. This estimate applies to plants that use coagulant/flocculents containing aluminum salts and secure their water supply from surface water sources. The average daily intake for each age group ranged from 2.0 μg/kg bw/d for adolescents and adults to 10.8 μg/kg bw/d for non-breastfed infants.

3.2.1.3 Soil

The mean total aluminum concentration in soil of approximately 41,000 mg/kg (section 2.3.2.4) was used to estimate the exposure of the Canadian population via soil. The average daily intake of aluminum from soil among infants was 166 μg/kg bw/d, and significantly higher in young children aged six months to four years old, who were found to have an estimated average daily intake of 268 μg/kg bw/d. For the other groups, the average daily intakes of total aluminum are progressively lower from 87 μg/kg bw/d for children aged 5 to 11 years old to 17 μg/kg bw/d for seniors.

3.2.1.4 Foods

For each age group defined in the Canadian population, the estimated mean dietary intake of total aluminum was derived using the fifth Total Diet Study completed in 2000–2002 (Dabeka 2007). Daily intakes of aluminum from food and beverages are presented in Table 3.1. For breastfed infants aged zero to six months old, the exposure to aluminum from human milk was approximately 12 μg/kg bw/d, whereas an intake of 85 μg/kg bw/d was calculated in non-breastfed infants. Among young children aged six months to four years old, the estimated mean daily intake from food was approximately 268 μg/kg bw/d. In the other groups, the mean daily intake of total aluminum ranged from 341 μg/kg bw/d in children aged 5 to 11 years old to 113 μg/kg bw/d in adults over 60 years old.

The above mean intake values of total aluminum in food were derived using a deterministic exposure assessment, which provides a single point estimate of intake but does not provide information about the full range of possible exposures within a population. The deterministic approach in this case is expected to overestimate mean estimates of exposure, in part because the aggregation of food categories inflates the contribution of less frequently consumed foods having higher levels of contamination. Further, the deterministic assessment does not take into account the day-to-day variability in the types of foods consumed by individuals.

Probabilistic exposure assessments estimate the probability of a given exposure in a population. The distribution of intakes that is generated provides more information about the full range of possible intakes in that population. Such statistical modelling can also account for intra- and interindividual variability in eating behaviours. As such, probabilistic exposure assessments, when the datasets are available to allow such assessments, are considered to provide a more accurate picture of exposure than deterministic exposure assessments.

3.2.1.5 Overall estimate of exposure in the Canadian population

The estimated mean daily intake of total aluminum was lower in breastfed than in non - breastfed infants, with levels of 179 and 262 μg/kg bw/d, respectively. The highest EDI of total aluminum was found in young children aged six months to four years old with 541 μg/kg bw/d, whereas for other age groups this intake decreased significantly to 432 μg/kg bw/d in children aged 5 to 11 years old, 293 μg/kg bw/d in adolescents, 163 μg/kg bw/d in adults aged 20 to 59 years old and finally 133 μg/kg bw/d in adults over 60 years old.

The contribution from various environmental media was evaluated for each of the age groups (Table 3.2). In young children aged six months to four years, approximately 50% of the aluminum intake was from food, 50% from ingestion of soil, and less than 1% from the ingestion of drinking water and inhaled particles. The contribution from the ingestion of food increased in the other age groups to 80% or more, whereas the contribution from soil decreased with age to 20% in children aged 5 to 11 years old and approximately 10% in the older age groups. The contribution from the ingestion of drinking water and inhaled particles is very low, at less than 2% or 0.2%, respectively for all age groups other than infants.

In infants, for the exclusively breastfed group, more than 90% of the total aluminum intake was found to be from the ingestion of soil and approximately 7% from the ingestion of human milk. For those infants who consumed infant formula and different food groups and beverages, approximately 30% of total aluminum intake was from the ingestion of food and about 63% from the ingestion of soil.[25]

With respect to the three salts—aluminum chloride, aluminum nitrate, and aluminum sulphate—the only media in which the mean concentration is significantly affected by these the use of these salts is drinking water, in which aluminum sulphate or aluminum chloride may be added during the treatment process. While aluminum sulphate is permitted as an additive in some food products, this use is infrequent and would be expected to have a very minor influence on the total aluminum intake from food. The question of the relative contribution of the three salts to overall exposure to aluminum is discussed in more detail in section 3.2.4.

For those who regularly use aluminum-containing over-the-counter oral therapeutic products (e.g., pharmaceuticals such as antacids), these products represent the major source of daily aluminum intake. Based on the manufacturers' maximum recommended daily doses, EDIs of aluminum from these products may reach approximately 31,000 μg/kg bw/d. However, these are not generally the three salts considered in this assessment.

[25] Soil would most likely be in the form of household dust for this age group.

Table 3.1 Estimated mean daily intake of total aluminum based on Canadian data

Source of exposure	Estimated mean daily intake of total aluminum (µg/kg bw/d)						
	Infants[1] (0–6 months)		Toddlers[2] (0.5–4 years)	Children[3] (5–11 years)	Teens[4] (12–19 years)	Adults[5] (20–59 years)	Seniors[6] (> 60 years)
	Breastfed (exclusively)	Non-breastfed					
Drinking water[7]	0	10.8	4.57	3.59	2.04	2.14	2.25
Food and beverages[8]	12.2	85.0	268	341	270	143	113
Ambient air[9]	0.05		0.1	0.08	0.05	0.04	0.03
Indoor air[10]	0.37		0.78	0.61	0.35	0.30	0.26
Soils[11]	166		268	87	21	18	17
TOTAL	179	262	541	432	293	163	133

[1] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.8 L of water per day (non breastfed) or 0 L of water per day (breastfed), and to ingest 30 mg of soil per day (Health Canada 1998a).
[2] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day (Health Canada 1998a).
[3] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day (Health Canada 1998a).
[4] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998a).
[5] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998a).
[6] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998a).
[7] Based on the mean total aluminum concentration from all the drinking water treatment plants in Canada, estimated to be 101.16 µg/L (see section 2.3.2.2.2).
[8] Based on dietary intake data from the fifth partial Total Diet Study in Canada (Dabeka 2007; see section 2.3.2.6). Data were adjusted for age categories from Health Canada (1998a). For breastfed infants, mean breast milk aluminum concentration of 0.11 mg/kg (section 2.3.2.6) was used, with a human milk density of 1.03 kg/L and an ingestion rate of 0.8 L/d.
[9] Based on the mean concentration of total aluminum for all Canadian data in ambient air between 1986 and 2006, which is 0.17 µg/m^3 in PM_{10} (see section 2.3.2.1.1).
[10] Based on average daytime and nighttime concentrations of all Canadian data in indoor air for total aluminum, which is about 1.49 µg/m^3 (see section 2.3.2.1.2).
[11] Based on the mean concentration of total aluminum of 41,475 mg/kg measured in soils and sediments on the entire Canadian territory (see section 2.3.2.4).

Table 3.2 Contribution (%) of each source of exposure based on Canadian mean daily intake of total aluminum

Source of exposure	**Contribution (%) of each source of exposure**						
	Infants (0–6 months)		Toddlers (0.5–4 years)	Children (5–11 years)	Teens (12–19 years)	Adults (20–59 years)	Seniors (> 60 years)
	Breastfed (exclusively)	Non breastfed					
Drinking water	0.00	4.1	0.84	0.83	0.70	1.31	1.69
Food and beverages	6.80	32.4	49.5	78.9	92.2	87.7	85.0
Ambient air	0.030	0.02	0.02	0.02	0.02	0.02	0.02
Indoor air	0.21	0.14	0.14	0.14	0.12	0.18	0.20
Soils	92.7	63.4	49.5	20.1	7.17	11.0	12.8
TOTAL	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**

3.2.2 Hazard characterization

The discussion in this section focuses on the broad characterization of the types of effects of concern for the human health risk assessment of aluminum, on the basis of both human and experimental animal data. The suitability of the different sources of data for the exposure-response analysis, presented in section 3.2.3, is evaluated as well.

3.2.2.1 Effects in humans

The epidemiological data on aluminum exposure in drinking water were not used in this assessment for developing the dose-response relationship (see section 3.2.3), because of the lack of evidence for a causal relationship between aluminum in drinking water and AD, and the lack of data on total exposure to aluminum, for which food is the predominant contributor. Nonetheless, the observed associations in some studies between aluminum in drinking water and the development of AD do support further consideration of neurotoxicity as an endpoint of concern in the human health risk assessment for aluminum.

Aluminum has been shown to produce neurotoxic effects in humans as well as bone and blood toxicity, during medical treatment in which the gastrointestinal barrier is bypassed (e.g., aluminum-induced encephalopathy through dialysis treatment in patients with renal failure). There is also some epidemiological evidence for long-term cognitive impairment, in pre-term infants receiving aluminum-containing nutritional solution intravenously, and associated with occupational exposures, as discussed in section 2.4.3.1. These exposure conditions are not applicable to the general population, particularly as the exposure to aluminum generally does not occur via ingestion, and therefore human studies have not been used as a basis for characterizing the dose-response relationship for environmental exposures (see section 3.2.3). However, this evidence does support the identification of neurotoxicity and developmental neurotoxicity as endpoints of concern in the human health risk assessment for aluminum.

With respect to the conditions of exposure in the general population, the most relevant available information is provided by the epidemiological investigations into the association between exposure to aluminum through drinking water and AD and other forms of dementia (see section 2.4.3.2). The use of these findings for first identifying an endpoint of concern (i.e., hazard identification), and then for evaluating the exposure-response relationship is discussed below.

The hypothesis of aluminum in drinking water as a risk factor for AD or impaired cognitive function in the elderly is controversial in the scientific community, and has important implications for public health. Hence, it is important to evaluate in detail the weight of evidence for the observed associations, in the context of traditional criteria for causality. This evaluation, for studies published prior to 1998 is presented in the Guidelines for Canadian Drinking Water Quality - Technical Documents: Aluminum (Health Canada 1998b) and in the SOS report (Environment Canada and Health Canada 2000). In the SOS report the criteria of consistency and specificity, strength, dose-response, temporality, biological plausibility, and coherence of the observed association were evaluated, and the conclusion was as follows:

"Overall ... the weight of evidence for causality for the observed associations between aluminum and Alzheimer's disease is weak, at best. There is only limited consistency in the results of the analytical epidemiological studies. While the criteria for diagnosis were generally more stringent in the studies in which there was a positive outcome, there was more consistent control of potential confounding factors in the studies in which no associations were reported. Moreover, while there is some evidence of exposure-response in the individual available studies for the reported association between aluminum and Alzheimer's disease, there is little consistency in results among the different investigations in this respect, at least based on the limited extent of comparison permitted by the available data. There are also limited data to serve as a basis of the extent to which the observed association between aluminum and Alzheimer's disease meets the criterion of temporality. Most limiting, however, in the assessment of the weight of evidence for causality of the observed association is the lack of relevant data on biological plausibility; indeed, there is no hypothesized plausible pathway from exposure to effect with measurable key events, for which sufficient investigation has been conducted to assess weight of evidence against traditional criteria of causality, such as consistency, strength, specificity, dose-response, temporal patterns, biological plausibility and coherence."

Since the publication of the SOS report, a significant positive association between AD and aluminum in drinking water has been observed in the additional analysis of the data from the PAQUID cohort in southwestern France (Rondeau et al. 2000; Rondeau et al. 2001, as described in section 2.4.3.2). While the exposure assessment in this cohort study is improved in relation to previous case-control studies, it is still limited by two factors: the quantification of the aluminum exposure of individuals from other dietary sources and the relatively narrow range of aluminum exposure in the population studied.

Recent reviews of the epidemiological literature have reiterated the limitations of the epidemiological data base, in its entirety, in regard to the causality of the occurrence of aluminum in the environment and AD, while also maintaining that the hypothesis cannot be rejected at this time (InVS-Afssa-Afssaps 2003; ATSDR 2006; JECFA 2006; Krewski et al. 2007). As a result of these limitations, JECFA (2006) and ATSDR (2006) chose not to base their regulatory values for aluminum intake on epidemiological studies.

3.2.2.2 Effects in experimental animals

The scientific community has primarily focused its investigations of aluminum toxicity on the endpoints of neurotoxicity and reproductive/developmental toxicity, principally because of the evidence from human case studies and epidemiological studies indicating that these effects may be of concern. A total of 138 toxicological studies, published from 1979 to 2007, reporting on neurotoxicity and reproductive/developmental effects of oral aluminum exposure in rodents, monkeys and dogs, have been evaluated for the present assessment.

The observations of the toxic effects of aluminum may be influenced by dose, aluminum salt, dosing regimen and exposure media as well as animal species and strain, age,

sex, and health status. Considering the database evaluated for this assessment, the different studies vary with respect to all of these factors, and with respect to the specific endpoints investigated. Moreover, the majority of studies compare animals exposed at a single dose to a control group. In these single-dose studies, the dose corresponding to a lowest observed effect level (LOEL) or to a no observed effect level (NOEL) is strongly influenced by the researcher's choice of administered dose.

In 2000, in its SOS report, Health Canada summarized the experimental database on aluminum toxicity as follows (Environment Canada and Health Canada 2000):

> *"Altered performance in a variety of neurobehavioural tests and pathological and biochemical changes to the brain have been observed in studies of the oral administration (i.e., drinking water, diet, gavage) of aluminum salts to mice, rats and monkeys for varying periods of time as adults or during gestation, weaning and/or post-weaning. Interpretation of the results of a number of these studies is limited by designs that focus on testing specific hypotheses rather than examination of a range of neurotoxicity endpoints, the administration of single doses or a lack of an observed dose–response, lack of information on concentrations of aluminum or bioavailability from basal diets, the use of specific ligands to enhance accumulation of aluminum and small group sizes. Indeed, there have been no studies in which a broad range of neurological endpoints (biochemical, behavioural and histopathological) have been investigated in a protocol including multiple dose groups."*

Since 2000 the database for neurological and reproductive/developmental endpoints has been considerably expanded. Yet the same limitations apply, most notably in regard to an emphasis on testing specific hypotheses rather than examining a range of neurotoxicity endpoints, testing of single doses or lack of an observed dose-response relationship, and small group sizes. There is no single study that has investigated multiple dose groups for a broad range of neurological endpoints.[26]

The database does, however, provide a broad range of studies carried out by researchers from many different laboratories. Considered in its entirety, it gives evidence for neurological, neurodevelopmental and reproductive toxicity in experimental animals, including motor (e.g., rotarod test and grip strength), sensory (e.g., auditory startle) and cognitive effects (e.g., maze learning and passive avoidance tests) as well as neuropathological (e.g., neuronal degeneration), and biochemical changes (e.g., alterations in energy metabolism, trace element tissue concentrations and neurotransmission systems).

While no single or limited number of studies provides an adequate basis for characterizing the dose-response relationship, consideration of the database, as a whole, does

[26] A good laboratory practice (GLP) study generally following OECD and U.S. EPA Developmental Neurotoxicity guidelines, commissioned by a consortium of aluminum salt producers, is currently underway. The results, however, will not be available before mid-2009.

provide a basis for approximately determining the lower range of doses at which researchers have repeatedly observed statistically significant changes in neurological, neurodevelopmental and/or reproductive endpoints in experimental animals orally exposed to aluminum salts.

3.2.3 Exposure-response analysis

The objective of the exposure-response analysis was to identify the lower range of doses for which oral exposure to aluminum has been shown to produce toxicologically significant effects in multiple studies.

In order to characterize the lower range of doses at which oral exposure to aluminum produces effects in experimental animals, two subsets of the studies, based primarily on exposure period, were evaluated: (a) neurotoxic effects in adults following subchronic or chronic exposure (greater than 90 days); and (b) neurodevelopmental and reproductive effects in prenatal/lactation exposure studies. The studies included in these subsets are briefly described in Tables C1 and C2 (Appendix C). These two exposure periods were considered to be of greatest relevance to the evaluation of risks from long-term exposure to aluminum. Studies pertaining to other age categories (juvenile or older animals) are discussed separately in section 3.2.3.1.

These subsets include studies with highly diverse experimental conditions, notably with respect to the animal species and strain, type of aluminum salt administered, exposure vehicle as well as other aspects of the experimental methodology.[27] There is also variability in the reporting of doses. Some researchers adjust the concentration in drinking water for a constant dose in mg Al/kg bw/d and report this value (e.g., Colomina et al. 2005; Colomina et al. 2002; Roig et al. 2006), while others estimate doses in terms of mg Al/kg bw/d based on measures of animal body weight and food and water intake, but keep the same concentration in the diet throughout the experiment (e.g., Golub and Germann 2001b; Golub et al. 2000). In other cases, the dose is reported only as a concentration administered via diet, drinking water or gavage, and the intake in mg Al/kg bw/d has been estimated using Health Canada (1994) reference values for animal body weight and intake.

[27] Further categorization of the studies, based on salt administered, animal species, exposure vehicle and a more precisely defined exposure period, was considered but found to be not feasible. Narrowly defined subgroups did not provide an adequate number of studies with common endpoints and dose ranges. On the other hand, the comparison of pooled studies (e.g., drinking water studies vs. dietary administration studies), in order to determine the relative importance of different experimental variables, is limited by the confounding between these variables. Researchers tend to chose similar sets of experimental conditions from one experiment to another. Thus differences in the LOELs observed in a series of studies might be attributed to a particular factor (e.g., drinking water vs. diet) but could also be the result of the researchers' choices to repeatedly use the same single dose of the same salt, in the same exposure vehicle (diet or drinking water). Likewise, evaluation of pools of single-dose studies can mask the influence of an experimental condition, as reported LOELs may be poor estimates of real effect levels.

In the case of the developmental studies, the LOELs are reported as the maternal dose at the beginning of gestation. In the studies where the concentration in drinking water or the diet remained constant, this dose would generally be lower than the received dose, due to increased food and water intake during gestation and lactation. For the purpose of human health risk assessment, however, the maternal dose at the beginning of pregnancy was considered, as this provided a common point of comparison between studies.

One condition that was applied to both subsets of studies was that the experimental administered dose constitutes the principal contribution to total aluminum. As previously discussed, the concentration of aluminum in standard laboratory rodent chow may be significant, contributing approximately 10 mg Al/kg bw/d in rats and 30 mg Al/kg bw/d in mice for a typical concentration of 250 ppm.[28] In the majority of studies, this base diet concentration is not measured. Base diet concentration would considerably impact the exposure-response analysis if: (a) the bioavailability of the aluminum contained in the chow was of a similar magnitude to the bioavailability of the administered aluminum; and (b) the lab chow were to contribute a large percentage of the total aluminum exposure. While it could be hypothesised that the aluminum in the lab chow, associated with ligands in the food matrix, would be less soluble and therefore less bioavailable than added aluminum, no experimental data were identified to assess the relative bioavailabilities of aluminum in lab chow and added aluminum salts. Therefore, with regard to those studies where base diet was not quantified, studies were included in the two subsets only if the administered dose (D_a) likely exceeded the base diet dose (i.e., $D_a > 10$ mg Al/kg bw/d for rats and $D_a > 30$ mg Al/kg bw/d for mice). This approach limits the influence of the unknown base diet aluminum concentration on the exposure-response analysis, but does introduce a bias against inclusion of low dose studies in the exposure-response analysis.[29] This issue is considered further in the discussion of uncertainties (section 3.2.3.2).

Other conditions applied in the compilation of these subsets were that the doses and other experimental conditions be reported unambiguously. In addition, in the subset of adult studies, studies of juvenile and older animals were not included. Studies based on these other exposure periods are discussed in section 3.2.3.1.

The LOELs of the studies meeting the conditions described above are presented graphically in Figure 3.1. In the four studies in which a LOEL for a specific endpoint is also

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[28] See discussion in section 2.4.4 on typical levels of aluminum in lab chow.

[29] The low-dose studies for adult exposure, in which base diet aluminum concentration is not reported, include findings of altered levels of neurotransmitters (Silva and Goncalves 2003; Dave et al. 2002; Bilkei-Gorzo 1993), of changes in the phospholipid content of synaptic plasma membrane (Pandya et al. 2001) or of increased lipid peroxidation in the brain (Kaneko et al. 2004, Pratico et al. 2002, Abd-Elghaffar et al. 2005). Some low-dose studies also documented increased neuronal damage (Varner et al. 1998, 1993; Somova et al. 1997; Abd-Elghaffar et al. 2005) and neuromotor and coordination effects (Bilkei-Gorzo 1993; Sahin et al. 1995). The low-dose prenatal/lactation exposure studies included findings of alterations in neurotransmission (Kim 2003; Ravi et al. 2000) and effects on fetal growth (Paternain et al. 1988; Domingo et al. 1987a).

associated with a NOEL, this is so indicated. Six other studies listed in Tables C1 and C2 found no effects for any endpoints measured (von Linstow Roloff et al. 2002; Domingo et al. 1996; Roig et al. 2006; McCormack et al. 1979; Colomina et al. 1994 and Katz et al. 1984). Consideration of these studies is important in assessing the consistency of the database and are included in the evaluation presented below. However, the studies are not included in Figure 3.1 as no corresponding LOELs for the endpoints were observed.

Considering the studies of Tables C1 and C2 collectively, the following observations concerning the exposure-response relationship for aluminum may be made:

- There is a wide variation in reported LOELs (from 1 to 663 mg Al/kg bw/d). As previously discussed, this variation would be expected, considering the diverse experimental conditions (species, strains, aluminum salt, dosing regimes, dosing vehicle, statistical power and endpoints measured).

- There is a predominance of single dose studies or studies where the LOEL was observed at the lowest dose. Thus, the LOELs in Figure 3.1 may be elevated with respect to the effect levels that might be observed in multiple dose studies.

- For the 16 subchronic and chronic exposure studies for neurotoxicity in adults, the LOELs range between 1 and 500 mg Al/kg bw/d (administered and combined doses—D_a and D_c—considered together). Among these studies the neurobehavioural endpoints examined included Morris water maze performance and impaired learning in the shuttle box as well as effects on reflex and motor activity. Biochemical endpoints included alterations in neurotransmission systems, increased apoptosis in the brain, alterations in synaptosomal membrane fluidity and increased lipid peroxidation in the brain.

- For the 22 studies of exposure during gestation and lactation, the LOELs (D_a and D_c) vary between 29 and 663 mg Al/kg bw/d. Neurobehavioural endpoints included grip strength, auditory startle, negative geotaxis and other reflexes, maze learning, thermal sensitivity, and motor development. The observed reproductive/developmental effects included a decrease in the number of corpora lutea and the number of implantation sites, a decrease in placental and fetal weight or reduced pup body weight, an increase in skeletal malformations, and an increase in the number of days to sexual maturity. In addition, alterations in essential element metabolism, deficits in synaptic plasticity in the hippocampus, a decrease in myelin sheath width as well as increased lipid peroxidation and a decrease in superoxide dismutase and catalase activity in the cerebrum and cerebellum were reported in developmental studies.

In order to estimate the lower range of doses at which oral exposure to aluminum produces toxicologically significant neurological or reproductive/developmental effects, the individual studies presented in Tables C1 and C2 were critically reviewed. The limitations of the collective database previously described—including the use of a single exposure dose, examination of a limited number of endpoints, lack of information on base diet aluminum

concentration and small group sizes—often apply to these studies as well. Nonetheless, some of the studies provided stronger evidence than others for establishing the dose range at which neurological and reproductive/developmental effects may occur. The following discussion focuses particularly on studies documenting LOELs at the lowest doses, and evaluates the findings in relation to three issues: (a) use of a low administered dose; (b) toxicological significance of different endpoints; and (c) methodological strengths and limitations and consistency of study findings.

(a) Use of a low administered dose:

Of the studies included in Figure 3.1 the lowest LOEL was observed by Huh et al. (2005). This study reported apoptosis as well as the activation of the catalytic activity of monoamine oxidases A and B in the brains of Sprague-Dawley rats at a reported combined dose of 1 mg Al/kg bw/d. The aluminum-exposed group received aluminum maltolate in drinking water over a period of 12 months.

This study reported an aluminum concentration of 11.5 ppm in the base diet. Although this is a relatively low value for laboratory chow, it does constitute an aluminum dose (0.6 mg Al/kg bw/d) of nearly twice that of the administered dose (0.38 mg Al/kg bw/d). The use of an administered dose less than the base diet dose raises the question of exposure misclassification of individual animals, as the normal variability in intake between animals may create overlap between the two groups with respect to the dose received. This is considered to be a major limitation of this study.

In spite of the extremely low administered dose, the animals receiving aluminum maltolate were found, after one year, to have approximately four times the amount of aluminum in the brain (462 ng/g) as compared to the controls (110 ng/g).[30] This finding suggested a comparable increase in both the fraction of aluminum absorbed into the bloodstream and/or the amount of aluminum distributed to the brain when the aluminum is administered as the maltolate salt. Recently, Zhou et al. (2008) found differences in aluminum oral bioavailability, which were not statistically significant, between the citrate, maltolate and fluoride salts in drinking water. The measured bioavailabilities of all the salts were low (estimated means of 0.5%, 0.61% and 0.35% for maltolate, citrate and fluoride, respectively) and approximately twice the estimated bioavailability of aluminum in food (0.1% to 0.3%, as presented in Table 2.7) as measured with the same experimental protocol.

[30] In contrast, Colomina et al. (2002) administered aluminum nitrate, enhanced with citrate, in drinking water, at an average dose of 94 mg Al/kg bw/d, to groups of male rats aged 21 days and 18 months old. The increase in whole brain aluminum concentration in the aluminum-exposed group was not statistically significant. Roig et al (2006) observed an increase of aluminum in brain regions of rats exposed to 100 mg Al/kg bw/d of aluminum nitrate with citrate in drinking water for one year. Observations were made in two-year-old rats, and increases were on the order of three- to ten-fold, depending on the brain region, and with a 22-fold increase in the striatum.

These findings suggest that while aluminum maltolate may be more bioavailable, the increase would not be sufficient to explain the results of Huh et al (2006).

In light of the uncertainty associated with the reported increased brain concentrations in the Huh et al. (2005) study, in addition to the methodological limitation of testing an administered dose that is less than the base diet dose, the study by Huh et al. (2005) was not retained for the purpose of estimating the lower range of aluminum doses at which neurological effects may be expected to occur.

Other investigations with relatively low doses over periods of 12 weeks or longer have also reported neurotoxic effects. These studies were not considered in the exposure-response analysis as the aluminum content in the laboratory chow was not reported, and thus, unlike the study by Huh et al. (2005), the relative contribution of the aluminum in the base diet could not be evaluated. However, it should be noted that LOELs ranging from 0.07 to 22 mg Al/kg bw/d (administered dose) have been associated with a significant increase in brain aluminum levels as well as significant increases in neurobehavioural or histopathological effects (refer to Kaur and Gill 2006; Kaur et al. 2006; Varner et al. 1993; Varner et al. 1994; Varner et al. 1998; Somonova et al. 1997; Fleming and Joshi 1987; Kaneko et al. 2004; and Abd-Elgahaffar et al. 2005). These results were found for different species and for different aluminum salts, administered either in drinking water or by gavage. Thus, the possibility of toxicologically significant neurological effects in this low dose range cannot be discounted. However, the difficulty of interpreting the results of these studies underlines the importance of: (a) quantifying the aluminum content in the base diet and drinking water; and (b) using a purified low-aluminum diet in studies in which the administered dose is also very low.

Among the investigations mentioned above, the study findings with respect to aluminum fluoride are of particular concern, because of the presence of both of these ions in drinking water, either naturally or through addition during the treatment process. Varner et al. (1993), Varner et al. (1994) and Varner et al. (1998), in observing increased aluminum levels in the brain associated with a low administered aluminum fluoride dose, suggested that fluoride may enhance the uptake of aluminum by the brain. At present, the scientific database is very limited with respect to the toxicokinetics and health effects specific to aluminum fluoride.

(b) Toxicological significance of different endpoints:

Considering the 16 subchronic and chronic adult exposure studies, the LOELs range between 19 and 500 mg Al/kg bw/d (administered and combined doses—D_a and D_c—considered together, and excluding the Huh et al. (2005) study). For neurobehavioural endpoints (Morris water maze performance, impaired learning in the shuttle box and motor activity), the LOELs of the seven relevant studies vary between 40 to 500 mg Al/kg bw/d (D_a and D_c), with four studies having LOELs at D_as of 40 to 70 mg Al/kg bw/d (Commissaris et al. 1982; Lal et al. 1993; Gong et al. 2005; Mameli et al. 2006). The neurobehavioural endpoints examined constitute standard elements of neurobehavioural testing and impaired performance is considered to be toxicologically significant in the experimental animal.

The biochemical effects observed in the remaining studies included alterations in neurotransmission systems, alterations in synaptosomal membrane fluidity and increased lipid peroxidation in the brain, and were associated with LOELs varying from 19 to 420 mg Al/kg bw/d. These observations provide supportive evidence for neurotoxicity observed via other endpoints as well as information on mechanisms of action, but are more difficult to evaluate with respect to toxicological significance. For this reason, studies with these endpoints were given less weight in the exposure-response evaluation, in comparison to studies that include neurobehavioural endpoints.

Considering the 22 studies of exposure during gestation and lactation, the LOELs (D_a and D_c) varied between 29 and 663 mg Al/kg bw/d. For neurobehavioural endpoints (grip strength, auditory startle, negative geotaxis and other reflexes, maze learning and thermal sensitivity, and motor development), the LOELs (administered doses) ranged from 50 to 155 mg Al/kg bw/d, with the LOELs of two studies falling in the range of 50 to 60 mg Al/kg bw/d (Colomina et al. 2005; Golub and Germann 2001b).

With respect to reproductive parameters, the lowest LOEL was reported by Belles et al. (1999), where aluminum nitrate was administered to pregnant mice via gavage at a dose of 29 mg Al/kg bw/d and observed an increase in the number of early deliveries and reduced fetal body weight. Reduced birth or fetal weight was also observed by Colomina et al. (1992) and Sharma and Mishra (2006) at LOELs ranging between 50 and 70 mg Al/kg bw/d. Morphological effects in offspring were also observed in the latter two studies.

The motor, reflex and learning endpoints examined in the developmental studies as well as the reproductive parameters of fetal growth and morphological variations are all standard endpoints included in neurodevelopmental testing procedures, and considered to be toxicologically significant.

(c) Evaluation of methodology and consistency of results in studies with LOELs of less than 70 mg Al/kg bw/d:

The methodologies and findings of the abovementioned studies with LOELs of less than 70 mg Al/kg bw/d for neurobehavioural or reproductive/developmental endpoints were compared in order to characterize the strength of evidence for the effects observed at these dose levels. With respect to the neurobehavioural effects in adults at exposures greater than 90 days, four studies were evaluated: Mameli et al. (2006), Gong et al. (2005), Lal et al. (1993) and Commissaris et al. (1982). The reproductive/developmental studies included Sharma and Mishra (2006), Belles et al. (1999), Colomina et al. (1992), Colomina et al. (2005) and Golub and Germann (2001b). In addition, investigations in which NOELs were observed for these same endpoints are discussed.

Neurobehavioural effects in adults

Of the four neurobehavioural studies in adults, all were carried out in rats using aluminum chloride, in drinking water (Gong et al. 2005; Mameli et al. 2006; Lal et al. 1993), or in the diet (Commissaris et al. 1982), for periods varying between 90 days and 11 months.

Several weaknesses were identified in the investigations of Commissaris et al. (1982) and Gong et al. (2005). First, exposure information in these two reports was expressed as concentrations in the food or drinking water, and no information was included on intake rates or body weight of the animals. Thus the administered doses (50 and 60 mg Al/kg bw/d, respectively) were calculated on the basis of default intake and body weight values (refer to Health Canada 1994), and are therefore associated with greater uncertainty than had the doses been reported by the researchers on the basis of experimental observations. Moreover, the concentration of aluminum in the base diet was not reported in the two studies, and so the combined dose could not be calculated.

The investigations of Commissaris et al. (1982) and Gong et al. (2005) were also limited by the use of a single aluminum dose and the absence of a group receiving sodium chloride. Thus, a dose-response relationship could not be examined, and the observed effects could not be definitively attributed to the aluminum ion. It should be added that these two investigations were carried out with the primary objective of examining the influence of other test substances on aluminum toxicity—parathyroid homone and Ginkgo biloba leaf extract, respectively—and not for the purpose of evaluating aluminum toxicity at different dose levels for different endpoints.

In the study of Lal et al. (1993), adult male Druckrey albino rats were exposed to an administered dose of 52 mg Al/kg bw/d for 180 days in drinking water. Although this dose was not reported directly in this form, information on daily water consumption and average body weight was provided, allowing for calculation of the dose based on experimental data. The investigation included a range of behavioural, biochemical and histopathological endpoints. The researchers observed reduced spontaneous motor activity and impaired learning in the shuttle box and maze tests, in addition to increased lipid peroxidation and decreased Mg^{2+} and $Na^{+}K^{+}$-ATPase activities in the brain. The aluminum concentration in different brain regions was significantly increased in the aluminum-exposed animals, but no pathological alterations were observed.

In the context of evaluating the exposure-response relationship, the study by Lal et al. (1993) is more informative than the Commissaris et al. (1982) and Gong et al. (2005) studies, in that the dose is more accurately reported, brain aluminum content was measured and a range of endpoints were examined, with generally consistent findings reported for the different endpoints. Its limitations include the use of a single dose, the absence of a group exposed to sodium chloride and the lack of information on the aluminum concentration in the base diet. Assuming a concentration of 250 ppm of aluminum in the laboratory chow (ATSDR 2006), the corresponding approximate aluminum dose would be 13 mg Al/kg bw/d, leading to an estimated combined dose for the Lal et al (1993) study of 65 mg Al/kg bw/d.

It should be noted that NOELs for impaired learning in the maze and shuttle box tests in aluminum-exposed adults have been observed at doses of 100 and 140 mg Al/kg bw/d,

respectively by Domingo et al. (1996) and VonLinstow Roloff et al. (2002). In the study by Domingo et al. (1996) the aluminum was administered to rats as Al nitrate, with added citrate, in drinking water for a period of 6.5 months. Von Linstow Roloff (2002) administered Al sulphate in drinking water to rats for a period of seven months.

Of these four studies, only Mameli et al. (2006) included more than one dose group, and were thereby able to establish a LOEL of 43 mg Al/kg bw/d and a NOEL of 22 mg Al/kg bw/d. At this administered dose the researchers found impairment of the vestibulo-ocular reflex in male rats of different ages (3, 10 and 24 months old) exposed to aluminum chloride in drinking water. Significant increases of aluminum were observed in brain regions (brainstem-cerebellum and cerebrum). This study, which used 20 animals per dose per age group, also included an exposure group for the salt, in this case sodium chloride, such that the observed effects could be more clearly attributed to the aluminum and not the chloride ion. It should be noted, however, that evidence from other studies supporting the effects of aluminum on the vestibulo-ocular reflex is not available, as this endpoint has not been evaluated by other researchers.

In the study by Mameli et al. (2006), the base diet aluminum concentration was measured but not clearly reported, nor was food intake measured. The LOEL of 43 mg Al/kg bw/d is thus the administered dose. The combined dose may be estimated at approximately 50 mg Al/kg bw/d, based on default values for rat dietary intake.

Considering the observations of LOELs and NOELs associated with neurobehavioural effects in adults as well as the probable combined doses, alterations in learning and reflexes may be observed at approximately 50 to 65 mg Al/kg bw/d, based on the LOELs of Mameli et al. (2006) and Lal et al. (1993) expressed as estimated combined dose.

Reproductive effects

With respect to reproductive effects, the lowest LOEL presented in Figure 3.1 is associated with the study of Belles et al. (1999). In this investigation, mice were exposed to aluminum nitrate via gavage from gestational day 6 to 15 at a dose of 29 mg Al/kg bw/d. In addition to the control group, one group received sodium nitrate at a similar nitrate dose. A high mortality (52%) in the aluminum-exposed pregnant mice was observed in this study, which was not observed in other developmental studies in which aluminum nitrate or other aluminum salts were administered at similar or greater doses. Other observations included reduced body weight gain in the dams during gestation and reduced fetal body weight. The number of early deliveries was also increased in the aluminum-exposed animals as compared to the control group, but there was no significant difference in this regard when compared to the sodium nitrate-exposed group.

This study is limited to a single dose, and the aluminum content in the base diet was not measured. The lack of information on base diet is particularly important in studies with mice because of their small body weight. A laboratory chow containing 250 ppm of aluminum would be equivalent to a dose of approximately 33 mg Al/kg bw/d, which is higher than the administered dose in this investigation.

Reduced maternal body weight gain and reduced fetal weight in aluminum-exposed animals were also observed at the LOELs associated with the Sharma and Mishra (2006) and Colomina et al. (1992) studies. A significant reduction in pup weight was also observed at the higher doses tested in the studies of Golub and Germann (2001b) and Colomina et al. (2005), at approximately 100 mg Al/kg bw/d.

In the study by Sharma and Mishra (2006), rats received 70 mg Al/kg bw/d as aluminum chloride via gavage during gestation and lactation. In addition to the effects on fetal weight, the authors observed an increase in skeletal malformations and in oxidative stress in the brains of mothers, fetuses and sucklings. The dose level in this study is based on the measured maternal weights. However, no information on base diet was included. The combined dose, based on a concentration of 250 ppm of aluminum in a typical lab chow and default values of Health Canada (1994), is estimated at approximately 83 mg Al/kg bw/d.

Colomina et al. (1992) administered aluminum lactate to mice through gavage. A LOEL of 57.5 mg Al/kg bw/d (administered dose) was observed for an increased incidence of morphological effects (cleft palate, delayed ossification of parietals), in addition to reduced fetal weight. This study did not report the aluminum content in the base diet. Considering the reported concentration in the laboratory chow used by this research group in other experiments of 42 ppm of aluminum, the estimated base diet dose would be approximately 5.5 mg Al/kg bw/d, based on Health Canada (1994) default values for body weight and food intake in mice. The combined dose would then be estimated at 63 mg Al/kg bw/d.

In contrast to the findings mentioned above, in the study of McCormack et al. (1979), rats were fed aluminum chloride in the diet at maternal dose levels of 25 and 50 mg Al/kg bw/d during gestation, and no differences in fetal growth or skeletal anomalies were observed. Colomina et al. (1994) found no differences in dam body weight, fetal growth or morphological variations in mice exposed via gavage to 104 mg Al/kg bw/d of aluminum hydroxide, during gestation. The latter finding may have resulted from the lower solubility and therefore the lower bioavailability of the hydroxide salt.

Considering the observations of LOELs and NOELs associated with reproductive effects, and the probable combined doses, reductions in fetal and pup body weight may be observed beginning at approximately 60 mg Al/kg bw/d (e.g., Colomina et al. (1992)). The study of Belles (1999), in which a LOEL of 29 mg Al/kg bw/d was observed for reduced fetal weight, is given less weight in this evaluation, in light of the uncertainty associated with the high maternal mortality rate observed in the exposed animals, and the elevated contribution of the base diet to aluminum exposure as compared to the administered dose.

Neurodevelopmental effects

With respect to neurodevelopmental effects, the lowest LOELs presented in Figure 3.1 are associated with the investigations of Colomina et al. (2005) and Golub and Germann (2001b). Both of these studies included exposure through gestation and lactation. The

experimental conditions of the two studies, however, differed in many other respects, and these are described briefly below.

Colomina, Roig et al. (2005) exposed female Sprague-Dawley rats to 0, 50, or 100 mg Al/kg bw/d as aluminum nitrate in drinking water with citric acids, in combination with a base diet dose of approximately 3 mg Al/kg bw/d. Aluminum exposure was maintained through gestation, lactation and the life of the dams.

The maternal effects of aluminum administration included decreased food intake (with reduced body weight) during gestation and lactation and decreased water intake during lactation in the 100 mg Al/kg bw/d dose group. No effects were observed with respect to the length of gestation, the number of litters or the number of fetuses per litter. With respect to the pups, there was a significant increase in the number of days until sexual maturation in males in the 100 mg Al/kg bw/d dose group and in females at both 50 and 100 mg Al/kg bw/d. A significant reduction in forelimb grip strength in males was observed in the 100 mg Al/kg bw/d dose group on PND 11 compared controls.

In the water maze task, assessing spatial learning, the performance of aluminum treated rats (50 mg Al/kg bw/d) was significantly improved in comparison to the control group. The pups in the 100 mg Al/kg bw/d dose group were not tested in the water maze test, because of altered maternal food and water intakes in this group. No differences in aluminum-exposed animals were observed with respect to surface righting, negative geotaxis or activity in an open field. The authors also measured aluminum concentration in brain regions but did not find increased levels in any regions in the aluminum-exposed animals.

The study of Golub and Germann (2001b) investigated the long-term consequences of prenatal exposures to aluminum in Swiss Webster mice, in conjunction with a suboptimal base diet. The base diet was designed to simulate the usual diet of young women in the U.S., with respect to estimated phosphate, calcium, iron, magnesium, and zinc intakes. Following breeding, dams were exposed to aluminum in the diet as aluminum lactate. The doses were equivalent to approximately < 1, 10, 50 and 100 mg Al/kg bw/d, as estimated at the beginning of gestation.

The dams were exposed throughout gestation and lactation. Following weaning at 21 days, the pups were fed the same diet as the dams for two weeks (although the per kg dose levels were higher). No effects were observed in the number of dams completing pregnancy, gestation length, weight gain of the dams (GD0 to GD15), litter size or birth weight. By weaning, both males and females in the two highest dose groups weighed significantly less than the controls, although by PND35 only the highest dose group showed this effect.

The female offspring of the highest dose group (maternal exposure of 100 mg Al/kg bw/d) were found to be slower in maze learning at three months old, as indicated by longer latencies during the first three sessions of the four-session learning series. All aluminum treated groups were similar to controls by the fourth session. Differences in aluminum exposed groups were also observed in the cue relocation trials, in which average

trial latency was significantly increased at the two highest dose levels (50 and 100 mg Al/kg bw/d) as compared to the control group.

In the motor testing of male offspring at five months old, males in the highest dose group (maternal exposure of 100 mg Al/kg bw/d) had significantly lower hindlimb grip strength and greater number of rotations in the rotarod test (animal losing footing). When body weight was taken into account, only the findings for the rotarod test remained significant.

The investigations by Colomina et al. (2005) and Golub and Germann (2001b) are methodologically superior in many respects to the majority of the studies described in Tables C1 and C2. Both include two dose levels in addition to the control group, quantify the aluminum dose associated with the base diet, and examine a range of reproductive and neurodevelopmental endpoints. The Colomina et al. (2005) study includes measurement of aluminum concentration in different brain regions. The Golub and Germann (2001b) study, however, used an experimental protocol designed to test the influence of a suboptimal diet, which limits comparisons of the findings with other investigations of aluminum toxicity, particularly as no groups were included with equivalent aluminum dose levels and a standard diet.

Interpretation of cognitive and motor test findings in the studies investigating the effects of aluminum exposure is also complicated by a possible biphasic dose-response relationship. For example, in the study by Roig et al. (2006), rats received aluminum nitrate in drinking water during gestation and lactation at administered doses of 50 and 100 mg Al/kg bw/d. No difference in the motor activity of aluminum-exposed pups and controls was found. However, the animals exposed to 50 mg Al/kg bw/d showed an improved performance in maze learning. The performance of animals exposed to 100 mg Al/kg bw/d was significantly reduced as compared to the animals exposed to 50 mg Al/kg bw/d, but not significantly different from controls. Colomina et al. (2005) also observed improved maze performance in aluminum-exposed animals, although the highest exposure group in that study was not tested for this endpoint.

Considering the neurodevelopmental studies described above, diminished performance in learning or motor tests may be observed in animals exposed prenatally or through lactation at maternal combined doses beginning at approximately 50 mg Al/kg bw/d. There is, however, considerable variability in various study results with respect to these endpoints, which also suggest a possible biphasic dose-response relationship in relation to maze learning.

3.2.3.1 Studies pertaining to other life stages

Some experimental animal studies have focused on life stages not included in the subsets discussed above. These are described below.

Golub and Keen (1999) investigated the effects of aluminum lactate administered in the diet to pubertal mice for four- or eight-week periods at doses of 17, 78, 122 and 152 mg Al/kg bw/d. A significant association between aluminum intake and reduced brain weight was observed in the four-week cohort at 152 mg Al/kg bw/d, but not in the eight-

week cohort, suggesting that effects in young animals are reversible, even as exposure continues. There were no consistent effects, however, on startle response or grip strength.

Rajasekaran (2000) administered 53 mg Al/kg bw/d of aluminum chloride via gavage to male pubertal Wistar rats for 30 days. Testing at the end of the exposure period showed a decrease in spontaneous motor activity in the exposed rats, but no effect on motor coordination. Acetyl cholinesterase activity was decreased in the cerebrum but not the cerebellum or brain stem.

Fattoretti et al. (2004) administered aluminum chloride in drinking water to 22-month-old rats, at a dose of 31 mg Al/kg bw/d for six months. They observed an increase in trace elements and aluminum in brain regions, and an increase in the area occupied by the mossy fibres in the hippocampal CA3 zone. No neurobehavioural endpoints were examined in this study.

Colomina et al. (2002) administered aluminum nitrate in drinking water (with citric acid) for 114 days to rats who were 18 months old at the start of the experiment. The weighted dose over the four months was 94 mg Al/kg bw/d. They found a decrease in mean body weight in aluminum-exposed older rats but no differences in brain aluminum concentration. No effects were observed in the passive avoidance test or in open-field activity. However, the percentage of perforated synapses in the brain increased with age and aluminum exposure.

A recent study by Walton (2007a, 2007b) of rats exposed from 12 months to the end of life investigated neurotoxicity endpoints at combined doses of 0.4 and 1.6 mg Al/kg bw/d, doses simulating current estimated low-end and high-end human exposures. Two of the six rats in the high exposure group developed significant impairment in memory tests in old age, and the brains of these rats were examined with respect to aluminum loading and inhibition of PPP2 activity (a major phosphate-removing enzyme active against tau hyperphosphorylation[31]). The study, limited by the small group size, did not report on differences between the two aluminum-exposure groups, and thus does not provide a basis for conclusions in regard to the relationship between observed biochemical and behavioural effects and aluminum exposure.

3.2.3.2 Identification of the level of concern and associated uncertainties

On the basis of the 43 studies presented in Tables C1 and C2, and considering additional studies on other age groups, it is recommended that a dose of 50 mg Al/kg bw/d, expressed as a combined dose of total aluminum, be considered as the level at which neurological and reproductive/developmental effects begin to be repeatedly observed in animal studies.

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[31] Neurofibrillary tangles in AD brains are formed from the hyperphosphorylation of tau protein.

While the dose of 50 mg Al/kg bw/d is an estimation of the lower end of a broad range of LOELs observed under different experimental conditions, it is not considered to be an overly conservative estimate of the effect level of concern. As previously discussed, there are two sources of bias against consideration of lower values of LOEL in the above characterization: (a) low-dose studies were not considered if the administered dose was less than the probable base diet dose; and (b) LOELs from single-dose studies may be overestimates of the actual effect levels. The dose of 50 mg Al/kg bw/d has, however, produced neurotoxic, reproductive and developmental effects in laboratory animals more consistently under a wide range of experimental conditions, as compared to lower doses. This exposure level is therefore retained for the purpose of the characterization of human health risks as the level of concern for neurotoxic, neurodevelopmental and reproductive effects.

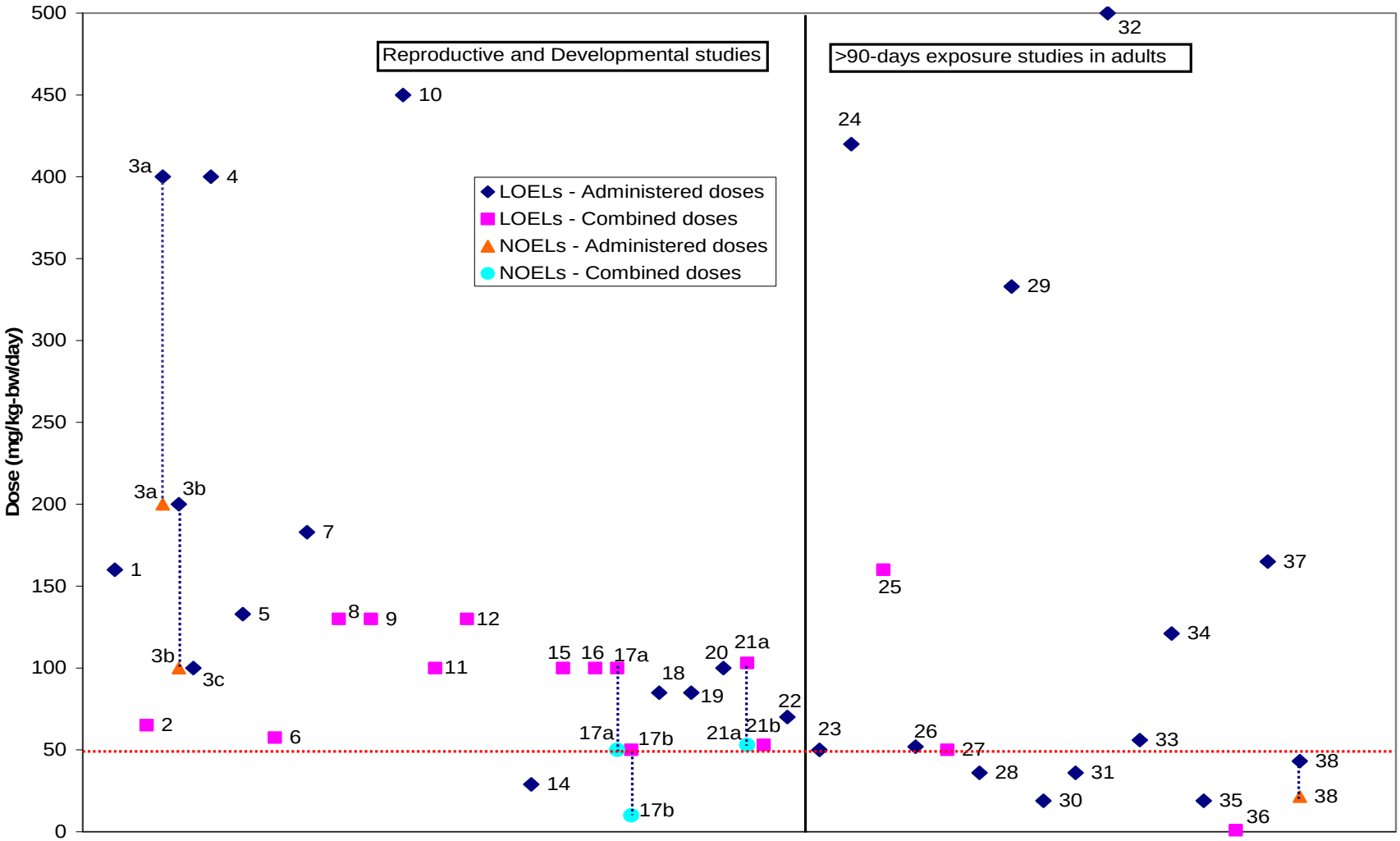

Figure 3.1 Compilation of the LOEL values from the two major subsets of studies (Adult exposure > 90 days and Reproductive/developmental) considered in the exposure-response analysis.
The numbers represent the 38 studies in which LOELs were observed, as summarized in Tables C1 and C2, and listed below. Where the base diet aluminum level is quantified, the LOEL is expressed as combined dose. NOELs associated with LOELs are indicated when observed.

Study references and endpoints:

Reproductive and developmental studies:

1. **Bernuzzi et al. 1986**: Reduced body weight of pups, impaired negative geotaxis.
2. **Golub et al. 1987**: Reduced birthweight, decreased body weight gain in pups.
3. **Bernuzzi et al. 1989**:
   - **a.** Impaired locomotor coordination;
   - **b.** Impaired righting reflex;
   - **c.** Impaired grasping reflex.
4. **Muller et al. 1990**: Impaired negative geotaxis, impaired performance in suspension and locomotor coordination tests.
5. **Gomez et al. 1991**: Reduced fetal body weight, increase in skeletal variations.
6. **Colomina et al. 1992**: Maternal toxicity, reduced fetal body weight (aluminum lactate), increased incidence of morphological effects (aluminum lactate).
7. **Misawa and Shigeta 1993**: Maternal toxicity, decreased pup weight, delay in pinna detachment and eye opening in females, delayed development of auditory startle in males.
8. **Golub et al. 1993**: Effects on Mn metabolism.
9. **Golub et al. 1994**: Reduced auditory startle response.
10. **Poulos et al. 1996**: Delayed expression of phosphorylated high molecular weight neurofilament protein in tracts in diencephalon, maternal toxicity.
11. **Golub et al. 1996**: Lower retention of both Mn and Fe.
12. **Verstraeten et al. 1998**: Increased phospholipid and galactolipid contents in brain myelin, increased lipid peroxidation.
13. **Llansola et al. 1999**: Decrease in pup body weight, decreased number of cells in cerebellum, disaggregation of microtubules and neuronal death in cerebellar neuron cultures.
14. **Belles et al. 1999**: Increased mortality of dams and increased early deliveries, reduced fetal body weight.
15. **Golub and Tarara 1999**: Decreased myelin sheath width.
16. **Golub et al. 2000**: Reduced forelimb and hindlimb grip strength, decreased thermal sensitivity.
17. **Golub and Germann (2001b)**:
    - **a.** Impaired performance in rotarod test (males);
    - **b.** Decreased weight gain in pups, impaired learning of maze with respect to cue utilization (females).
18. **Wang et al. 2002a**: Reduced body weight, deficits in synaptic plasticity in dentate gyrus of hippocampus.
19. **Chen et al. 2002**: Deficits in synaptic plasticity in dentate gyrus of hippocampus.
20. **Nehru and Anand 2005**: Increased lipid peroxidation, decreased superoxide dismutase and catalase activity in cerebrum and cerebellum.
21. **Colomina et al. 2005**:
    - **a.** Reduced forelimb strength in males;
    - **b.** Increased number of days to sexual maturation.
22. **Sharma and Mishra 2006**: Decreased number of corpora lutea, number of implantation sites, placental and fetal weight, increased skeletal malformations, increased oxidative stress in brains of mothers/fetuses and sucklings.

> 90 days exposure studies in adults:

23. **Commissaris et al. 1982**: Reduced motor activity, impaired learning (shuttle box).
24. **Johnson et al. 1992**: Decreased levels of microtubule associated protein-2 and spectrin in hippocampus.
25. **Golub et al. 1992**: Decreased motor activity, hindlimb grip strength and auditory and air puff startle responsiveness.
26. **Lal et al. 1993**: Reduced spontaneous motor activity; impaired learning (shuttle box, maze), increased brain lipid peroxidation, reduced Mg^{2+}- and $Na^{+}K^{+}$-ATPase activities.
27. **Florence et al. 1994**: Cytoplasmic vacuolization in astrocytes and neurons.
28. **Gupta and Shukla 1995**: Increased lipid peroxidation in brain.
29. **Zatta et al. 2002**: Increased acetylcholinesterase activity.
30. **Silva et al. 2002**: Increased synaptosomal membrane fluidity, decreased cholesterol/phospholipid ratio in synaptosomes.
31. **Flora et al. 2003**: Evidence of increased lipid peroxidation in brain.
32. **Jing et al. 2004**: Impaired performance in Morris water maze, altered synapses in hippocampus and frontal cortex.
33. **Gong et al. 2005**: Impaired performance in Morris water maze.
34. **Shi-Lei et al. 2005**: Impaired performance in Morris water maze, decrease in long-term potentiation in hippocampal slices.
35. **Silva et al. 2005**: Decreased Na+/K+-ATPase activity in brain cortex synaptosomes.
36. **Huh et al. 2005**: Induced apoptosis in brain, increased efficiency of monoamine oxidases and increased level of caspase 3 and 12 in brain.
37. **Rodella et al. 2006**: Decreased nitrergic neurons in the somatosensory cortex.
38. **Mameli et al. 2006**: Impaired vestibulo-ocular reflex.

3.2.4 Human health risk characterization for aluminum sulphate, aluminum chloride, and aluminum nitrate

As noted in the Introduction (section 1) three aluminum salts are specifically named for assessment on the PSL: chloride, nitrate and sulphate. Although the data available for the assessment do not allow for accurate quantification of exposure associated with specific salts, it is possible to qualitatively estimate their relative contribution to different environmental media (see Table 3.2).

Based on the use pattern of these three salts, described in section 2.2.1, the major use of sulphate and chloride salts is in water treatment, therefore exposure to these particular salts would be expected via drinking water. Aluminum sulphate has a minor use as a food additive; other aluminum-containing additives are much more widely used. Aluminum nitrate use is limited in comparison to the sulphate and chloride salts. It is used in fertilizers and as a chemical reagent in various industries and is not expected to contribute significantly to aluminum in food and soil, the principal media of total aluminum exposure.

Based on these use patterns, the only media in which the mean concentration is significantly affected by the use of these salts is drinking water. Although the contribution of aluminum via these salts cannot be accurately quantified, in order to quantitatively compare the exposure level of concern with potential exposure to aluminum from the three salts, as a surrogate for exposure it is assumed that all aluminum in drinking water is derived from aluminum chloride and aluminum sulphate.

Therefore, the human health risk characterization for the three salts is based on the comparison of the exposure level of concern of 50 mg/kg bw/d, identified in the exposure-response analysis of section 3.2.3, and the age-group with the highest average daily intake of total aluminum from drinking water (10.8 μg/kg bw/d in non-breastfed infants, see Table 3.1). The ratio of these two levels, generally referred to as the margin of exposure (MOE), is greater than 4000. This margin of exposure is considered adequate, taking into account the fact that aluminum exposure from the three salts is overestimated in this calculation, and the following considerations.

To account for toxicokinetic and toxicodynamic variability and uncertainty, a factor of at least 100 within the MOE is considered appropriate. As there is little consensus as to the mode of action, and multiple mechanisms are likely involved, the delineation of chemical-specific adjustment factors is not possible here. Effects at the lower-bound were generally small changes in performance in motor activity and learning tests identified across a range of studies, and the MOE is considered adequate to account for uncertainties in the identification of this lower-bound.

The adequacy of the collective database for the neurotoxicity and reproductive/developmental toxicity of orally-administered aluminum was reviewed in section 3.2.2.2. As discussed, there

is a clear need for further investigation in experimental animals, in which studies are designed to provide a basis for determining a critical dose for risk assessment. The existing database is nonetheless extensive, providing a basis for the determination of the lower range of LOELs observed in the different studies, carried out under different experimental conditions and for an array of aluminum salts. The neurobehavioural and neurodevelopmental effects most frequently associated with the range of LOELs may be characterized as small but statistically significant changes in performance in motor activity and learning tests.

Collectively the limited aluminum bioavailability data do not indicate that the relative bioavailabilities of aluminum in drinking water, soil and different types of food are significantly different (see section 2.3.3.1). Therefore, it is not anticipated that aluminum from drinking water would contribute relatively more bioavailable aluminum, in proportion to its external dose, as compared with other sources. In addition there is no evidence to suggest that there are differences in relative bioavailability between humans and experimental animals.

3.2.5 Uncertainties and degree of confidence in human health risk characterization

There is a moderately high degree of confidence in the deterministic exposure assessment for aluminum, as it relates to the average external dose associated with food, drinking water, soil and air, due to a large database of experimental information for most media. There is more uncertainty with respect to the maximum or high-end exposures in the population for the different media due to the variability in measured levels.

For total aluminum, food is the principal source of exposure, followed by soil, while exposure via drinking water and air combined is less than 2 % of total aluminum intake. Based on their use pattern, the three aluminum salts on the PSL are not significant contributors to the principal media of total aluminum exposure. Given the importance of food in the total exposure to aluminum, a probabilistic analysis of the exposure to aluminum from foods accounting for intakes by different subsets of the Canadian population is warranted. In addition, such an analysis should distinguish aluminum originating from food additives from natural aluminum sources in foods.

The greatest uncertainty with respect to the exposure assessment is the uncertainty and variability relating to the extent to which different aluminum salts are absorbed from the different media. Although some experimental bioavailability data are available for food and water, collectively the limited aluminum bioavailability data do not indicate that the relative bioavailabilities of aluminum in drinking water, soil and different types of food are significantly different. However, further research in this area, particularly in regard to soil, could provide evidence for significant differences that would in turn influence the human health risk characterization.

3.2.6 Recommendations for research

Areas for further research are described briefly below, in order to identify the main avenues for reducing the uncertainties associated with the human health database for aluminum.

3.2.6.1 Exposure assessment

Consideration of bioavailability is important to the characterization of human health risks of aluminum if relative bioavailabilities for different exposure media and different species (i.e., humans and experimental animals) differ from unity. This hypothesis could be explored through the determination of bioaccessibilities of aluminum in aluminum-treated drinking water, different soil and dust samples, in selected food items (e.g., processed cheese and packaged bakery items), and in laboratory animal chow, followed by the comparison of these in vitro bioaccessibilities with the in vivo bioavailability of aluminum determined in experimental studies for a given media.

In light of the wide use of aluminum-containing products applied to the skin, the dermal absorption of aluminum in humans should be more adequately characterized.

3.2.6.2 Exposure-response assessment

Further epidemiological study of aluminum exposure in the Canadian population is called for, to the extent that such research addresses the limitations of previous studies, including the characterization of aluminum exposure by dietary and other sources.

Additional experimental animal studies on toxicokinetics of different salts, including aluminum fluoride as well as the neurological and neurodevelopmental effects of aluminum, is necessary to provide information for better characterizing the exposure-response relationship. Following OECD guidelines for neurotoxicity and neurodevelopmental toxicity, these studies would include adequate numbers of animals, multiple doses, and examination of a standard array of neurological and neurodevelopmental endpoints. Note that one such study is currently underway in Canada.

3.3 Conclusion

CEPA 1999 64(a) and 64 (b): Based on the available data, it is concluded that the three aluminum salts, aluminum chloride, aluminum nitrate and aluminum sulphate, 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.

CEPA 1999 64(c): Based on available data concerning the exposure of the Canadian population to aluminum chloride, aluminum nitrate and aluminum sulphate, and in consideration of the health effects observed in humans and in experimental animals, it is concluded that these aluminum salts 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.

It is therefore concluded that the three aluminum salts, aluminum chloride, aluminum nitrate and aluminum sulphate, do not meet the definition of "toxic" as set out in section 64 of CEPA 1999.

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APPENDICES

Appendix A

Search methodology, PSL assessment of aluminum salts

Appendix B

Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water

Appendix C

Table C1 Subset of experimental animal studies for consideration in the exposure-response analysis: neurotoxic effects in exposed adults.

Table C2 Subset of experimental animal studies for consideration in the exposure-response analysis: developmental neurotoxicity or reproductive effects (prenatal exposure and/or exposure during lactation).

Appendix A

Search Methodology, PSL Assessment of Aluminum Salts

Toxicological and Epidemiological Data

A comprehensive search of the toxicological and epidemiological literature in relation to the health effects of aluminum was carried out in preparation of the SOS report published in 2000 (Environment Canada and Health Canada 2000). Since publication of this report, literature searches were conducted using the databases Toxline, Pubmed, and Current Contents as well as the organizational Web sites from the standard Existing Substances Division literature search list (ATSDR, ECETOC, IPCS, NICNAS, Health Canada, National Toxicology Program, WHO/Air, WHO/Water). The keywords (in truncated forms) included "aluminum" plus "toxicity", "neurotoxicity", "epidemiology", "bioavailability", "mode of action", "reproductive" and "developmental". For databases functioning on the basis of CAS registration numbers, the CAS RN of aluminum chloride (7446-70-0), aluminum nitrate (13473-90-0) and aluminum sulphate (10043-01-3) were used.

The comprehensive literature search was conducted through 2007. Some articles published in 2008 may also be included.

In addition to evaluating original study reports in the peer-reviewed literature, Health Canada consulted four recent comprehensive reviews of the literature on the toxic effects of aluminum: ATSDR (2006); InVS-Afssa-Afssaps (2003); JECFA (2006); and Krewski et al. (2007). These reviews were used primarily to supplement the literature search and are also cited as sources for some toxicological and exposure information, where appropriate. However, for all issues central to Health Canada's evaluation of human health risks, the original articles were consulted and cited.

Exposure Data (see text for sources of data for exposure estimates).

Environmental evaluation

Data relevant to the risk characterization of aluminum chloride, aluminum nitrate and aluminum sulphate to the environment were identified from existing review documents, published reference texts and online searches of the following databases: Aqualine, ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts; 1996), BIOSIS (Biosciences Information Services; 1990–1996), CAB (Commonwealth Agricultural Bureaux), CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources; 1996), Chemical Abstracts (Chemical Abstracts Service, Columbus, Ohio), CHRIS (Chemical Hazard Release Information System; 1964–1985), Current Contents (Institute for Scientific Information; 1993–1996), ELIAS (Environmental Library Integrated Automated System, Environment Canada library; January 1996), Enviroline (R.R. Bowker Publishing Co.; November 1995–June 1996), Environmental Abstracts (1975–February 1996), Environmental Bibliography (Environmental

Studies Institute, International Academy at Santa Barbara; 1990–1996), GEOREF (Geo Reference Information System, American Geological Institute; 1990–1996), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine; 1990–1996), Life Sciences (Cambridge Scientific Abstracts; 1990–1996), NTIS (National Technical Information Service, U.S. Department of Commerce), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine), POLTOX (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1995), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health; 1996), Toxline (U.S. National Library of Medicine; 1990–1996), TRI93 (Toxic Chemical Release Inventory, U.S. Environmental Protection Agency, Office of Toxic Substances; 1993), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, U.S. Environmental Protection Agency; up to December 21, 1994), WASTEINFO (Waste Management Information Bureau of the American Energy Agency; 1973–September 1995) and Water Resources Abstracts (U.S. Geological Survey, U.S. Department of the Interior; 1990–1996). A further search of the scientific literature was conducted in 2007 using SciFinder, an electronic interface that allows access to six databases: CA Plus (Literature from journals, patents, books, conferences, etc.), Registry (substances), Chemlist (regulatory listing), ChemCats (commercial chemical suppliers), CASReact (reaction database) and Medline.

As well as retrieving references from literature database searches, direct contacts were made with researchers, academics and other government agencies. In addition, a survey of Canadian industry was carried out under authority of section 16 of CEPA (Environment Canada 1997b), and a second review aimed at identifying changes in use trends and quantities was conducted in 2007 (Cheminfo Services Inc. 2008). Companies were required to provide information on uses, releases, environmental concentrations, effects or other data that were available to them and related to aluminum salts. Ongoing scans were conducted of the open literature, conference proceedings and the Internet for relevant information. Data obtained to August 2008 were considered in this assessment report.

Appendix B

Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water

Location Collection period	References Study type	Study population and health outcomes	Exposure measure	Results	Comments
Ontario 1981–1991	McLachlan et al. (1996) Case-control study	Cases and controls based on brains donated to Canadian Brain Tissue Bank. Cases: a1—296 AD based on clinical history of dementia and histopathology criteria (neuritic plaques and NFTs in specific brain regions); a2—89 AD as above coexisting with other neuropathologic process. Controls: c1—125 with no brain histopathology; c2—170 with other neurodegenerative diseases.	Total Al in drinking water based on the data of the Water Quality Surveillance Programme of the Ontario Ministry of the Environment for municipal supplies serving place of residence and residential history (1981–1991).	Not weighted for residential history: al vs c1 + c2: Al≥100 vs <100 µg/L, OR = 1.7 (95% CI 1.2–2.6) Al≥125 vs <125 µg/L, OR = 3.6 (95% CI 1.4–9.9) Al≥150 vs <150 µg/L, OR = 4.4 (95% CI 0.98–20) Al≥175 vs <175 µg/L, OR = 7.6 (95% CI 0.98–61) a1 + a2 vs c1 + c2: Al≥100 vs <100 µg/L, OR = 1.7 (95% CI 1.2–2.5) Weighted for 10-year residential history: a1 vs c1 + c2: Al≥100 vs <100 µg/L, OR = 2.6 (95% CI 1.2–5.7) a1 + a2 vs c1 + c2: Al≥100 vs <100 µg/L, OR = 2.5 (95% CI 1.2–5.3) a1 vs c2: Al≥100 vs <100 µg/L, OR = 2.5 (95% CI 1.1–5.6)	No control for age, sex, education, occupation, etc. Exposure weighted for 10-year residential history for 119 cases and 51 controls. AD clinical diagnostic criteria not stated.
Ontario 1984–1991	Forbes et al. (1995b) Forbes and McLachlan (1996) Cross-sectional study	AD or presenile dementia based on death certificate data (ICD-9 331.0 and ICD-9 290.1) from LSA cohort. Forbes et al. (1995b): ≈3,000 death certificates reporting dementia (AD and presenile dementia). Forbes and McLachlan (1996): 1,041 death certificates reporting AD (≥85 years of age).	Total Al in drinking water based on the data of the Water Quality Surveillance Programme of the Ontario Ministry of the Environment for municipal supplies serving place of residence at time of death.	Forbes et al. (1995b): For individuals of ≥75 years of age with AD: For Al alone: Al≤67 µg/L, RR = 1.00 Al = 68–200 µg/L, RR = 0.91 (95% CI 0.82–1.01) Al≥336 µg/L, RR = 3.15 (95% CI 1.85–5.36) Adjustment for pH: Al≤67 µg/L, pH<7.85, RR = 1.00 Al = 68–200 µg/L, pH = 7.85–7.95, RR = 0.91 (95% CI 0.82–1.00) Al≥336 µg/L, pH≥7.95, RR = 3.27 (95% CI 1.92–5.57) Adjustment for F: Al≤67 µg/L, RR = 1.00 Al = 68–200 µg/L, F<300 µg/L, RR = 0.95 (95% CI 0.84–1.06)	No control for sex, education, occupation, etc. Possible inaccuracies in death certificate data due to the different certification practices of local doctors. No information on duration of exposure.

Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water					
Location Collection period	References Study type	Study population and health outcomes	Exposure measure	Results	Comments
				Al≥336 µg/L, F≥860 µg/L, RR = 3.10 (95% CI 1.81–5.27) Adjustment for Al/F interaction term: Al≤67 µg/L, F<300 µg/L, RR = 1.00 Al = 68–200 µg/L, RR = 1.11 (95% CI 0.92–1.33) Al≥336 µg/L, RR = 3.88 (95% CI 2.22–6.77) Al≤67 µg/L, F≥860 µg/L, RR = 1.00 Al = 68–200 µg/L, RR = 0.85 (95% CI 0.74–0.98) Al≥336 µg/L, RR = 0.98 (95% CI 0.14–6.97) Adjustment for Si: Al≤67 µg/L, RR = 1.00 Al = 68–200 µg/L, Si<1.5 mg/L, RR = 0.90 (95% CI 0.81–1.00) Al≥336 µg/L, Si≥1.5 mg/L, RR = 3.14 (95%CI 1.84–5.34) Adjustment for Al/Si interaction term: Al≤67 µg/L, Si<1.5 mg/L, RR = 1.00 Al = 68–200 µg/L, RR = 1.00 (95% CI 0.89–1.13) Al≥336 µg/L, RR = 4.04 (95% CI 2.32–7.03) Al≤67 µg/L, Si≥1.5 mg/L, RR = 1.00 Al = 68–200 µg/L, RR = 0.67 (95% CI 0.55–0.82) Al≥336 µg/L, RR = 0.88 (95% CI 0.12–6.29) Similar analyses with individuals with AD and presenile dementia, with presenile dementia alone, and with AD individuals of all ages were presented. The RRs were smaller. Forbes and McLachlan (1996): For individuals ≥85 years of age: For Al alone: Al = 68–250 µg/L vs ≤67 µg/L, RR = 0.85, p<0.05 Al>250 µg/L vs ≤67 µg/L, RR = 4.76, p<0.05 Adjustment for water source: Al = 68–250 µg/L vs ≤67 µg/L, RR = 0.88, p>0.05 Al>250 µg/L vs ≤67 µg/L, RR = 4.93, p<0.05 Adjustment for water source, Si:	RR corresponds to rate ratio where the population reference was from Ontario Longitudinal Study of Aging.

Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water					
Location Collection period	References Study type	Study population and health outcomes	Exposure measure	Results	Comments
				Al = 68–250 µg/L vs ≤67 µg/L, RR = 0.91, p>0.05 Al>250 µg/L vs ≤67 µg/L, RR = 5.07, p<0.05 Adjustment for water source, Si, Fe: Al = 68–250 µg/L vs ≤67 µg/L, RR = 0.89, p>0.05 Al>250 µg/L vs. ≤67 µg/L, RR = 6.27, p<0.05 Adjustment for water source, Si, Fe, pH: Al = 68–250 µg/L vs ≤67 µg/L, RR = 0.91, p>0.05 Al>250 µg/L vs ≤67 µg/L, RR = 7.38, p<0.05 Adjustment for water source, Si, Fe, pH, F: Al = 68–250 µg/L vs ≤67 µg/L, RR = 0.90, p>0.05 Al>250 µg/L vs. ≤ 67 µg/L, RR= 7.56, p < 0.05 Adjustment for water source, Si, Fe, pH, F, turbidity: Al = 68–250 µg/L vs ≤67 µg/L, RR = 0.89, p>0.05 Al>250 µg/L vs ≤ 67 µg/L, RR = 9.95, p<0.05	
Ontario 1990–1991	Forbes et al. (1992) Forbes et al. (1994) Forbes and Agwani (1994) Forbes et al. (1995a) Cross-sectional study	Males with cognitive impairment based on interview/questionnaire with modified mental status test for subjects from the LSA cohort. For deceased persons, the questionnaires were administered to survivors or proxy respondants. Forbes et al. (1992): 485 males. Forbes et al. (1994): 290 males for analysis restricted to treated surface drinking water and 485 males for other analysis. Forbes and Agwani (1994):	Total Al in drinking water based on the data of the Water Quality Surveillance Programme of the Ontario Ministry of the Environment for municipal supplies serving place of residence and residential history. Medians of Al and F concentrations	Forbes et al. (1992): Based on treated water: Al≥84.7 µg/L vs Al<84.7 µg/L OR = 1.14 (p>0.05) Al<84.7 µg/L, F>880 µg/L, OR = 1.00 Al≥84.7 µg/L, F>880 µg/L, OR = 1.69 (p>0.05) Al<84.7 µg/L, F<880 µg/L, OR = 2.21 (p<0.05) Al≥84.7 µg/L, F<880 µg/L, OR = 2.72 (p<0.01) Al<84.7 µg/L, F<880 µg/L, OR = 1.00 Al<84.7 µg/L, F>880 µg/L, OR = 0.45 (p<0.05) Al≥84.7 µg/L, F<880 µg/L, OR = 1.23 (p>0.05) Al≥84.7 µg/L, F<880 µg/L, OR = 1.00 other combinations of Al and F, OR≈0.61 (p>0.05) Al<84.7 µg/L, F>880 µg/L, OR = 1.00 Al≥84.7 µg/L, F>880 µg/L, OR = 1.69 (p>0.05) other combinations of Al and F, OR = 1.95 (p<0.05) Similar analyses with raw water concentrations were presented but no significant association was reported. Forbes et al. (1994):	Forbes et al. (1992), Forbes et al. (1994), Forbes and Agwani, (1994), Forbes et al.(1995a): Exposure not weighted for residential history. Cognitive impairments generally slight. Forbes et al. (1992), Forbes and Agwani, (1994): No control for age, education, occupation, etc. Forbes et al. (1994),

Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water					
Location Collection period	References Study type	Study population and health outcomes	Exposure measure	Results	Comments
		530 males. Forbes et al. (1995a): 494–541 males for each analysis.	are the cut-off values.	Restricted to treated surface drinking water (N = 290): Al≥84.7 vs <84.7 µg/L, OR = 1.53 (95% CI 0.94–2.51) Al<84.7 µg/L, F≥880 µg/L, OR = 1.00 Al≥84.7 µg/L, F≥880 µg/L, OR = 2.13 (95% CI 1.09–4.12) Al<84.7 µg/L, F<880 µg/L, OR = 2.75 (95% CI 1.20–6.27) Al≥84.7 µg/L, F<880 µg/L, OR = 3.98 (95% CI 1.72–9.19) Forbes et al. (1994): Increased ORs when analysis restricted to subjects residing >5 years at current address. Analyses based on all treated drinking water (N = 485): pH<7.85 (N = 68) Al≥84.7 vs <84.7 µg/L, OR = 0.76 (95% CI 0.28–2.06) Al≥84.7 vs <84.7 µg/L with F<880 µg/L, OR = 0.91 (95% CI 0.30–2.74) pH = 7.85–8.05 (N = 54) Al≥84.7 vs <84.7 µg/L, OR = 0.68 (95% CI 0.21–2.19) Al≥84.7 vs <84.7 µg/L with F<880 µg/L, OR = 0.67 (95% CI 0.07–6.41) pH>8.05 (N = 363) Al≥84.7 vs <84.7 µg/L, OR = 1.30 (95% CI 0.85–2.04) Al≥84.7 vs <84.7 µg/L with F<880 µg/L, OR = 1.36 (95% CI 0.55–3.39) Al≥84.7 vs <84.7 µg/L, F≥880 vs <880 µg/L, OR = 0.87 (95% CI 0.50–1.52) Al<84.7 µg/L, F≥880 vs <880 µg/L, OR = 0.47 (95% CI 0.23–0.97) Logistic regression adjusted for F, pH, water source, age, education, health, income and number of moves: Al≥84.7 vs <84.7 µg/L, OR = 1.72 (95% CI 1.08–2.75) Forbes and Agwani (1994): Logistic regression adjusted for F, pH, turbidity, dissolved organic carbon and water source:	Forbes et al. (1995a): Selected analyses included control for education, health status at age 62, income at age 45, number of moves and age.

Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water					
Location Collection period	References Study type	Study population and health outcomes	Exposure measure	Results	Comments
				Al≥84.7 vs <84.7 µg/L, OR = 1.97 (95% CI 1.21–3.22) Logistic regression adjusted for F, pH, turbidity, dissolved organic carbon, water source and detailed source: Al≥84.7 vs <84.7 µg/L, OR = 2.27 (95% CI 1.27–4.07) Forbes et al. (1995a): Logistic regression adjusted for F, pH, turbidity, dissolved organic carbon, Si, Fe, water source, education, health status, income and number of moves (N = 530): Without age term: Al≥84.7 vs <84.7 µg/L, OR = 2.19 (95% CI 1.29–3.71) With age term: Al≥84.7 vs <84.7 µg/L, OR = 2.19 (95% CI 1.29–3.71) With age term and Al/Si interaction term: Al≥84.7 vs <84.7 µg/L, OR = 2.35 (95% CI 1.32–4.18) Logistic regression adjusted for F, pH, Si, water source and Al/Si interaction (N = 541): Al≥84.7 vs <84.7 µg/L, OR = 1.98 (95% CI 1.20–3.26) Analysis for Si (N = 494): Al≥84.7 vs <84.7 µg/L, OR = 1.47 (95% CI 0.99–2.20) Al<84.7 µg/L, Si≥790 vs <790 µg/L, OR = 2.20 (95% CI 1.02–4.74) Al≥84.7 µg/L, Si≥790 vs <790 µg/L, OR = 0.89 (95% CI 0.54–1.47)	
Ontario 1986–1987	Neri and Hewitt (1991) Neri et al. (1992) Case-control	Cases: AD and presenile dementia based on ICD criteria from individuals' hospital discharge data. Controls: other diagnoses (not psychiatric or neurological) matched to cases for age/sex.	Total Al in drinking water based on the data of the Water Quality Surveillance Programme of the Ontario Ministry of the	Neri and Hewitt (1991); Neri et al. (1992): Significant dose-response between AD and concentrations ≥10 µg/L ($p<0.05$). Neri and Hewitt (1991): <10 µg/L, RR = 1.0 10–99 µg/L, RR = 1.13 100–199 µg/L, RR = 1.26 >200 µg/L, RR = 1.46	Control for age and sex. Stronger dose-response upon reanalysis restricted to age >75 years (Smith 1995). No information on the history of

Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water					
Location Collection period	References Study type	Study population and health outcomes	Exposure measure	Results	Comments
		≥55 years of age. Neri and Hewitt (1991): 2,232 cases/2,232 controls. Neri et al. (1992): 2,258 cases/2,258 controls.	Environment for municipal supplies serving place of current residence.	95% CI or p value are not mentioned Neri et al. (1992): <10 µg/L, RR = 1.00 10–99 µg/L, RR = 1.15 100–199 µg/L, RR = 1.45 >200 µg/L, RR = 1.46 95% CI or p value are not mentioned	exposure. Possible inaccuracies in death certificate data due to the different certification practices of local doctors.
Quebec (Saguenay-Lac-Saint-Jean) 1994	Gauthier et al. (2000) Case-control study	Cases: 68 probable and possible AD based on a three-step procedure: (1) MMS examination, (2) DSM-IV criteria, (3) NINCDS-ADRDA and ICD-10. Controls: 68 free of cognitive impairment, matched with cases for age and sex. ≥70 years of age.	Al in drinking water based on water samples of 54 municipalities collected four times from 1995 to 1996. Al species (e.g., dissolved, monomeric, polymeric) were quantified. The fourth quartile of the concentration of each Al species was the cut-off value.	For long-term exposure to Al (1945 to onset): No significant association for any Al species. For exposure estimated at onset (vs <fourth quartile): Total (>77.2 µg/L): OR = 2.10 (95% CI 0.83–5.35) Total dissolved (>38.9 µg/L): OR = 1.93 (95% CI 0.79–4.67) Monomeric organic (>12.2 µg/L): OR = 2.67 (95% CI 1.04–6.90) Monomeric inorganic (>8.4 µg/L): OR = 0.71 (95% CI 0.29–1.72) Al-OH (>8 µg/L): OR = 0.53 (95% CI 0.20–1.42) Al-F (>0.3 µg/L): OR = 0.67 (95% CI 0.26–1.67) Al-Si (>0.04 µg/L): OR = 0.67 (95% CI 0.26–1.69) Polymeric (>14.6 µg/L): OR = 1.98 (95% CI 0.79–4.98)	Examination of the speciation of Al in drinking water. Control for age, sex, education level, family history, ApoE ε4 allele and occupational exposure.
France (southwestern: Gironde and Dordogne) 1988–1989	Jacqmin et al. (1994) Jacqmin-Gadda et al. (1996) Cross-sectional	Cognitive impairment based on the MMS examinations of individuals ≥65 years of age from the PAQUID cohort. Jacqmin et al. (1994): 3,469 individuals.	Total Al in drinking water based on data from treatment plant or distribution system serving place of	Jacqmin et al. (1994): No significant association with Al without adjustment for pH; association positive for pH≤7.3, association negative for pH≥7.3 (p values not mentioned). Logistic regression adjusted for age, sex, education, occupation, calcium, pH:	Control for age, sex, education levels, principal lifetime occupation and calcium. Exposure not weighted for

Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water					
Location Collection period	References Study type	Study population and health outcomes	Exposure measure	Results	Comments
	study	Jacqmin-Gadda et al. (1996): 3,430 individuals.	residence (from two analysis surveys). Data from distribution system were weighted to take into account the period length of use of each treatment plant over the previous 10 years (1981–1991) and the hourly flow or the relative contribution of the treatment plant.	OR = 5.2 (95% CI 1.1–25.1),with increase of logarithm of the Al concentration (1 mg Al/L) OR = 0.80 (95% CI 0.65–0.98), with increase of logarithm of the Al concentration (1 mg Al/L) with the pH/Al interaction term No significant association (p>0.05) when adjusted for education and occupation. Jacqmin-Gadda et al. (1996): Logistic regression adjusted for age, sex, education, occupation, calcium, pH, Si: Only significant association (p<0.05) with Al when the cutpoint was the first quartile of Al (vs median and third quartile): Al≥3.5 µg/L vs <3.5 µg/L: OR = 1.65 (95% CI 0.80–3.39) (without Al/Si interaction term) OR = 3.94 (95% CI 1.39–11.2) (with Al/Si interaction term) Logistic regression adjusted for personal characteristics and calcium: Al<3.5 µg/L, pH<7.35, Si<10.4 mg/L, OR = 1.00 Al≥3.5 µg/L: pH≥7.35, Si≥10.4 mg/L, OR = 0.75 (95% CI 0.59–0.96) pH≥7.35, Si<10.4 mg/L, OR = 0.89 (95% CI 0.64–1.22) pH<7.35, Si≥10.4 mg/L, OR = 0.74 (95% CI 0.53–1.02) pH < 7.35, Si < 10.4 mg/L, OR = 1.30 (95%CI 0.75-2.24)	residential history.
France (southwestern: Gironde and Dordogne) 1988–1989 to 1997	Rondeau et al. (2000) Rondeau et al. (2001) Longitudinal study (follow-up analysis in eight years)	Dementia and AD based on a two-step procedure: (1) DSM-III criteria, (2) for those with positive DSM results or decline of MMS score (>2 points), NINCDS-ADRDA criteria for AD and Hachinski score for vascular dementia. Re-evaluation of the subjects one, three, five and eight years after the initial visit (the subjects from Dordogne were not re-evaluated after one year).	Total Al in drinking water based on data from treatment plant or distribution system serving place of residence (from two analysis surveys). Data from distribution system were	RR for 253 cases of dementia: Adjustment for age and sex: Al≥100 vs <100 µg/L, RR = 2.33 (95% CI 1.42–3.82) Increase of 100 µg/L Al, RR = 1.36 (95% CI 1.15–1.61) Adjustment for age, sex, educational level, wine consumption and place of residence: Al<3.8 µg/L, RR = 1 Al≥3.8 vs <11.0 µg/L, RR = 1.03 (95% CI 0.74–1.43) Al≥11.0 vs <100 µg/L, RR = 0.98 (95% CI 0.69–1.40) Al≥100 µg/L, RR = 2.00 (95% CI 1.15–3.50) Al≥100 vs <100 µg/L, RR = 1.99 (95% CI 1.20–3.28) Increase of 100 µg/L Al, RR = 1.25 (95% CI 1.05–1.50) RR for 182 cases of AD:	Control for age, sex, education, wine consumption and place of residence. Exposure not weighted for residential history.

Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water					
Location Collection period	References Study type	Study population and health outcomes	Exposure measure	Results	Comments
		Initially, 2,698 nondemented subjects ≥65 years of age from the PAQUID cohort participated in this study	weighted to take into account the period length of use of each treatment plant over the previous 10 years (1981–1991) and the hourly flow or the relative contribution of the treatment plant.	Adjustment for age and sex: Al≥100 vs <100 µg/L, RR = 2.20 (95% CI 1.24–3.84) Increase of 100 µg/L Al, RR = 1.46 (95% CI 1.23–1.74) Adjustment for age, sex, educational level, wine consumption and place of residence: Al<3.8 µg/L, RR = 1 Al≥3.8 vs <11.0 µg/L, RR = 1.16 (95% CI 0.78–1.72) Al≥11.0 vs <100 µg/L, RR = 0.97 (95% CI 0.63–1.49) Al≥100 µg/L, RR = 2.27 (95% CI 1.19–4.34) Al≥100 vs <100 µg/L, RR = 2.14 (95% CI 1.21–3.80) Increase of 100 µg/L Al, RR = 1.35 (95% CI 1.11–1.62) RR for 105 cases of dementia (among 1,638 individuals): Adjustment for mineral water consumption, age, sex, education level, wine consumption and place of residence: Al≥100 vs <100 µg/L, RR = 3.36 (95% CI 1.74–6.49)	
France (southwestern: Gironde and Dordogne) 1988–1989	Michel et al. (1991) Cross-sectional study	Possible and probable AD based on a two-step procedure: (1) DSM-III, (2) NINCDS-ADRDA criteria in 2,731 individuals ≥65 years of age from the PAQUID cohort.	Total Al in drinking water based on data from treatment plant or distribution system serving place of residence (years of collection not mentioned).	Spearman rank correlation between Al concentration and AD was significantly different from zero (p<0.05). Logistic regression adjusted for age, education and place of residence: Increase of 10 µg/L, RR = 1.16, p = 0.0014 Increase of 100 µg/L, RR = 4.53 (95% CI 3.36–6.10)	Control for age, education, rural and urban residence. Relationship between Al and AD discounted based on updated analyses of water Al levels post-publication (Smith 1995; WHO 1997).
Eight regions of England and Wales 1986–1992	Martyn et al. (1997) Case-control study	Cases: 106 with clinical diagnosis of AD or normal computer tomography (CT) scan or cerebral atrophy, with a progressive deterioration of cognition in the absence of other causes for dementia. Controls: 99 patients with other types of dementia (normal CT), 226 patients	Al in drinking water based on data from treatment plant or distribution system serving place of residence and residential history from age of 25 years to	No significant association between AD and drinking water concentrations based on several OR (27 OR were presented and were not significant p>0.05): Al = 15–44, Al = 45–109 and Al≥110 µg/L in comparison to Al<15 µg/L When: Al concentrations were averaged over 10 years before diagnosis Al concentrations were averaged from age 25 to 10 years before diagnosis	Control for age, neuroradiology centre where diagnosis was made and distance of residence from neuroradiology centre. AD clinical diagnostic criteria

Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water					
Location Collection period	References Study type	Study population and health outcomes	Exposure measure	Results	Comments
		with brain cancer and 441 patients with other neurological disorders. Cases and controls were all males born between 1916 and 1945.	diagnosis.	Al concentrations were averaged over 10 years before diagnosis For the three sets of controls (i.e., other dementia, brain cancer, other diagnoses). No significant association between AD and Al in drinking water when Si<6 mg/L (again based on 27 OR, with ≈40 cases, ≈34 patients with other dementia, ≈60 patients with brain cancer and ≈166 patients with other diagnoses).	not stated.
Northern England 1990–1992	Forster et al. (1995) Case-control study	Cases: 109 AD-type presenile dementia diagnosed before 65 years of age based on a three-step procedure: (1) hospital case notes (NINCDS-ADRDA and DSM criteria), (2) MMS examination, (3) geriatric mental state examination. Controls: 109 from general population paired for age and sex with exclusion of potentially dementia.	Al in drinking water based on data from water treatment plant serving place of residence, and residential history for longest residence in the 10 years before disease onset. Consumption of tea and of antacid based on interview data.	Al in drinking water 10 years before dementia onset: Al<50 vs >50 µg/L, OR = 1.2 (95% CI 0.67–2.37) Al>50 vs <50 µg/L, OR = 0.8 (95% CI 0.42–1.50) Al>99 vs <99 µg/L, OR = 0.8 (95% CI 0.44–1.49) Al>149 vs <149 µg/L, OR = 1.0 (95% CI 0.41–2.43) Same conclusions when the exposure is based on Al in drinking water at birthplace (N = 80 cases/control). >4 cups tea/day, OR = 1.4 (95% CI 0.81–2.63) Prolonged antacids used, OR = 1.6 (95% CI 0.77–3.51)	Control for age and sex. Same conclusions with control for family history of dementia. No information on presence or absence of Al in antacids.
Northern England (three districts: North Tyneside, Sunderland and Durham) 1982–1985	Wood et al. (1988) Cross-sectional study	Dementia in 386 patients with hip fracture >55 years of age (no information about the mental test).	Al in drinking water based on data from water treatment plants either in two districts where water is not treated with aluminum coagulants (low Al) or in a district where water is treated with alum (high	No significant difference in mental test scores between the residents from district with high-Al level (180–250 µg/L) and those from districts with low-Al levels (≤50 µg/L).	Control for age and sex. Primary focus of study was bone mass/hip fracture. No information on the history of exposure. Details of mental test scores not provided.

Table B1 Epidemiological investigations into neurological disease and aluminum in drinking water					
Location Collection period	References Study type	Study population and health outcomes	Exposure measure	Results	Comments
			Al) (1982–1985), and place of residence.		
Switzerland (Zurich) ≈1989	Wettstein et al. (1991) Cross-sectional study	Cognitive impairment based on MMS scores in 805 residents of two districts aged 81–85 years (400/district) and residing in each district >15 years.	Al in drinking water based on data from water treatment plants either in a district where water is not treated with aluminum coagulants (low Al) or in a district where water is treated with alum (high Al), and place of residence.	No significant difference in MMS scores between the residents from the district with low mean Al level (4 µg/L) and those from the district with high meanAl level (98 µg/L).	Control for socioeconomic status, age and education. No significant differences in Al serum, Al urine or Al urine/creatinine ratio in 20 patients with probable AD in comparison to 20 control patients.

Notes:
AD = Alzheimer's disease
Al = Aluminium
F = Fluoride
LSA = Ontario Longitudinal Study of Aging
NFT = neurofibrillary tangles
OR = Odds ratio
PAQUID = Principle Lifetime Occupation and Cognitive Impairment in a French Elderly Cohort study (≥65 years old)
RR = Relative risk
Si = Silicon
Criteria for Alzheimers or dementia diseases:
ADRDA = Alzheimer's Disease and Related Disorders Associations
DSM = Diagnostic and Statistical Manual of Mental Disorders
ICD = International Classification of Diseases (World Health Organization)
MMS = mini-mental state examination
NINCDS = National Institute of Neurological and Communicative Disorders and Stroke

Appendix C

Table C1 Subset of experimental animal studies for consideration in the exposure-response analysis: neurotoxic effects in exposed adults

Species, sex, strain and number Al species (number of dose levels in addition to control)	Exposure Dose levels in study: D_a (administered dose), or D_c (combined dose)	Critical neurotoxic effects in adults (>90-day exposure studies)	LOEL or NOEL (mg Al/kg bw/d) D_a = administered dose D_c = combined dose	References
RATS				
Male Sprague-Dawley rats (five per group) Al sulphate	Drinking water, for various periods up to 12 months One dose level: D_a: 165 mg Al/kg bw/d	Decrease in nitroxidergic neurons in the somatosensory cortex.	**LOEL** = 165 (D_a)	Rodella et al. (2006)
Wistar rats (3 age groups: 3, 10, 24 months) (20 per dose per age group) Al chloride	Drinking water, for 90 days Three dose levels: D_a: 11.1, 21.5 or 43.1 mg Al/kg bw/d	Impaired vestibulo-ocular reflex (results not influenced by age)	**LOEL** = 43.1 (D_a) **NOEL** = 21.5 (D_a)	Mameli et al. (2006)
Male Sprague-Dawley rats (six per group) Al maltolate	Drinking water, for 12 months One dose level: D_a: 0.38 mg Al/kg bw/d*	Induced apoptosis in brain; Increased efficiency of monoamine oxidases; Increase in level of caspase 3 and 12 in brain.	**LOEL** = 1.0 (D_c)	Huh et al. (2005)
Male Wistar rats (seven per group) Al chloride	Gavage (101 mg Al/kg bw/d), for one month, drinking water (45 mg Al/kg bw/d) for additional four months One dose level: D_a: 56 mg Al/kg bw/d* (weighted average dose)	Impaired performance in Morris water maze; Increased expression of amyloid precursor protein and caspase 3 in hippocampus.	**LOEL** = 56 (D_a)	Gong et al. (2005)
Male Wistar rats (ten per group) Al chloride	Diet for four months One dose level: D_a: 19 mg Al/kg bw/d** (assuming same weight gain as in 2002)	Decrease in Na+/K+-ATPase activity in brain cortex synaptosomes.	**LOEL** = 19 (D_a)	Silva et al. (2005)
Sprague-Dawley rats (nine per group) Al chloride	Gavage, for three months One dose level: D_a: 121 mg Al/kg bw/d	Impaired performance in Morris water maze; Decrease in long-term potentiation in hippocampal slices.	**LOEL** = 121 (D_a)	Shi-Lei et al. (2005)

Table C1 Subset of experimental animal studies for consideration in the exposure-response analysis: neurotoxic effects in exposed adults				
Species, sex, strain and number Al species (number of dose levels in addition to control)	Exposure Dose levels in study: D_a (administered dose), or D_c (combined dose)	Critical neurotoxic effects in adults (>90-day exposure studies)	LOEL or NOEL (mg Al/kg bw/d) D_a = administered dose D_c = combined dose	References
Male rats (strain not specified) (20–40 per group) Al species not specified (indicated to be water-soluble)	Gavage, for three months One dose level: D_a: 500 mg Al/kg bw/d	Impaired performance in Morris water maze; Altered synapses in hippocampus and frontal cortex.	**LOEL** = 500 (D_a)	Jing et al. (2004)
Male Wistar rats (ten per group) Al nitrate	Drinking water, for eight months One dose level: D_a: 36 mg Al/kg bw/d*	Evidence of increased lipid peroxidation in brain.	**LOEL** = 36 (D_a)	Flora et al. (2003)
Male Wistar rats (ten per group) Al chloride	Diet for four months One dose level: D_a: 19 mg Al/kg bw/d**	Increase in synaptosomal membrane fluidity; Decrease in cholesterol/phospholipid ratio in synaptosomes.	**LOEL** = 19 (D_a)	Silva et al. (2002)
Male Lister hooded rats (11–24 per group) Al sulphate	Drinking water, for up to seven months One dose level: D_a: 140 mg Al/kg bw/d*	Progressive working memory in water maze.	**NOEL** = 140 (D_a)	Von Linstow Roloff et al. (2002)
Male Sprague-Dawley rats (ten per group) Al nitrate with citrate (two dose levels)	Drinking water, for 6.5 months Two dose levels: D_a: 50 or 100 mg Al/kg bw/d	No effects on open field activity or on shuttle box performance (passive avoidance).	**NOEL** = 100 (D_a) No information on base diet (see Sanchez et al. 1997) where lab chow intake is estimated up to 13 mg/kg bw/d. D_c = 113.	Domingo et al. (1996)
Male Druckrey albino rats (40 per group) Al chloride	Drinking water, for 12 months One dose level: D_a: 36 mg Al/kg bw/d**	Increase in lipid peroxidation in brain.	**LOEL** = 36 (D_a)	Gupta and Shukla (1995)
Wistar rats (6–8 per group) Al citrate	Diet for six months One dose level: D_a: 50 mg Al/kg bw/d*	Cytoplasmic vacuolation in astrocytes and neurons.	**LOEL** = 50 (D_c)	Florence et al. (1994)
Male Druckrey albino rats (90 per exposure group; 6 to 10 animals per test group) Al chloride	Drinking water, for six months One dose level: D_a: 52 mg Al/kg bw/d**	Reduction in spontaneous motor activity; Impaired learning (shuttle box, maze); Increase in brain lipid peroxidation; Reduction in Mg^{2+}- and Na^+K^+-ATPase activities.	**LOEL** = 52 (D_a)	Lal et al. (1993)

Table C1 Subset of experimental animal studies for consideration in the exposure-response analysis: neurotoxic effects in exposed adults				
Species, sex, strain and number Al species (number of dose levels in addition to control)	Exposure Dose levels in study: D_a (administered dose), or D_c (combined dose)	Critical neurotoxic effects in adults (>90-day exposure studies)	LOEL or NOEL (mg Al/kg bw/d) D_a = administered dose D_c = combined dose	References
Male Sprague-Dawley rats (4–6 per group) Al sulphate	Drinking water, for three months One dose level: D_a: 420 mg Al/kg bw/d*	Decrease in levels of microtubule associated protein-2 and spectrin in hippocampus.	**LOEL** = 420 (D_a)	Johnson et al. (1992)
Male Sprague-Dawley rats (8-14 per group) Al chloride	Diet for 11 months One dose level: D_a: 50 mg Al/kg bw/d*	Reduction in motor activity; Impaired learning (shuttle box).	**LOEL** = 50 (D_a)	Commissaris et al. (1982)
MICE				
CD mice (10 per group) Al lactate	Gavage, for three months One dose level: D_a: 333 mg Al/kg bw/d*	Increase in acetylcholinesterase activity.	**LOEL** = 333 (D_a)	Zatta et al. (2002)
Swiss Webster mice (10–12 per group) Al lactate	Diet for 90 days One dose level: D_c: 160 mg Al/kg bw/d**	Decrease in motor activity, hindlimb grip strength, and auditory and air puff startle responsiveness.	**LOEL** = 160 (D_c)	Golub et al. (1992)
DOGS				
Beagle dogs (6M, 6F per dose) Acidic SALP	Diet for 6 months Three dose levels: D_a: 9.5, 29.0 or 90.0 mg Al/kg bw/d	No difference in body weight; No ocular changes; No effect on haematological parameters; No change in organ weight.	**NOEL** = 90 (D_a)	Katz et al. (1984)

* Dose calculated with Health Canada's reference values for body weights and intakes (Health Canada 1994).

** Dose calculated with author's reported body weights and intakes.

Table C2 Subset of experimental animal studies for consideration in the exposure-response analysis: developmental neurotoxicity or reproductive effects (prenatal exposure and/or exposure during lactation)				
Species, strain and number Al species (number of dose levels in addition to control)	Exposure GD = gestational day PND = postnatal day	Critical effects in pups (or dams where indicated)	LOEL or NOEL (mg Al/kg bw/d) D_a = administered dose D_c = combined dose	References
RATS				
Sprague-Dawley rats (12 per group) Al nitrate with citrate	Drinking water, during gestation and lactation Two maternal dose levels: D_a: 50 or 100 mg Al/kg bw/d	Biphasic effect on learning: improved performance at D_a= 50 mg/kg bw/d, but no difference compared to controls at D_a= 100 mg/kg bw/d; No effect on motor activity.	**NOEL** = 103 (D_c)	Roig et al. (2006)
Wistar rats (eight per group) Al chloride	Gavage, during gestation and lactation One maternal dose level: D_a: 70 mg Al/kg bw/d	Decrease in placental and fetal weight; Increase in number of resorptions; Increase in skeletal malformations; Increase in oxidative stress in brains of mothers/fetuses and sucklings.	**LOEL** = 70 (D_a)	Sharma and Mishra (2006);
Sprague-Dawley rats (5–6 per group) Al chloride	Gavage, during lactation, pups also exposed 39 days after weaning via gavage One maternal dose level: D_a: 100 mg Al/kg bw/d	Increased lipid peroxidation, decrease in superoxide dismutase and catalase activity in cerebrum and cerebellum.	**LOEL** = 100 (D_a)	Nehru and Anand (2005)
Sprague-Dawley rats (10–14 per group) Al nitrate with citrate	Drinking water, during gestation and lactation Two maternal dose levels: D_a: 50 or 100 mg Al/kg bw/d	Increase in number of days to sexual maturation.	**LOEL** = 53 (D_c) (females) **LOEL** = 103 (D_c) (males)	Colomina et al. (2005)
		Improved performance in learning tests (passive avoidance, water maze).	**LOEL** = 103 (D_c)	
		Reduction in forelimb strength in males.	**LOEL** = 103 (D_c) **NOEL** = 53 (D_c)	
Wistar rats (≈ seven pups per group) Al chloride	Drinking water, during lactation One maternal dose level: D_a: 85 mg Al/kg bw/d*	Deficits in synaptic plasticity in dentate gyrus of hippocampus.	**LOEL** = 85 (D_a)	Chen et al. (2002)

Table C2 Subset of experimental animal studies for consideration in the exposure-response analysis: developmental neurotoxicity or reproductive effects (prenatal exposure and/or exposure during lactation)				
Species, strain and number Al species (number of dose levels in addition to control)	Exposure GD = gestational day PND = postnatal day	Critical effects in pups (or dams where indicated)	LOEL or NOEL (mg Al/kg bw/d) D_a = administered dose D_c = combined dose	References
Wistar rats (4–10 per group) Al chloride	Drinking water, in three groups: gestation, lactation, and lactation and lifetime One maternal dose level: D_a: 85 mg Al/kg bw/d* (same dose for pups following lactation)	Reduced body weight; Deficits in synaptic plasticity in dentate gyrus of hippocampus. (greatest effect in rats exposed from parturition throughout life, while prenatal exposure was associated with the least effect)	**LOEL** = 85 (D_a)	Wang et al. (2002a)
Wistar rats (number not specified) Al sulphate	Drinking water, during gestation One maternal dose level: D_a: 63 mg Al/kg bw/d*	Decrease in pup body weight; Decreased number of cells in cerebellum; Disaggregation of microtubules and neuronal death in cerebellar neuron cultures.	**LOEL** = 663 (D_a)	Llansola et al. (1999)
Long Evans rats (number not specified) Al lactate	Drinking water, during gestation or prior to mating and then during gestation and lactation One maternal dose level: D_a: 450 mg Al/kg bw/d*	Delayed expression of phosphorylated high molecular weight neurofilament protein in tracts in diencephalon; Maternal toxicity.	**LOEL** = 450 (D_a)	Poulos et al. (1996)
THA rats (8–20 pups per group) Al chloride	Gavage, dams exposed one time (GD8) 2 maternal dose levels: D_a: 183 or 366 mg Al/kg bw/d	Maternal toxicity; Decreased pup weight; Delay in pinna detachment and eye opening in females; Delayed development of auditory startle in males.	**LOEL** = 183 (D_a)	Misawa and Shigeta (1993)
Sprague-Dawley rats (15–19 dams per group) Al hydroxide with and without citrate	Gavage, during gestation One maternal dose level: D_a: 133 mg Al/kg bw/d	Fetal body weight reduced; Skeletal variations increased in Al hydroxide + citrate group.	**LOEL** = 133 (D_a)	Gomez et al. (1991)
Wistar rats (6–9 dams per group) Al lactate	Diet during gestation One maternal dose level: D_a: 400 mg Al/kg bw/d	Impaired negative geotaxis; Impaired performance in suspension and locomotor coordination tests.	**LOEL** = 400 (D_a)	Muller et al. (1990)
		No effects in righting or grasping reflex.	**NOEL** = 400 (D_a)	

Table C2 Subset of experimental animal studies for consideration in the exposure-response analysis: developmental neurotoxicity or reproductive effects (prenatal exposure and/or exposure during lactation)

Species, strain and number Al species (number of dose levels in addition to control)	Exposure GD = gestational day PND = postnatal day		Critical effects in pups (or dams where indicated)	LOEL or NOEL (mg Al/kg bw/d) D_a = administered dose D_c = combined dose	References
Wistar rats (6–12 dams per group) Al chloride and Al lactate	Diet during gestation Three maternal dose levels	Al chloride: 100, 300 and 400 mg Al/kg bw/d	Impaired grasping reflex and impaired righting reflex.	**LOEL** = 300 (D_a) **NOEL** = 100(D_a)	Bernuzzi et al. (1989b)
			Negative geotaxis and locomotor coordination.	**LOEL** = 400 (D_a) **NOEL** = 300 (D_a)	
		Al lactate: 100, 200 and 400 mg Al/kg bw/d	Impaired grasping reflex.	**LOEL** = 100 (D_a)	
			Impaired righting reflex.	**LOEL** = 200 (D_a) **NOEL** = 100 (D_a)	
			Negative geotaxis.	**NOEL** = 400 (D_a)	
			Impaired locomotor coordination.	**LOEL** = 400 (D_a) **NOEL** = 200 (D_a)	
Wistar rats (12 to 14 dams per groups) Al chloride	Diet, during gestation Two maternal dose levels: D_a: 160 or 200 mg Al/kg bw/d		Reduced body weight of pups; Impaired negative geotaxis.	**LOEL** = 160 (D_a)	Bernuzzi et al. (1986)
Wistar rats (6–8 per group) Al chloride	Diet during gestation Two maternal dose levels: D_c: 25 or 50 mg Al/kg bw/d*		No differences in number of live fetuses and resorbed/dead fetuses, fetal body weight and length, or in skeletal anomalies.	**NOEL** = 50 (D_a)	McCormack et al. (1979)
MICE					
Swiss Webster mice (15–17 pups per dose group per sex) Al lactate Less than optimal diet—trace element reduction in lab chow based on deficiencies measured in U.S. women.	Diet during gestation and lactation, continued exposure of pups via diet for 14 days. Three maternal dose levels: D_c: 10, 50 and 100 mg Al/kg bw/d		Decreased weight gain in pups; Impaired learning of maze with respect to cue utilization (females).	**LOEL** = 50 (D_c) **NOEL** = 10 (D_c)	Golub and Germann (2001b)
			Impaired performance in rotarod test (males).	**LOEL** = 100 (D_c) **NOEL** = 50 (D_c)	
Swiss Webster mice (15–19 pups per dose group) Al lactate	Diet during gestation and lactation, continued exposure of pups via diet to PND 35 One maternal dose level: D_c: 100 mg Al/kg bw/d		Reduced forelimb and hindlimb grip strength; Decreased thermal sensitivity.	**LOEL** = 100 (D_c)	Golub et al. (2000)

Table C2 Subset of experimental animal studies for consideration in the exposure-response analysis: developmental neurotoxicity or reproductive effects (prenatal exposure and/or exposure during lactation)				
Species, strain and number Al species (number of dose levels in addition to control)	Exposure GD = gestational day PND = postnatal day	Critical effects in pups (or dams where indicated)	LOEL or NOEL (mg Al/kg bw/d) D_a = administered dose D_c = combined dose	References
Swiss Webster mice (six pups per dose group) Al lactate	Diet during gestation and lactation, continued from PND 21–45. One maternal dose level: D_c: 100 mg Al/kg bw/d	Decrease in myelin sheath width.	**LOEL** = 100 (D_c)	Golub and Tarara (1999)
Charles River CD1 mice (10–32 dams per group) Al nitrate	Gavage, dams exposed during gestation One maternal dose level: D_c: 29 mg Al/kg bw/d	Increased mortality of dams; Reduced fetal body weight.	**LOEL** = 29 (D_a)	Belles et al. (1999)
NIH mice (seven dams per group) Al lactate	Diet, dams exposed during gestation and lactation, pups then exposed PND 21–40 One maternal dose level: D_a: 100 mg Al/kg bw/d	Increased phospholipid and galactolipid contents in brain myelin; Increased lipid peroxidation.	**LOEL** = 130 (D_c)	Verstraeten et al. (1998)
Swiss Webster mice and Sprague-Dawley rats (8–12 per group) Al lactate	Diet, dams exposed during gestation and lactation One maternal dose level: D_c: 100 mg Al/kg bw/d	Lower retention of both Mn and Fe following gavage of solutions with these elements.	**LOEL** = 100 (D_c)	Golub et al. (1996)
Swiss mice (number not specified) Al hydroxyde (with and without ascorbic acid)	Gavage, during gestation One dose level: D_a: 103.8 mg Al/kg bw/d	No differences found in body weight of dams; No malformations or developmental variations observed.	**NOEL** = 103.8 (D_a)	Colomina et al. (1994)
Swiss Webster mice (12 pups per group) Al lactate	Diet, dams exposed during gestation and lactation, continued exposure of one group via diet during lifespan One maternal dose level: D_a: 100 mg Al/kg bw/d	Reduced auditory startle response.	**LOEL** = 130 (D_c)	Golub et al. (1994)

Table C2 Subset of experimental animal studies for consideration in the exposure-response analysis: developmental neurotoxicity or reproductive effects (prenatal exposure and/or exposure during lactation)				
Species, strain and number Al species (number of dose levels in addition to control)	Exposure GD = gestational day PND = postnatal day	Critical effects in pups (or dams where indicated)	LOEL or NOEL (mg Al/kg bw/d) D_a = administered dose D_c = combined dose	References
Swiss Webster mice (6–8 pups per group) Al lactate	Diet, dams exposed during gestation and lactation, continued exposure of one group via diet during lifespan One maternal dose level: D_c: 130 mg Al/kg bw/d	Effects on manganese metabolism.	**LOEL** = 130 (D_c)	Golub et al. (1993)
Swiss mice (10–13 dams per group) Al hydroxide or Al lactate	Gavage, dams exposed during gestation One maternal dose level: D_a: 57.5 mg Al/kg bw/d	Maternal toxicity; Fetal body weight reduced in Al lactate group; Increased incidence of morphological effects (cleft palate, delayed ossification of parietals) in Al lactate group.	**LOEL** = 57.5 (D_a)	Colomina et al. (1992)

*Dose calculated with Health Canada's reference values for body weights and intakes (Health Canada 1994).
**Dose calculated with author's reported body weights and intakes.