

Canadian Environmental Protection Act, 1999

PRIORITY SUBSTANCES LIST

STATE OF THE SCIENCE REPORT

for

**ALUMINUM CHLORIDE,
ALUMINUM NITRATE
and
ALUMINUM SULFATE**

Environment Canada
Health Canada

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LIST OF ACRONYMS AND ABBREVIATIONS

A β	β -amyloid protein
AD	Alzheimer's disease
ADRDA	Alzheimer's Disease and Related Disorders Associations
ATPase	adenosine triphosphatase
BCF	bioconcentration factor
cAMP	cyclic adenosine monophosphate
CAS	Chemical Abstracts Service
CEPA	<i>Canadian Environmental Protection Act</i>
CEPA 1999	<i>Canadian Environmental Protection Act, 1999</i>
cGMP	cyclic guanosine monophosphate
CI	confidence interval
CT	computer tomography
CTV	Critical Toxicity Value
DIN	Drug Identification Number
DNA	deoxyribonucleic acid
DOC	dissolved organic carbon
DOM	dissolved organic matter
DSM	Diagnostic and Statistical Manual of Mental Disorders
d.w.	dry weight
DWSP	Drinking Water Surveillance Program
DWTP	drinking water treatment plant
EEV	Estimated Exposure Value
ENEV	Estimated No-Effects Value
EPA	Environmental Protection Agency
GF-AAS	graphite furnace atomic absorption analysis
ICD	International Classification of Diseases
kg-bw	kilogram body weight
LC ₅₀	median lethal concentration
LMMS	laser microprobe mass spectrometry
LOAEC	Lowest-Observed-Adverse-Effect Concentration
LOEC	Lowest-Observed-Effect Concentration
LSA	Longitudinal Study of Aging
MAP-2	microtubule associated protein-2
MMS	Mini Mental Status test
mRNA	messenger ribonucleic acid
MWTP	municipal wastewater treatment plant
MWWTP	municipal water and wastewater treatment plant
NFT	neurofibrillary tangle
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NOEC	No-Observed-Effect Concentration
OR	odds ratio
PAC	polyaluminum chloride

PAQUID	Principle Lifetime Occupation and Cognitive Impairment in a French Elderly Cohort
PAS	polyaluminum sulfate
PHF	paired helical filament
PM _{2.5}	particulate matter less than or equal to 2.5 µm in diameter
PM ₁₀	particulate matter less than or equal to 10 µm in diameter
P&P	pulp and paper
PSL	Priority Substances List
RFP	Request for Proposals
RMOC	Regional Municipality of Ottawa-Carleton
RR	relative risk
TBARS	thiobarbituric acid reactive substances
w.w.	wet weight

SYNOPSIS

In Canada, pulp and paper mills and municipal water treatment plants (either drinking water or wastewater) are major users of aluminum chloride, aluminum nitrate and aluminum sulfate. They account for about 75% of the 270 000 tonnes of aluminum salts used in Canada in 1996.

Aluminum sulfate can enter the Canadian environment from natural sources in restricted geological environments; however, since aluminum is present in most rocks, dominantly in aluminosilicate minerals, which weather and slowly release aluminum to the surface environment, releases of aluminum from aluminum sulfate 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, and some are released to Canadian surface waters. The amount of anthropogenic aluminum released is small compared with natural aluminum releases. Concentrations of aluminum are highest in wastewaters released by drinking water treatment plants (DWTPs). However, direct releases of process waters from DWTPs are regulated by many provincial authorities, and these releases typically occur in circumneutral water, where aluminum's solubility is minimal. Disposal of sludge produced by DWTPs 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.

Extensive recent data on total aluminum concentrations in Canadian surface water are available, but 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 the 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 aluminum salts, and on the Estimated No-Effects Values 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.

Aluminum chloride, aluminum nitrate and aluminum sulfate do not deplete stratospheric ozone, contribute to the formation of ozone in the troposphere or influence climate change.

The general population of Canada is exposed to aluminum primarily by ingestion from food, soil and drinking water. Available data on aluminum levels in these media are primarily for total aluminum rather than for dissolved, monomeric or other fractions. Foods with the highest concentrations of aluminum include those with aluminum-containing food additives (e.g., cakes and muffins) and foods that have naturally elevated levels of aluminum (e.g., raisins, shellfish, cucumbers). Since aluminum is naturally present in rocks and soil, exposure can occur through inadvertent ingestion of soil on food, from the hands, etc. Aluminum is present in drinking water from natural sources and from the use of aluminum-based coagulants in DWTPs to remove organic compounds, microorganisms and particulate matter. Airborne dust particles containing aluminum can be inhaled from indoor and ambient air. Those who use cosmetics can be dermally

exposed to aluminum-containing active ingredients, and those who use aluminum-containing medications (e.g., antacids and buffered aspirins) can ingest significant quantities of aluminum. Generally, the bioavailability of aluminum via inhalation, ingestion and dermal exposure appears to be relatively low — in the range of tenths of a percent to a few percent.

Building on previous initiatives by Health Canada, the weight of evidence for potentially critical neurological effects of aluminum has been considered, primarily as a basis for delineation of previously developed research plans. While the evidence of an association between exposure to aluminum and Alzheimer's disease is weak, it cannot be dismissed completely in view of the consistency of some results with several lines of circumstantial evidence. In view of the potentially significant public health implications if the association were causal, this area is considered a priority for research. Specifically investigation of the biological plausibility in appropriate animal models is recommended.

1.0 INTRODUCTION

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires the federal 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.

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

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.

Since it is the dissolved aluminum species formed when these compounds dissociate, and not the compounds themselves, that are bioavailable and can adversely affect organisms, the environmental part of this report examines risks associated with exposures to dissolved forms of aluminum associated with the use of these aluminum salts. In relation to human health, consideration of individual aluminum compounds is precluded, due to lack of information on species of aluminum to which the general population is exposed in the general environment.

The search strategies employed in the identification of data relevant to characterization of potential effects on the environment (prior to January 1999) and human health (prior to January 2000) are presented in Appendix A. Review articles were consulted where appropriate. All original studies that form the basis for assessing the environmental exposure and effects of aluminum chloride, aluminum nitrate and aluminum sulfate have been critically evaluated by staff of Environment Canada.

Preparation of the environmental components of the characterization was led by A. Gosselin of Environment Canada. Sections of the Report and the supporting documentation related to the environmental characterization of aluminum chloride, aluminum nitrate and aluminum sulfate (Bélanger *et al.*, 1999; Germain *et al.*, 1999; Roy, 1999a) were prepared or reviewed by the members of the Environmental Resource Group, established by Environment Canada to support the environmental part of this report:

P. Doyle, Environment Canada
C. Gagnon, Environment Canada
R.G. Garrett, Geological Survey of Canada
A. Germain, Environment Canada
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Environmental sections of the supporting documentation were also reviewed by:

C. Cronan, University of Maine
L. Curtis, Oregon State University
D.S. Jeffries, National Water Research Institute
R. Lapointe, Société d'électrolyse et de chimie Alcan Ltée
C. Neville, Ontario Ministry of the Environment
J. Smith, National Water Research Institute
W. Wagner, Natural Resources Canada

The sections of this report related to characterization of environmental effects were reviewed by members of the Environmental Resource Group as well as by:

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C. Cronan, University of Maine
L. Curtis, Oregon State University
R. Lapointe, Société d'électrolyse et de chimie Alcan Ltée
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W. Wagner, Natural Resources Canada

The health-related sections of this Report build on several previous initiatives of Health Canada related to aluminum in drinking water. Aluminum has been considered recently by the Federal-Provincial Subcommittee on Drinking Water in its continuing revision of the "Guidelines for Canadian Drinking Water Quality." Following a review of the relevant information, the Subcommittee concluded that the available data were inadequate as a basis for development of a health-based guideline for aluminum in drinking water (Health Canada, 1998).

To address the inadequacy of data for developing a health-based drinking water guideline, Health Canada convened an international workshop on September 3-4, 1997, to investigate the feasibility of conducting further study of the potential critical endpoint — i.e., neurotoxicity (Health Canada, 1997). The workshop, from which there were several recommendations for relevant further study, was co-sponsored by the Office of Water of the U.S. Environmental Protection Agency (EPA). The following experts participated:

K. Bailey, Water Research Centre
T.P. Flaten, Norwegian University of Science and Technology
W.F. Forbes, University of Ottawa
M.J. Gardner, Water Research Centre
M.S. Golub, University of California
S. Gupta, Health Canada (*Scientific Coordinator*)
A. Mahfouz, U.S. EPA
D.R.C. McLachlan (retired from University of Toronto)
D. Rice, Health Canada
D.J. Savory, University of Virginia
B.H. Thomas, Health Canada (*Chair*)
J. Walton, Australian Institute for Biomedical Research Ltd.
R.A. Yokel, University of Kentucky

As follow-up to the workshop, Health Canada established an Expert Steering Committee on Aluminum and Animal Neurotoxicity to develop a Request for Proposals (RFP) for a study or studies on the neurotoxicity of aluminum as a basis for risk assessment by both Health Canada and the U.S. EPA.

The first meeting of the Steering Committee was held in Montréal, Quebec, on May 30–31, 1999. Participants included the following:

I. Arnold, Alcan Aluminum Ltd.
P. Campbell, Université du Québec
H. Durham, McGill University
D. Krewski, University of Ottawa
J. Lindsay, Health Canada
P. Mouton, Johns Hopkins University
E. Ohanian, U.S. EPA
G. Plaa, Université de Montréal (*Chair*)
B.H. Thomas, Health Canada

The Steering Committee developed study designs for multigeneration studies in mice to further investigate the biological plausibility of purported associations between aluminum and Alzheimer's disease.

In relation to toxicity, this report addresses only potentially critical (i.e., neurological) effects in humans and supporting evidence. Available data to serve as a basis for characterization of the potential of aluminum to induce effects other than those on the neurological system, such as carcinogenicity, genotoxicity and reproductive, developmental and other systemic or organ system effects, are limited. Indeed, there are few experimental studies conducted to recent standards by relevant routes of exposure in which the effects of a range of doses have been examined, with adequate account of dietary exposure. Based on the limited available data, effects observed consistently at lowest doses in experimental animals are those on the neurological

system, specifically neurobehavioural effects in offspring exposed during development and tested as adults or in exposed adults. Aluminum has also been implicated in the induction of several neurological disorders in humans.

In this report, the weight of evidence for these potentially critical neurological effects is considered, therefore, primarily as a basis for delineation of the above-mentioned research plan. Potential exposure of the general population is also addressed primarily to provide perspective on the principal sources and media of exposure and potential bioavailability therefrom. The extent of primary review of relevant information and level of documentation included herein reflect the limited scope and objectives of this report, which builds upon previous initiatives by Health Canada.

The health-related sections on toxicity of this report are based, in part, on the deliberations of a Task Group on Aluminum of the International Programme on Chemical Safety in which staff of Health Canada participated (WHO, 1997) and updates in critical areas, as identified below.

A critical review of the epidemiological data relevant to the characterization of the weight of evidence for neurotoxicity of aluminum was prepared by A. Smargiassi, Université du Québec à Montréal, and subsequently reviewed by:

J. Lindsay, Laboratory Centre for Disease Control, Health Canada
C. Martyn, University of Southampton
L. Smith, Ontario Ministry of Health and Long-term Care

A critical review of data relevant to the characterization of the potential mode of the neurotoxicity of aluminum was prepared by J. Savory, University of Virginia, and subsequently reviewed by:

P.R. Mouton, Johns Hopkins School of Medicine
M. Strong, University of Western Ontario
T. Wisniewski, New York University School of Medicine

A critical review of the available data on the bioavailability of aluminum was prepared by R.A. Yokel and P.J. McNamara, University of Kentucky, and subsequently reviewed by:

M.J. Gardner, Water Research Centre
E. Nieboer, McMaster University
N. Priest, Middlesex University

The health-related sections of this State of the Science Report were prepared by the following staff of Health Canada:

M.E. Meek
J. Paterson

The health-related sections of this Report were reviewed by H. Durham, McGill University and J. Lindsay, Laboratory Centre for Disease Control, Health Canada and approved by the Health Protection Branch Risk Management meeting.

The entire State of the Science Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

The text of the Report has been structured to address environmental effects initially, followed by effects on human health.

2.0 SUMMARY OF CRITICAL INFORMATION

2.1 Identity and physical/chemical properties

Aluminum chloride is also known as aluminum trichloride, aluminum chloride (1:3) and trichloroaluminum (ATSDR, 1992). It has the Chemical Abstracts Service (CAS) registry number 7446-70-0, and its chemical formula is AlCl_3 . In its hydrated form, $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$, 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). Its CAS registry number is 13473-90-0, and its chemical formula is $\text{Al}(\text{NO}_3)_3$. The nonahydrate aluminum nitrate, $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (CAS No. 7784-27-2), is the stable form of this compound.

Aluminum sulfate can also be identified as alum, alumsulfate (2:3), aluminum trisulfate, dialuminum sulfate and dialuminum trisulfate. Its CAS registry number is 10043-01-3, and its chemical formula is $\text{Al}_2(\text{SO}_4)_3$. Alum is often represented as $\text{Al}_2(\text{SO}_4)_3 \cdot 14\text{H}_2\text{O}$. It may be found in different hydrated forms. The commercial product, called cake alum or patent alum, is an octadecahydrate aluminum sulfate, $\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$.

In addition to these three compounds, aluminum polymers such as polyaluminum sulfate (PAS) and polyaluminum chloride (PAC) are used in water treatment. The general formula for PAS is $\text{Al}_a(\text{OH})_b(\text{SO}_4)_c$, where $b + 2c = 3a$; for PAC, the general formula is $\text{Al}_a(\text{OH})_b\text{Cl}_c$, where b/a is usually about 2.5 (e.g., $\text{Al}_2(\text{OH})_5\text{Cl}$). Mixed aluminum polymers may also be used; their general formula is $\text{Al}_a(\text{OH})_b\text{Cl}_c(\text{SO}_4)_d$, and b/a varies between 0.4 and 0.6.

At room temperature, aluminum chloride is a white, grey or yellow to greenish solid (Budavari *et al.*, 1989). It fumes in air and explodes when in contact with water. Hexahydrated aluminum chloride is either a colourless crystal or a white or slightly yellow crystal or powder. Aluminum nitrate is a crystal that deliquesces rapidly in a humid atmosphere. Aluminum sulfate is a white, lustrous crystal or powder. When heated, aluminum chloride will sublime at 181°C , and aluminum nitrate and aluminum sulfate will decompose at 135°C and 770°C , respectively (Budavari *et al.*, 1989; Lewis, 1992). Hydrated aluminum chloride, aluminum nitrate and aluminum sulfate are very soluble in water. Physicochemical properties of the three aluminum salts are presented in Table 1.

2.2 Entry characterization

2.2.1 Production, importation, exportation and use

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, in the cracking of petroleum and in the manufacture of lubricants. In its hydrated form, it is used by pharmaceutical industries and in the preparation of adhesive, paint pigment, resins, fertilizers, deodorants, antiperspirants and astringents (Germain *et al.*, 1999). In water treatment, it is used mainly in polymeric forms as a coagulant.

In 1996, approximately 13 500 tonnes of aluminum chloride and PAC were produced in Canada, 1670 tonnes imported and 5900 tonnes exported, for an apparent consumption of 9270 tonnes (Table 2). According to the sales reported by the different suppliers, pulp and paper (P&P) industries and municipal water and wastewater treatment plants (MWWTPs) consumed, respectively, 30% and 45% of all aluminum chloride and PAC sold in Canada.

2.2.1.2 Aluminum nitrate

Aluminum nitrate can be used as a chemical reagent, in the leather tanning industry, as an antiperspirant, as a corrosion inhibitor, in uranium extraction and as a nitrating agent (Budavari *et al.*, 1989). In Canada, only one user was identified in a survey done in 1997 by Environment Canada (1997b). This user reported that less than 400 kg of aluminum nitrate were included in fertilizers and exported to the United States in 1996 (Germain *et al.*, 1999).

2.2.1.3 Aluminum sulfate

Aluminum sulfate is used primarily in water and wastewater treatment. There are other applications, however, in the leather industry, in the paper industry, as a mordant in dyeing, in fireproofing and waterproofing of textiles, in manufacturing of resins, in fertilizer preparation and in paint pigment preparation in Canada (Germain *et al.*, 1999). Aluminum sulfate can also be used in waterproofing concrete, in decolorizing petrol, in antiperspirants and pesticides (Budavari *et al.*, 1989) and in the treatment of eutrophic or mesotrophic lakes to reduce the amount of nutrients present in the water. It may also be found in food such as baking powder.

Approximately 252 000 tonnes of aluminum sulfate were produced in Canada in 1996, 15 500 tonnes imported and 7060 tonnes exported (Table 2). The apparent consumption was thus about 261 000 tonnes (Germain *et al.*, 1999). The P&P industries and MWWTPs were the main users of aluminum sulfate with, respectively, 21% and 55% of the sales reported. Some MWWTPs reported that they used PAS. However, the quantities involved are small compared with those of aluminum sulfate or aluminum chloride.

2.2.2 Sources and releases

Aluminum sulfate 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 sulfate minerals; however, since aluminum is a common constituent of rocks, where it occurs dominantly in aluminosilicate minerals (e.g., kaolinite, boehmite, clay, gibbsite, feldspar, etc.), which weather and slowly release aluminum to the surface environment, releases of aluminum from aluminum sulfate cannot be distinguished from other natural aluminum releases. These releases would, however, be small compared with releases from aluminosilicate minerals.

Aluminum chloride, aluminum nitrate and aluminum sulfate are produced commercially and used in many applications in Canada. Although they are present in some commercial products, associated releases to the environment are expected to be small. They are used in large amounts 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 ($\text{Al}(\text{OH})_3$). Sludge produced by MWWTPs or industries is sent to landfills or spread on land. 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 is sent to sewers, spread on land or landfilled. Backwash waters (used to clean filters) are also regulated by some provinces; they cannot be discharged directly into an open body of water unless it is shown that there are no adverse effects on the receiving body of water.

Although the majority of the aluminum so released is in particulate hydroxide form, some will be dissolved. Since it is the monomeric aluminum present in the dissolved fraction that can adversely affect organisms, the following discussion considers releases of aluminum in general, focusing mostly on dissolved forms. This approach was necessary because very few studies reported 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 anionic and cationic 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 amounts 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) global stream flux of 2.05 g/m^2 per year, we estimated a total aluminum release (including particulate material) of 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 (2–20 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 identified by the Ministers' Expert Advisory Panel (1995). Accidental releases were reported to Environment Canada's National Analysis of Trends in Emergencies System (NATES) database. Between 1974 and 1991, 24 events released 316.2 tonnes of aluminum sulfate, 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).

Releases of aluminum salts or aluminum resulting from the industrial use of aluminum salts (excluding municipal water treatment operations) totalled approximately 8800 tonnes in 1996 (Table 3), with most (8124 tonnes) going to surface waters (Germain *et al.*, 1999). Some releases were transferred to municipal wastewater treatment plants (MWTPs) (305 tonnes) or disposed of by landfarming (317 tonnes). Mean total aluminum levels measured or calculated in wastewater released into rivers by P&P industries ranged from 0.46 to 4.8 mg/L. Mean total aluminum levels measured for other types of industries ranged from 0.01 to 2.3 mg/L. Environmental Effects Monitoring (EEM) reports provided by the P&P industries mention the distance from the point of release needed to dilute the effluents to less than 1% in the receiving water body. In some cases, effluents were diluted to less than 1% within a few metres; in others, it took up to 300 km. In these cases, water inputs from other rivers were needed in order to reach the 1% dilution.

Municipal water treatment plants, either DWTPs or MWTPs, are the main users of aluminum chloride and aluminum sulfate. Aluminum salts are used as a flocculant or a coagulant 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 ($\text{Al}(\text{OH})_3$) or soluble form (e.g., $\text{Al}(\text{OH})_2^+$, $\text{Al}(\text{OH})_4^-$), dictated by the conditions of the treatment process.

Many of the provinces regulate the releases of process wastewater by DWTPs. In many cases, only backwash waters can be released to the receiving environment. In some cases, older plants are allowed to continue their practice if no major improvements are done.

Approximately half of the 240 DWTPs that answered the questionnaire sent by Environment Canada (Environment Canada, 1997b) reported use of aluminum chloride or aluminum sulfate to treat water. Approximately 30% of these release their sludges containing aluminum directly to rivers (in all cases, the receiving environment was circumneutral; Germain

et al., 1999). These releases account for 58% of the 574 000 tonnes of sludges disposed of in Canada annually (Table 4). Using the available information, we estimated that aluminum released by DWTPs directly into Canadian rivers and on soil by landfarming practices represents approximately 3000 tonnes. Release to sewers with subsequent treatment by MWTPs is the other main disposal practice (32%). A few DWTPs use spreading on agricultural land or landfarming as a disposal practice; about 1700 tonnes are disposed of this way annually. 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.

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 d.w.) was released in water (i.e., 0.20–0.32 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 10 different DWTPs containing up to 2900 mg total Al/L; Calgary's DWTP was one of the plants studied.

Only Calgary's DWTP reported the aluminum content in the 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).

Usually, backwash occurs every 48–72 hours for a given filter, and a complete filter backwash cycle extends over 30–35 minutes, with most of the aluminum being released in the first minutes of the cycle. Sludge containing aluminum is also released at the clarifier or at the sedimentation basin, depending on the equipment present at each plant. Some purge the sludge building up in the clarifier or sedimentation tank for 30 seconds every 10 minutes, for 1 minute every half-hour, or for 5–10 minutes every 2 days, and others “empty” their sedimentation basin once every 3–4 months. Hutchison *et al.* (1973) reported total aluminum levels in backwash waters, clarifiers and sedimentation tanks for approximately 105 DWTPs in Ontario; mean values were 6.2 mg/L, 133.5 mg/L and 1256 mg/L, respectively. On average, backwashes and “purgings” use between 5% and 10% of treated water. The estimated average total aluminum concentrations in effluents are presented in Table 5 for some Canadian DWTPs. These DWTPs are those for which estimated average aluminum levels in effluent were highest among the 30 plants reporting direct releases to the environment (between 5.6 and 155 mg/L).

Not all the MWTPs use aluminum-based coagulants; a quarter of the 287 MWTPs that responded to the Environment Canada questionnaire (Environment Canada, 1997b) treat wastewater with one of the aluminum salts. MWTPs are not permitted to dispose of the sludge produced during water treatment in the rivers. Nearly 90% of the sludges produced are disposed of by agricultural spreading (222 000 tonnes) or landfill (91 000 tonnes) (Germain *et al.*, 1999).

Mean total aluminum levels in the effluent of MWTPs using aluminum salts varied from 0.03 up to 0.84 mg/L, and the maximum value reported by one plant reached 1.8 mg/L. Some plants do not use aluminum-based coagulant but still reported aluminum levels in their effluents; their mean total aluminum levels ranged from 0.003 up to 0.90 mg/L (Germain *et al.*, 1999). These figures are in the same order of magnitude as those reported by Orr *et al.* (1992) for 10 Ontario MWTPs and by MEF and Environnement Canada (1998) for 15 Quebec MWTPs.

P&P mills are the other major user of aluminum salts. In Ontario, MISA (1990) reported mean total aluminum levels ranging from 0.12 up to 6.1 mg/L for the different mills. After 1995, P&P mills had to respect the federal Pulp and Paper Effluent Regulations promulgated in 1992 under the *Fisheries Act*. In Quebec, this resulted in a 57% decrease in total aluminum levels in mill effluent, with reported levels ranging from 0.16 mg/L up to 1.89 mg/L (Germain *et al.*, 1999). Total aluminum concentrations reported by two P&P mills and estimated dissolved inorganic aluminum concentrations in receiving water are presented in Table 5; levels are lower than those for most DWTPs.

2.3 Exposure characterization

2.3.1 Environmental fate

The sections below summarize the information available on the distribution and fate of aluminum and aluminum chloride, aluminum nitrate and aluminum sulfate. More detailed fate information is discussed in supporting documents prepared for this characterization (Bélanger *et al.*, 1999; Germain *et al.*, 1999; Roy, 1999a).

2.3.1.1 Air

In air, hydrated aluminum chloride will react with moisture and produce hydrochloric acid and aluminum oxide (Vasiloff, 1991). It is likely that aluminum nitrate and aluminum sulfate will react the same way and form nitric and sulfuric acids, respectively. Since these aluminum salts are usually not emitted to air, the amount of aluminum present in air that is related to the aluminum salts being considered here would be negligible compared with the amount coming from natural erosion of soil.

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). Soil minerals such as gibbsite and jurbanite are considered as 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 considered in this report are highly soluble and 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 its partitioning among different physical and chemical forms, and solubility are affected by a wide variety of environmental parameters, including pH, temperature, dissolved organic carbon (DOC) and numerous other 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. The reactivity of aluminum, its geochemical behaviour in the aquatic medium as well as its bioavailability depend on its speciation (Neville *et al.*, 1988).

There are two general types of ligands that can form strong complexes with aluminum in solution. Inorganic ligands include anions such as sulfate (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 will basically determine which type of complex is 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, however, of primary importance to the fate and behaviour of aluminum.

DOC will complex aluminum in water, forming aluminum–organic complexes and reducing concentrations of monomeric forms of aluminum (Frag *et al.*, 1993; Parent *et al.*, 1996). At pH 4.5, 1 mg DOC/L can complex approximately 0.025 mg Al/L, with its complexing capacity increasing as pH increases (Neville *et al.*, 1988). Fractions of dissolved organic aluminum in various rivers in Canada were estimated with MINEQL+ and WHAM models; results varied between 1% and 94%, with the highest values at the lowest pH in the range of pH considered (6.5–8.5) (Fortin and Campbell, 1999).

Aluminum is a strongly hydrolysing metal and is relatively insoluble in the neutral pH range (6.0–8.0) (Figure 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., $\text{Al}(\text{OH})^{2+}$, $\text{Al}(\text{OH})_2^+$). Aluminum solubility is at a minimum near pH 6.5 at 20°C and then increases as the anion, $\text{Al}(\text{OH})_4^-$, 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 form Al^{3+} and $\text{Al}(\text{OH})^{2+}$. In the pH range 5.7–6.7, aluminum hydroxide species dominate, including $\text{Al}(\text{OH})^{2+}$ and $\text{Al}(\text{OH})_2^+$. In this range, aluminum solubility is low, and availability to aquatic biota should also be low. At pH >6.7, $\text{Al}(\text{OH})_4^-$ becomes the dominant species. Aluminum–hydroxide complexes predominate over aluminum–fluoride complexes under alkaline conditions. However, calculated aluminum speciation in some rivers in Canada indicated that only one river has a significant concentration (>1%) of aluminum–fluoride complexes; this river had a pH below 7 (Fortin and Campbell, 1999).

Aluminum mononuclear 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 notably over 4.5:



Polymerization gradually proceeds to larger structures, eventually leading to the formation of the Al_{13} polycation (Parker and Bertsch, 1992a,b). 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).

When released into water, within DWTPs, for example, 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 or sludge, which separates from the water phase. A small fraction of the aluminum can stay in the water in either colloidal or truly 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:



When used to treat sewage water, alum will also react with phosphate, and the reaction gives (Romano, 1971; Barnes, 1985):



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

2.3.1.3 Soil

Atmospheric deposition of aluminum is attributed mostly to the deposition of dust particles and is generally low (Driscoll *et al.*, 1994). Aluminum is the third most abundant element in the earth’s crust and makes up approximately 8% of its rocks and minerals (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. On the other hand, 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 bioavailability of aluminum to plant 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).

In eastern Canada, the atmospheric deposition of strong acids, such as nitric acid and sulfuric acid, has accelerated the soil's natural acidification. 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.

The 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 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^- . Consequently, aluminum–hydroxide complexes predominate over aluminum–fluoride complexes in alkaline conditions.

The complexation of aluminum with sulfate is weaker than that with fluoride. However, in acidic soils where the sulfate concentration is high, aluminum may also form aluminum–sulfate complexes (Driscoll and Postek, 1996). At low sulfate concentrations, AlSO_4^+ is the dominant aqueous form, whereas $\text{Al(SO}_4)_2^-$ is predominant in soil solutions with higher sulfate concentrations. Brown and Driscoll (1992) showed that several aluminosilicate complexes, including AlSiO(OH)_3^{2+} , are present in various regions of the eastern United States and Canada.

It has been shown that most dissolved aluminum in the 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 sites, 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 represented 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.

The use of alum sludge as a soil amendment is the primary pathway by which aluminum present in the three compounds being considered in this report enters the terrestrial environment. However, the amount of aluminum added to soil through this practice is small in comparison with aluminum naturally present in soil. Moreover, since spreading on agricultural land is permitted only when the pH is greater than 6.0 or when liming and fertilization (if necessary) are done, the solubility (and hence bioavailability) of this aluminum is expected to be very limited.

2.3.1.4 Sediment

Sediments, where the metal is generally considered as biologically unavailable, are an important compartment 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 it can be bound to organic matter (fulvic/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 inputs of acid (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 calculations 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 DWTPs directly to surface waters is the primary pathway by which aluminum from the three compounds being assessed enters sediment. If the water velocity is low at the point of discharge, much of the sludge released will settle onto the surface of local sediment. Since in Canada the waters receiving such discharges are typically circumneutral, the solubility (and hence bioavailability) of aluminum in the sludge will generally be minimal.

2.3.1.5 Biota

Few studies have examined the 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, e.g., 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 1365 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 d.w. for the entire body and <0.1 nmol/g d.w. for the internal structures. Most aluminum either is 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 1300 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 (325–3526). BCFs calculated for grain and forage crops ranged from 4 to 1260 in foliage and from 200 to 6000 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

In order to identify aluminum levels in the Canadian environment, federal and provincial databases were consulted. Results obtained were expressed in different forms, according to media and analytical methods used. The methods used usually provide comparable results for a given form (e.g., total, extractable or dissolved) of aluminum. Data that were of questionable quality were not retained.

2.3.2.1 Ambient air

The aluminum content of particulate matter that is smaller than 10 µm in diameter (PM₁₀) in air varies depending upon the region and municipality where measurements are made (Germain *et al.*, 1999). In 30 ambient air sites sampled over a 10-year period (1986–1995), mostly in urban locations across Canada, total aluminum concentrations measured in individual samples of PM₁₀ ranged from the limit of detection (approximately 0.001 µg/m³) to 24.94 µg/m³. The mean for each sampling site varied from 0.046 to 1.31 µg/m³. The lowest mean concentration was measured in Sutton, Quebec, a reference site, and the highest was measured in Vancouver, B.C. The Vancouver site also had the highest maximum value measured in Canada. In general, however, the aluminum salts considered in this characterization are unlikely to have contributed significantly to levels of aluminum measured in ambient air, because they are typically not released to air.

2.3.2.2 Indoor air

In a study conducted in Riverside, California, daytime and nighttime personal exposure PM₁₀ samples were collected from 178 non-smokers; concurrently, PM₁₀ and PM_{2.5} (particulate matter smaller than 2.5 µm in diameter) samples were collected from stationary monitors inside and outside their residences (Clayton *et al.*, 1993; Thomas *et al.*, 1993). Aluminum was measurable in more than 50% of daytime or nighttime personal exposure PM₁₀ samples but in less than 20% of fixed-location indoor and outdoor PM_{2.5} samples. Levels greater than 0.55 µg/m³ were considered measurable. Daytime median concentrations of aluminum were 1.9, 2.5 and 3.4 µg/m³ for the PM₁₀ indoor, outdoor and personal exposure monitors, respectively; the corresponding nighttime concentrations were 0.99, 1.7 and 1.0 µg/m³ (Clayton *et al.*, 1993). Based on a mass-balance model with multivariate analysis, outdoor air was estimated to be the major source of aluminum-containing particles in indoor air, and cooking and smoking were identified as major indoor sources of aluminum in air (Özkaynak *et al.*, 1996).

2.3.2.3 Surface water

Aluminum is a naturally occurring element and is present in all the 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 (0.01–0.1 µm) and organic aluminum (aluminum bound with soluble organic ligands) that are included in this fraction are not bioavailable.

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 from the Abitibi, Quebec, region. Mean dissolved aluminum concentrations varied from 0.01 to 0.08 mg/L; the highest dissolved aluminum value reported was 0.9 mg/L, in British Columbia.

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.*, 1999). 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 the Regional Municipality of Ottawa-Carleton's (RMOC) DWTP in water samples taken during 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 discharge. In the Kaministiquia River, the increase in mean total aluminum noted from upstream to downstream stations corresponds approximately to the inputs from the P&P 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 1990–1996 period is equivalent to the predicted aluminum increase of 0.069 mg/L calculated with the aluminum releases reported by the mill (Germain *et al.*, 1999). 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 MINEQL+ model and estimated concentrations in effluents, assuming solubility controlled by microcrystalline gibbsite (Fortin and Campbell, 1999). Using boehmite as the controlling phase provided lower dissolved inorganic aluminum levels (0.005 mg/L and 0.007 mg/L, respectively).

2.3.2.4 Drinking water

Aluminum is present in drinking water from natural sources and due to the use of salts such as alum or polyaluminum chloride as coagulants in DWTPs to remove organic compounds, microorganisms and particulate matter (Health Canada, 1998).

Data on concentrations of aluminum in drinking water were obtained from monitoring programs in five provinces and territories for the years 1990–1998. Samples were collected from municipal distribution systems for treatment plants with surface water sources and from municipal wells. The majority of the data are for an acid-leachable aluminum fraction that

generally involves sample acidification in the field with nitric acid and filtration (using 0.4- to 0.45- μm filters) prior to analysis if solids are present. Because it does not require vigorous digestion, the acid-leachable fraction is less expensive and more practical for routine analysis; in the absence of significant amounts of particulate matter, it is assumed to approximate total aluminum.

The frequency of detection of aluminum at the provincial/territorial sites ranged from 35% for the Northwest Territories in 1990–1992 (18/52 sites) to 100% for Ontario in 1996–1997 (124/124 sites) (Facey and Smith, 1993; OMEE, 1998). Detection limits ranged from 0.1 $\mu\text{g/L}$ in Alberta to 60 $\mu\text{g/L}$ in the Northwest Territories (Facey and Smith, 1993; Alberta Environmental Protection, 1998). Arithmetic mean concentrations of aluminum ranged from 20 $\mu\text{g/L}$ in New Brunswick for 1995–1998 to 208 $\mu\text{g/L}$ in Alberta for 1998 (New Brunswick Department of the Environment, 1996, 1998a,b; Alberta Environmental Protection, 1998). The highest mean concentration of aluminum for an individual sampling site, 3300 $\mu\text{g/L}$, occurred in a distribution system site in Manitoba, and the lowest mean concentration, < 0.1 $\mu\text{g/L}$ (detection limit), in several sites in Alberta (Manitoba Environment, 1996; Alberta Environmental Protection, 1998).

For New Brunswick, data on aluminum levels in a variety of different sources of drinking water, including municipal distribution systems, municipal reservoirs, municipal wells and domestic (private) wells, were obtained for the years 1995–1998. Mean concentrations of aluminum were 20, 47, 20 and 44 $\mu\text{g/L}$ for the municipal distribution systems, municipal reservoirs, municipal wells and domestic wells, respectively. Among the municipal distributions systems, reservoirs and wells, the highest mean concentration of aluminum, 221 $\mu\text{g/L}$, occurred at municipal well sites, and the lowest, < 2 $\mu\text{g/L}$ (detection limit), occurred in both the municipal wells and distribution systems. Each domestic well was sampled only once, and the highest and lowest aluminum levels recorded were 3500 $\mu\text{g/L}$ and the detection limit, respectively.

2.3.2.5 Soil

According to data provided by the Geological Survey of Canada (Garrett, 1998), median total aluminum levels for soils and their associated glacial till parent materials lie in the range of 5.0–5.6% in the Prairies and 6.1–6.8% in southern Ontario. The Prairie values are slightly lower than those for southern Ontario, probably due to the greater proportion of Prairie surface materials derived from carbonate (limestone and dolomite) and sandstone bedrock sources than in the southern Ontario survey area, where aluminum-rich Precambrian Shield rocks are more abundant (Germain *et al.*, 1999). The Ontario Ministry of the Environment has developed typical range values (OTR_{98}), which indicate the expected maximum concentrations for different elements or compounds. The aluminum OTR_{98} value for old urban parkland is 2.7% and for rural parkland, 3.0%, based on a partial extraction with nitric acid (OMEE, 1994). In soil collected in a sugar maple (*Acer saccharum* Marsh.) stand located at St. Hippolyte in the Lower Laurentians, Quebec, oxalate-extractable aluminum levels ranged from 0.1% to 2.9% (Hendershot and Courchesne, 1991). It should be remembered that these total and strong acid-extractable aluminum data provide little indication of the amounts of aluminum that might be bioavailable.

In general, unless the soil pH falls below 4, levels of the Al^{3+} bioavailable form 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 0.016–0.397 mg/L in limed plots (Su and Evans, 1996).

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 2330 mg Al/kg d.w., and the alum residual, 6350 mg/kg d.w. In cropland soil, relatively bioavailable aluminum (measured with a Mehlich III extraction procedure) varied between 405 and 543 mg/kg d.w. (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 bioavailable aluminum to 770 mg/kg d.w. and 1115 mg/kg d.w., respectively. In another experiment, alum residual containing 150 000 mg Al/kg d.w. 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.

2.3.2.6 Sediment

Based on limited data, total aluminum levels in Canadian sediments are of the same order of magnitude as those measured in soils, 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 discharges from RMOC's DWTP. The total aluminum content of sediment from a control site was 1.7%, while the value closest to the outfall was 12.5% (Germain *et al.*, 1999). However, based on the data available, the area with high aluminum levels extended no more than a few hundred metres downstream from the discharge point.

2.3.2.7 Vegetation

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* Michx.) foliage collected from trees near an aluminum chloride producer in Sarnia, Ontario. Total aluminum levels ranged from 25 to 170 mg/kg d.w. in 1989 and from 57 to 395 mg/kg d.w. 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).¹

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* L.) in control and treated soils. Statistical differences in aluminum contents were noted only in corn tissues. Aluminum levels were lower (15.1 mg/kg d.w. vs. 18.6–19.6 mg/kg d.w.) 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 d.w.) and treated (152–170 mg/kg d.w.) soil.

2.3.2.8 Food

Levels of aluminum were determined in a 1993–1996 market basket survey of various foodstuffs collected from six Canadian cities: Halifax, Montréal, Ottawa, Toronto, Vancouver and Winnipeg (Dabeka *et al.*, 1999). Data included concentrations of aluminum in 124 individual food items of the various food composite groups routinely consumed by the general population of Canada (Environmental Health Directorate, 1998). The fraction analysed was total aluminum based on nitric and perchloric acid digestion of the samples, and detection limits ranged from 0.005 to 7.6 µg/g (Dabeka, 1999). Mean concentrations of aluminum were 0.27 µg/g in eggs, 0.34–1.1 µg/g in mixed dishes and soups, 0.02–1.3 µg/g in vegetables, 0.07–1.5 µg/g in dairy products, 1.8–4.0 µg/g in nuts and seeds, 0.09–4.4 µg/g in beverages (including soft drinks and alcohol), 0.02–4.2 µg/g in fruit, 0.08–5.6 µg/g in foods containing primarily sugar, 0.43–7.0 µg/g in meat and poultry, 0.14–7.2 µg/g in fats, 0.53–12 µg/g in fish and 0.15–165 µg/g in cereal products (Dabeka *et al.*, 1999).

Relatively high levels of aluminum can occur naturally in foods such as raisins (17 µg/g), shellfish (12 µg/g) and cucumbers (6 µg/g) (Dabeka *et al.*, 1999). However, some of the highest mean concentrations that were determined, for cakes (165 µg/g), muffins (93 µg/g), pancakes (85 µg/g) and danishes and donuts (46 µg/g) are, at least in part, due to the use of aluminum-containing food additives in these products. The Food and Drug Regulations of the *Food and Drugs Act* permit the use of aluminum-containing additives (e.g., calcium aluminum silicate, sodium aluminum silicate, sodium aluminum phosphate, aluminum sulfate, etc.) as agents for anticaking, colouring, emulsifying, gelling, stabilizing, thickening and other uses in a variety of food products. The Food and Drug Regulations indicate that the maximum levels of most aluminum-containing food additives should be in accordance with good manufacturing practice. For other additives, specific maximum levels of use prescribed in the Regulations range from 0.036% (360 µg/g) for aluminum sulfate in egg products to 3.5% for sodium aluminum phosphate in creamed and processed cheese products (Health Canada, 2000).

¹ 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 sulfate plants.

Data from the six-city market basket survey also included levels of aluminum in infant formula. The mean concentrations of aluminum in ready-to-use milk- and soya-based formula were 0.06 and 0.85 $\mu\text{g/g}$, respectively (Dabeka *et al.*, 1999). In an earlier study, Dabeka and McKenzie (1992) measured total aluminum in 282 samples of infant formula and evaporated milk sold in Canada. Mean concentrations for milk-based ready-to-use, concentrated liquid and powdered formula were 0.18, 0.27 and 1.4 $\mu\text{g/g}$, respectively, and the corresponding concentrations for soya-based formula were 1.6, 1.4 and 5.2 $\mu\text{g/g}$, respectively.² The mean concentration of aluminum in evaporated milk was 0.08 $\mu\text{g/g}$.

A wide range of concentrations of aluminum have been reported in breast milk from various countries, which may, in part, be due to the variation in methods of analysis and sample preparation used. Mean concentrations range from 9.2 $\mu\text{g/L}$ (0.009 $\mu\text{g/g}$)³ determined by acid digestion and graphite furnace atomic absorption analysis (GF-AAS) of samples from 15 U.K. women to 380 $\mu\text{g/L}$ (0.37 $\mu\text{g/g}$) estimated for 42 Croatian women using similar sample preparation and analysis methods (Hawkins *et al.*, 1994; Mandić *et al.*, 1995). Levels of aluminum in breast milk reported in two Canadian studies fall within the range of levels reported for other countries. Using a unique non-destructive rapid neutron activation method, Bergerious and Boisvert (1979) determined an average aluminum concentration of 350 $\mu\text{g/L}$ (0.34 $\mu\text{g/g}$) for samples from 5 Quebec women, whereas Koo *et al.* (1988), using GF-AAS analysis, reported a median aluminum concentration of 14 $\mu\text{g/L}$ (0.014 $\mu\text{g/g}$) for breast milk from 12 Alberta women.

The aluminum content of foods and beverages, especially salty, alkaline or acidic foods, may be increased following cooking in aluminum pots and pans or storage in aluminum containers (ATSDR, 1999). Lione (1983) reported that the aluminum content of tomatoes increased from 1.3 mg/100 g d.w. uncooked to 32 mg/100 g d.w. following 2 hours of cooking in an aluminum pot and to 53 mg/100 g d.w. after overnight storage in the same pot. Greger *et al.* (1985) noted that cooking in aluminum versus stainless steel cookware significantly increased the aluminum content of applesauce (7.1 vs. 0.12 $\mu\text{g/g}$ w.w.), roast beef (0.85 vs. 0.21 $\mu\text{g/g}$ w.w.), cabbage (3.6 vs. 0.20 $\mu\text{g/g}$ w.w.) and eggs (1.6 vs. 0.13 $\mu\text{g/g}$ w.w.). However, the aluminum content of foods such as green beans, cod, ham and rice was not significantly altered. Concentrations of aluminum in beverages such as coffee and acidic soft drinks can also be increased following brewing in aluminum coffee percolators and storage in aluminum soft drink cans, respectively (Lione *et al.*, 1984; Muller *et al.*, 1993; Abercrombie and Fowler, 1997).

² Values for milk- and soya-based concentrated liquid and powdered formula were for undiluted products (Dabeka and McKenzie, 1992).

³ Breast milk density assumed to be 1.03 g/mL (Environmental Health Directorate, 1998).

2.3.2.9 Consumer products

Aluminum compounds are used in a variety of over-the-counter medicinal products sold in Canada, such as antacids and adsorbents for the treatment of heartburn, gas and indigestion (e.g., aluminum hydroxide); analgesics or buffered aspirins (e.g., dihydroxyaluminum aminoacetate); local anti-infectives for cold and canker sores (e.g., aluminum chloride); and hemostatics to control bleeding from minor cuts (e.g., aluminum potassium sulfate). Concentrations of aluminum compounds in over-the-counter products sold in Canada were obtained from the Health Canada Drug Product Database. The Drug Product Database contains brand name, Drug Identification Number (DIN), ingredient and other information for approximately 20 000 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 5900–90 000 ppm for antacids and adsorbents, 11 000 ppm for cathartics and laxatives, 16 000 ppm for analgesics, 21 000 ppm for local mucosal anesthetics (heartburn medication) and 5500–110 000 ppm for antidiarrheal agents (Health Canada, 1999a).⁴ For topically (dermally) administered products, concentrations range from 661 ppm for an anti-infective liquid for the prevention of swimmer's ear to 58 000 ppm in an astringent powder used to treat eczema, poison ivy, insect bites, etc. (Health Canada, 1999a).

Compounds such as aluminum chlorohydrate, aluminum hydroxide, aluminum starch octenylsuccinate, aluminum-based dyes and aluminum silicate are also used in antiwrinkle preparations, dentrifices, eye and face makeup, shampoo, lipstick, moisturizers and other cosmetic products sold in Canada. Concentrations of aluminum compounds in cosmetic products were obtained from 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. Based on available information on the aluminum content of active ingredients listed in the Cosmetic Notification System, estimated concentrations of elemental aluminum in cosmetic products range from 346 to 330 000 µg/g for antiwrinkle preparations, 235 to 3300 µg/g for barrier creams, 1600 to 10 000 µg/g for dentrifices, 2000 to 93 000 µg/g for deodorants, 40 to 1.0×10^6 µg/g for eye makeup, 42 to 35 000 µg/g for face makeup, 210 to 700 µg/g for fragrances, 1600 to 16 000 for hair conditioner, 442 to 30 000 µg/g for hair dye, 158 to 52 000 µg/g for lipstick, 1000 to 100 000 µg/g for manicure preparations, 3500 to 13 000 µg/g for various powders, 78 to 100 000 µg/g for skin cleansers and 235–100 000 for skin moisturizers (Health Canada, 1999b).

⁴ Concentrations expressed in ppm (parts per million) are equivalent to µg/g for products in tablet or powder form or mg/L for products in liquid, suspension or jelly form.

2.4 Effects characterization

2.4.1 Ecotoxicology

Below, a brief summary of effects data for the most sensitive terrestrial and aquatic organisms is presented. More extensive descriptions of environmental effects are provided in several reviews (ATSDR, 1992, 1999; 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 this monomeric aluminum, 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.

Many studies were published regarding aluminum toxicity, but only studies published since 1980 with good quality controls or procedures were retained. Studies with dissolved aluminum levels greater than the aluminum limit of solubility were discarded.

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, we examined studies looking at the impact of aluminum at many pHs, but paid particular attention to those conducted in circumneutral conditions similar to those occurring where aluminum salts or aluminum resulting from the use of one of the salts considered are released. Because of this constraint, the most relevant effects data identified were for fish.

2.4.1.1.1 Pelagic

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 Ca²⁺ and Mg²⁺ 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 improves survival (Booth *et al.*, 1988; Mount *et al.*, 1988; Sadler and Lynam, 1988), reduces losses of plasma ions (Brown, 1981; Sadler and Lynam, 1988; McDonald *et al.*, 1989) and reduces accumulation of aluminum on gills (Wood *et al.*, 1988a,b).

The toxicity of dissolved aluminum is reduced in the presence of inorganic ligands, such as fluorides, sulfates 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 bioavailability 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) and fulvic acid (Neville, 1985; Lydersen *et al.*, 1990; Witters *et al.*, 1990; Roy and Campbell, 1997). In laboratory studies with amphibians (frog eggs and tadpoles), LC₅₀s 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 LC₅₀ 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 *D. retrocurva*. France and Stokes (1987) concluded that stress from aluminum exposure was secondary to the stress of low-pH exposure for survival of *Hyaella 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 4–5) waters if concentrations exceed 200 µg inorganic Al/L.

At pH 6.0–6.5, 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 6.5–8.0, 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; Hall and Hall, 1989; 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.

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_{50s} for exposures of rainbow trout in the pH range 8.0–8.6. The LC_{50s} 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 most, if not all, of the dissolved aluminum at this pH was the monomeric aluminate ion, AlOH₄⁻.

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.

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, but no reference to this kind of use was found for Canada. Lamb and Bailey (1981) concluded that a well-planned 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). 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) 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. 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 the smothering effect from sludge may prove to be more important than aluminum content to aquatic organisms. In studies related to wastewater releases by DWTPs, AEC (1984) reported smothering effects related to settled sludge on sediments following their release to rivers in Alberta.

2.4.1.2 Terrestrial organisms

The following discussion focuses on the effects of aluminum on sensitive plant species, since toxicity data identified for other soil-dwelling organisms (e.g., microorganisms, fungi and invertebrates) were very limited. 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). 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.

Aluminum present in solution, soil solution or soil itself 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* L.) (Thornton *et al.*, 1986a,b). 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* L.) (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* Mill.) (Cumming and Weinstein, 1990). Seedlings inoculated with mycorrhizal fungus, *Pisolithus tinctorius* (Pers.), 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* L.), 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 10-fold. 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* L.) cultivars and eight common wheat (*Triticum aestivum* L.) 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*, *T. subterraneum* and *T. 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* L. 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 aluminum bioavailability.

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 4.5–4.7).

Although inorganic monomeric forms of dissolved aluminum (Al^{3+} , $\text{Al}(\text{OH})^{2+}$ and $\text{Al}(\text{OH})_2^+$) are believed to be the most bioavailable and responsible for most toxic effects (Alva *et al.*, 1986; Noble *et al.*, 1988), information on the concentrations of different dissolved aluminum complexes was not reported in the effects studies reviewed. However, since all of the studies indicating particular sensitivity 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 *Abiotic atmospheric effects*

Based on available information on the physical and chemical properties of aluminum chloride, aluminum nitrate and aluminum sulfate, and the fact that releases of these substances to the atmosphere in Canada are negligible (Section 2.2.2), these aluminum salts are not considered to be involved in the depletion of stratospheric ozone, tropospheric ozone formation or climate change.

2.4.3 *Experimental animals and in vitro*

Identified information on neurological effects in laboratory animals of aluminum salts administered orally, dermally or by inhalation is briefly summarized in this section in the context of the limited scope and objectives of this report, which builds on previous initiatives by Health Canada. The results of the majority of these studies have been reviewed elsewhere (Domingo, 1995; Golub and Domingo, 1996; WHO, 1997; ATSDR, 1999). Tables 6 and 7 contain brief descriptions of the species considered, exposure levels, duration and principal neurological results for each study.

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. In general, there has been no significant evidence of Alzheimer’s disease-like neuropathology in studies of the oral administration of aluminum to mice and rats (WHO, 1997; ATSDR, 1999).

Neurobehavioural alterations in adult mice and rats following the administration of aluminum salts in drinking water, in diet or by gavage for periods ranging from 1 month to 1 year include decreased locomotor activity (Commissaris *et al.*, 1982; Golub *et al.*, 1989, 1992a; Lal *et al.*, 1993), motor coordination (rota-rod treadmill performance) (Bowdler *et al.*, 1979; Şahin *et al.*, 1995) and grip strength (Golub *et al.*, 1992a; Oteiza *et al.*, 1993), learning and memory deficits (impaired maze performance, active and passive conditioned avoidance responses) (Commissaris *et al.*, 1982; Fleming and Joshi, 1987; Connor *et al.*, 1988, 1989; Bilkei-Gorzó, 1993; Lal *et al.*, 1993; Zheng and Liang, 1998), increased sensitivity to flicker (Bowdler *et al.*, 1979) and increased (Oteiza *et al.*, 1993) and decreased (Golub *et al.*, 1992a) startle responsiveness (Table 6).

Histopathological changes to the brain have been reported in several studies in which rats consumed drinking water or diets supplemented with aluminum salts for periods ranging from 21 days to 6 months (Table 6). In some cases, effects such as cytoplasmic vacuolization and swelling of astrocytic processes and neuronal nuclear vacuolization and inclusions were scattered throughout the brain parenchyma (Florence *et al.*, 1994). In other studies, multifocal neuronal degeneration, abnormal and damaged neurons and reduced neuronal density were identified in specific brain regions (e.g., cerebral cortex, subcortical region, hippocampus, base of brain) (Roy *et al.*, 1991; Varner *et al.*, 1993, 1998; Somova *et al.*, 1997). Somova *et al.* (1997) observed deformity and vacuolization of nuclei and neurofibrillary degeneration localized in the hippocampus after administering aluminum chloride to rats in drinking water for 6 months, but the neurofibrillary degeneration was distinct from the neurofibrillary tangles (NFTs) of Alzheimer’s disease. It has been postulated that the neuropathological effects observed in some of these studies (Varner *et al.*, 1993, 1998; Florence *et al.*, 1994) may have been the result of increased bioavailability of aluminum due to the administration of the citrate and fluoride salts (ATSDR, 1999).

Some of the biochemical changes to the brains of adult mice, rats and monkeys resulting from oral administration of aluminum salts for varying periods of time include alterations to second messenger systems (Johnson and Jope, 1987; Johnson *et al.*, 1992; Hermenegildo *et al.*, 1999), evidence of oxidative damage (lipid peroxidation) and effects on antioxidant systems (Fraga *et al.*, 1990; Lal *et al.*, 1993; Gupta and Shukla, 1995; Katyal *et al.*, 1997; Abd El-Fattah *et al.*, 1998; Sarin *et al.*, 1998). Alterations to membrane lipid content and membrane-bound enzyme activities (Lal *et al.*, 1993; Sarin *et al.*, 1998), effects on cholinergic enzyme activities

(Bilkei-Gorzó, 1993; Kumar, 1998), decreased levels and increased phosphorylation of microtubule-associated and neurofilament proteins (Johnson *et al.*, 1992; Jope and Johnson, 1992) and alterations to catecholamine levels (Flora *et al.*, 1991) have also been observed.

Gestational, lactational and/or post-weaning exposure of rats and mice to aluminum salts through the diet or by gavage has produced neurobehavioural effects in offspring; in some cases, these effects have persisted into adulthood (Table 7). Some of the most commonly observed effects include decreased grip strength (Golub *et al.*, 1992b, 1995), reduced temperature sensitivity (Donald *et al.*, 1989; Golub *et al.*, 1992b), reduced auditory startle responsiveness (Misawa and Shigeta, 1993; Golub *et al.*, 1994) and impaired negative geotaxis response (Bernuzzi *et al.*, 1986, 1989a; Muller *et al.*, 1990; Golub *et al.*, 1992b). Decreased activity levels (Cherroret *et al.*, 1992; Misawa and Shigeta, 1993) and locomotor coordination (Bernuzzi *et al.*, 1989a,b; Muller *et al.*, 1990) and impaired righting reflex (Bernuzzi *et al.*, 1986, 1989b) have also been observed.

Exposure of mice and rats to aluminum salts during gestation, lactation and post-weaning also produced some evidence of disturbances in brain biochemistry, such as alterations in brain lipid contents and increased lipid peroxidation (Verstraeten *et al.*, 1998), 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), decreased concentrations of manganese in brain (Golub *et al.*, 1992b, 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).

2.4.4 Humans

In this section, information on the neurological effects for which associations with aluminum have been reported in humans following oral, dermal or inhalation exposure is briefly summarized in the context of the limited scope and objectives of this report, which builds on previous initiatives by Health Canada. Most of this information has been reviewed elsewhere (Nieboer *et al.*, 1995; WHO, 1997; ATSDR, 1999; Smargiassi, 1999). Initially, a brief summary of the results of available epidemiological studies of associations between aluminum in the general environment and Alzheimer's disease or cognitive dysfunction is presented; more detailed descriptions of the relevant individual analytical epidemiological studies of aluminum in drinking water are provided in Table 8. Information on neurobehavioural effects in workers occupationally exposed to aluminum is also briefly summarized based primarily on the results of previous reviews (Nieboer *et al.*, 1995; WHO, 1997; ATSDR, 1999; Smargiassi, 1999).

An association between Alzheimer's disease or cognitive dysfunction and exposure to aluminum in drinking water has been examined in analytical epidemiological studies (i.e., cohort, case–control and cross-sectional) conducted in populations from Ontario, Quebec, England, France and Switzerland (Table 8). Positive results have been reported for the studies from Ontario (four studies) (Neri and Hewitt, 1991; Neri *et al.*, 1992; Forbes *et al.*, 1992; 1994; 1995a; 1995b; Forbes and Agwani, 1994; Forbes and McLachlan, 1996; McLachlan *et al.*, 1996), Quebec (one

study) (Gauthier *et al.*, in press) and France (two studies) (Michel *et al.*, 1991; Jacqmin *et al.*, 1994; Jacqmin-Gadda *et al.*, 1996).

One of the studies from Ontario consisted of a series of analyses of the relationships between cognitive impairment, aluminum and physical-chemical parameters in drinking water conducted on the same sample population from the Ontario Longitudinal Study of Aging (LSA) (Forbes *et al.*, 1992; 1994; 1995a; Forbes and Agwani, 1994). A second study from Ontario (Forbes *et al.*, 1995b; Forbes and McLachlan, 1996) included an analysis of the association between aluminum in drinking water and Alzheimer's disease or presenile dementia recorded on death certificates and a follow-up analysis based on the same dataset but with a different age grouping and exposure categories, and adjusting for different water quality parameters. Neri and Hewitt (1991) examined the relationship between Alzheimer's disease or presenile dementia and aluminum using hospital discharge records from Ontario and Neri *et al.* (1992) later updated this analysis. The fourth study from Ontario was a case-control analysis of Alzheimer's disease in brain tissue bank donors and concentrations of aluminum in residential drinking water (McLachlan *et al.*, 1996). The degree of overlap between the cohorts from these four studies is unclear. The single positive study from Quebec was a case-control analysis of Alzheimer's disease and exposure to various aluminum species in residential drinking water (Gauthier *et al.*, in press).

Both of the positive studies from France were based on the Principle Lifetime Occupation and Cognitive Impairment in a French Elderly Cohort (PAQUID). In the first study (Michel *et al.*, 1991) a positive association between aluminum in drinking water and Alzheimer's disease was reported, but the results have been discounted because of a reliance on outdated information on concentrations in drinking water (Jacqmin *et al.*, 1994; Smith, 1995; WHO, 1997). The second French study included an initial report of the effect of pH on the association between aluminum and cognitive impairment (Jacqmin *et al.*, 1994) and a follow-up report in which the analysis was expanded to include the effect of silica (Jacqmin-Gadda *et al.*, 1996).

Studies in which no association was observed included three conducted on populations from England (Forster *et al.*, 1995; Martyn *et al.*, 1997; Wood *et al.*, 1988) and one from Switzerland (Wettstein *et al.*, 1991). The studies from England consisted of two case-control studies of Alzheimer's type presenile dementia and Alzheimer's disease in populations from a number of different regions across the country (Forster *et al.*, 1995; Martyn *et al.*, 1997) and a cross-sectional study of the relationship between dementia in patients from northern England and aluminum in drinking water (Wood *et al.*, 1988). The degree of overlap between the populations analysed in these studies is not clear. The negative study from Switzerland was a cross-sectional examination of dementia in octogenarians from Zurich and aluminum in drinking water (Wettstein *et al.*, 1991).

Although not as inherently sensitive as the analytical studies, in four ecological epidemiological studies conducted over the past 15 years, there has been a positive association between the occurrence of Alzheimer's disease and aluminum in drinking water (Vogt *et al.*, 1986; Martyn *et al.*, 1989; Flaten, 1990; Frecker, 1991).

In the analytical epidemiological studies conducted in France and Ontario, physical-chemical parameters in water such as pH, fluoride, and silica were reported to be cofactors for the association between aluminum in drinking water and Alzheimer's disease or cognitive dysfunction. For instance, the association between aluminum and cognitive impairment observed by Jacqmin *et al.* (1994) was positive for pHs ≤ 7.3 and negative for pHs > 7.3 , and in the follow-up analysis (Jacqmin-Gadda *et al.*, 1996), there was a significant positive association only when both pH and silica were low (7.35 and 10.4 $\mu\text{g/L}$, respectively). In their examination of the association between cognitive impairment and aluminum, fluoride and pH, Forbes *et al.* (1992; 1994) observed the lowest risks when levels of aluminum were relatively low ($< 84.7 \mu\text{g/L}$), levels of fluoride were relatively high ($\geq 880 \mu\text{g/L}$) and pHs were neutral (7.85-8.05). Based on these results, the authors suggested that more bioavailable forms of aluminum may be present at acidic or basic pHs and the effects of these forms of aluminum are decreased in the presence of fluoride (Forbes *et al.*, 1994). Forbes *et al.* (1995a) also reported variations in associations between aluminum and cognitive impairment with low ($< 790 \mu\text{g/L}$) and high levels ($\geq 790 \mu\text{g/L}$) of silica. They observed the lowest risks when levels of aluminum and silica were both low or when levels of both substances were high. These results are consistent with those from the Ontario study of death certificates by Forbes *et al.* (1995b) in which some of the highest risks for Alzheimer's disease were observed when concentrations of aluminum of $\geq 336 \mu\text{g Al/L}$ were combined with high pHs (≥ 7.95), low levels of fluoride ($< 300 \mu\text{g/L}$) or low levels of silica ($< 1500 \mu\text{g/L}$). However, in the study from England by Martyn *et al.* (1997) in which no association was observed between exposure to aluminum and Alzheimer's disease, restricting the analysis to subjects exposed to low levels of silica in drinking water ($< 6 \text{ mg/L}$) did not alter the overall results.

There have been no or only very weak associations between exposures to aluminum in antacids and Alzheimer's disease 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). Associations between Alzheimer's disease 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, misclassification due to varying brands and subtypes of antiperspirant with varying aluminum contents, etc.) (Graves *et al.*, 1990; CSHA, 1994). In a recent pilot study, there was an association between Alzheimer's disease and the consumption of foods containing high levels of aluminum food additives; however, the sample size was very small, and the association was significant only for selected categories of food containing additives (Rogers and Simon, 1999).

Subclinical neurological effects have been observed in a number of studies of workers (aluminum potroom and foundry, welders and miners) chronically exposed to aluminum. Many of these studies involved small numbers of workers and involved the assessment of exposure based on occupation rather than urinary, serum or 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 adverse neurological effects observed included impaired motor function (Hošovski *et al.*, 1990; Sjögren *et al.*, 1996; Kilburn, 1998), decreased performance on cognitive tests (attention-memory

visuospatial function) (Hošovski *et al.*, 1990; Rifat *et al.*, 1990; Bast-Pettersen *et al.*, 1994; Kilburn, 1998; Akila *et al.*, 1999), reports of subjective neuropsychiatric symptoms (Sjögren *et al.*, 1990; White *et al.*, 1992; Sim *et al.*, 1997) and quantitative electroencephalographic changes (Hänninen *et al.*, 1994).

In one case–control study from England (Salib and Hillier, 1996) and two from the United States (Gun *et al.*, 1997; Graves *et al.*, 1998), the relationship between the occurrence of Alzheimer’s disease and occupational exposure to aluminum has been investigated. In each study, disease status was defined by standard criteria (e.g., NINCDS-ADRDA and/or DSM),⁵ 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 Alzheimer’s disease.

2.4.5 Supporting data — Aluminum and Alzheimer’s disease

In addition to the association between aluminum in drinking water and the occurrence of Alzheimer’s disease observed in some epidemiological studies (Section 2.4.4), a number of other lines of evidence have been considered by some as support for a role for aluminum in the development of the disease. For example, the induction of Alzheimer’s-like neuropathology in the brains of certain species of experimental animals following administration of aluminum and the detection of elevated levels of aluminum in bulk brain tissue and in NFTs and neuritic plaques from Alzheimer’s patients have been suggested as implicating aluminum in the etiology of the disease. Additional cited evidence includes observations of interactions between aluminum and β -amyloid protein (A β), the principal protein component of neuritic plaques, and the positive results observed following the trial use of an aluminum chelator, desferrioxamine, for the treatment of Alzheimer’s disease. Finally, evidence of a role for aluminum in the etiology of two other adverse neurological conditions in humans, dialysis encephalopathy and a Western Pacific variant of amyotrophic lateral sclerosis, has also been considered by some to provide support for the plausibility of the association between aluminum and Alzheimer’s disease.

Information on these lines of evidence has been reviewed previously (WHO, 1997; Savory, 2000) and is summarized below.

As discussed previously (Section 2.4.3), the oral administration of aluminum to mice and rats has not produced significant evidence of Alzheimer’s-type neuropathology (e.g., Alzheimer’s-type NFTs or neuritic plaques). In contrast, administration of aluminum by non-traditional routes of exposure (e.g., intrathecal, intracerebral, subcutaneous, etc.) to certain species (e.g., rabbit, cat, guinea pig, ferret, etc.) can produce a progressive encephalopathy with extensive neurofibrillary pathology (e.g., neurofilament aggregates) (WHO, 1997; ATSDR, 1999). Although this aluminum-induced neurofibrillary pathology has some similarity with that seen in Alzheimer’s disease, there are significant ultrastructural and biochemical differences that

⁵ NINCDS is the National Institute of Neurological and Communicative Disorders and Stroke. ADRDA is the Alzheimer’s Disease and Related Disorders Associations. DSM is the Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association.

remain to be resolved. Aluminum-induced neurofilament aggregates are composed of 10-nm straight neurofilaments, whereas Alzheimer's disease NFTs are made up primarily of 20- to 24-nm paired helical filaments (PHFs). At a finer ultrastructural level, the protofilaments in the NFTs from Alzheimer's disease patients are larger than those from aluminum-induced neurofilament aggregates (3.2 vs. 2.0 nm). The staining characteristics of NFTs from Alzheimer's brains also differ from those of neurofilament aggregates in experimental animals (fluorescence with thioflavin S and birefringence with Congo red). Alzheimer's disease NFTs have a different peptide composition from aluminum-induced neurofilament aggregates (hyperphosphorylated tau vs. triplets of neurofilament protein) and different immunoreactivity (anti-tau and anti-ubiquitin vs. anti-neurofilament protein) (Wisniewski and Wen, 1992). However, in a recent study by Huang *et al.* (1997), aluminum-induced neurofilamentous aggregates reacted with a variety of monoclonal antibodies that recognize the phosphorylated and non-phosphorylated forms of tau, and Shin *et al.* (1995) reported that aluminum can bind, aggregate and stabilize tau *in vitro* and *in vivo*. While neuritic plaques are not a feature of aluminum-induced encephalopathy in animals, immunoreactivity to A β and its parent molecule, amyloid precursor protein, has been observed in neurons from both rabbits and rats treated with aluminum (Shigematsu and McGeer, 1992; Huang *et al.*, 1997).

The presence of aluminum at the target site has also been investigated in the context of its possible role in the pathogenesis of Alzheimer's disease. However, results of available studies are inconsistent. Elevated levels of aluminum in bulk brain tissue from Alzheimer's disease patients have been observed in several studies (Crapper *et al.*, 1973; Trapp *et al.*, 1978; Yoshimasu *et al.*, 1980; Ward and Mason, 1987; Xu *et al.*, 1992). However, other researchers have reported no such increases (McDermott *et al.*, 1977; Markesbery *et al.*, 1981; Jacobs *et al.*, 1989) or mixed results (Traub *et al.*, 1981). Methods of analysis based on neutron activation analysis and electrothermal atomic absorption spectrometry were employed both in studies where elevated aluminum levels were reported and in studies where no elevations were observed. In the most extensive bulk tissue analysis, there were no differences between the aluminum content of frontal and temporal cortex specimens from 92 Alzheimer's disease patients compared with controls (Bjertness *et al.*, 1996). To refine the analyses beyond bulk brain tissue, microanalytical techniques have been employed to detect aluminum in NFTs. However, the results of these analyses have been somewhat mixed, as Perl and Brody (1980) measured aluminum in neurons containing NFTs using scanning electron microscopy and energy dispersive X-ray spectrometry, but this finding was not confirmed by two other groups using the same technique (Jacobs *et al.*, 1989; Chafi *et al.*, 1991). Good *et al.* (1992) used a more sensitive technique, laser microprobe mass spectrometry (LMMS), and reported an accumulation of aluminum in neurons containing NFTs from Alzheimer's brains. This result has been questioned due to possible contamination of fixatives and stains (Makjanic *et al.*, 1998) and the contradictory results of an analysis by Lovell *et al.* (1993) in which similar amounts of aluminum were determined in neurons containing NFTs and NFT-free neurons from Alzheimer's disease brains using LMMS. However, there was no evidence of aluminum contamination upon later analysis of the stains and instrument settings differed between the two studies (Good and Perl, 1993; Lovell *et al.*, 1993; Savory, 2000). Hence, the presence of aluminum in NFT-bearing neurons as identified by LMMS cannot be ruled out. The cores of neuritic plaques have been analysed for the presence of aluminosilicates, with Candy *et al.* (1986) reporting positive results with energy dispersive X-ray spectrometry, but Landsberg

et al. (1993) unable to detect aluminum in plaque cores using particle-induced X-ray emission. Hence, there is little consistency in the results of the most refined studies; consequently, the weight of evidence of elevated aluminum levels in bulk brain tissue, NFTs and neuritic plaques from Alzheimer's patients is unconvincing, at present.

A β is a major component of the neuritic plaques that are characteristic of Alzheimer's disease, and there are reports that aluminum is capable of interacting with this protein both *in vivo* and *in vitro*. For instance, aluminum enhanced the aggregation of human A β into insoluble plaques *in vitro* (Mantyh *et al.*, 1993). However, the aggregation of A β is also promoted by other metal ions, and Bush *et al.* (1994) observed that a much greater proportion of synthetic human A β ₁₋₄₀ peptide aggregated in the presence of zinc than in the presence of aluminum on an equimolar basis. Aluminum also promotes a change in conformation of A β from α -helical to β -turn and random coil structures, which may, in turn, be the mechanism for aluminum-induced blockage of calcium channels formed in membranes by A β (Arispe *et al.*, 1993; Exley *et al.*, 1993). In addition, using A β ₂₅₋₃₅ peptide, Exley *et al.* (1995) observed that in the presence of glucose, physiological concentrations of aluminum enhanced the aggregation of A β fibrils into structures similar to the PHFs in NFTs.

Dialysis encephalopathy is a well-recognized condition associated with aluminum intoxication. It is characterized by disordered speech, problems with swallowing (dysphagia), myoclonic jerks, epileptic seizures, dementia, spasms, inhalation pneumonia and death due to the dysphagia (Nieboer *et al.*, 1995). Dialysis encephalopathy can occur in adults and children with chronic renal failure due to long-term exposure to dialysis fluids and parenteral solutions containing aluminum or orally administered aluminum containing phosphate binders for the control of secondary hyperparathyroidism (Wills and Savory, 1989; Nieboer *et al.*, 1995; WHO, 1997). Although dialysis encephalopathy occurs in a specific subpopulation due to iatrogenic aluminum exposure, A β -reactive plaques and NFTs are present in brains from both dialysis encephalopathy and Alzheimer's disease patients (Brun and Dictor, 1981; Scholtz *et al.*, 1987; Candy *et al.*, 1992; Harrington *et al.*, 1994). However, the characteristic PHFs that make up Alzheimer's disease NFTs have not been identified in dialysis encephalopathy brains, and, unlike Alzheimer's disease, aluminum in dialysis encephalopathy appears to be located in the glial cells and walls of blood vessels (Good and Perl, 1988; Wisniewski and Wen, 1992). In addition, it has been noted that the A β -reactive plaques in the study of Candy *et al.* (1992) were diffuse plaques, not associated with clinical disease (Wisniewski *et al.*, 1997), and, in the study of Harrington *et al.* (1994), the level of A β in dialysis encephalopathy brain tissue was not correlated with the amount of aluminum present. Finally, the initial clinical presentation of dialysis encephalopathy is very different from the initial signs of memory loss and difficulties with space and time orientation that are characteristic of Alzheimer's disease (Wisniewski and Rabe, 1992; Nieboer *et al.*, 1995).

Desferrioxamine is an aluminum chelator used in the treatment of dialysis encephalopathy. The results of clinical trials in which this compound was used to treat Alzheimer's disease have been cited as supporting a role for aluminum in the etiology of the disease. In a 2-year single-blind clinical trial, the progression of dementia was decreased in a desferrioxamine treatment group (intramuscular administration) compared with patients given

oral placebos (Crapper McLachlan *et al.*, 1991, 1993). However, it is difficult to attribute these results to chelation of aluminum *per se*, because desferrioxamine chelates other trivalent ions (e.g., Fe³⁺) and has anti-inflammatory properties (Hirschelmann and Bekemeir, 1986), which may have beneficial effects on Alzheimer's disease unrelated to the chelation of aluminum (McGeer and Rogers, 1992). Also, there were important differences between the treatment and placebo groups (treatment: intramuscular administration and unblinded vs. placebo: oral administration and blinded), and the difference between the groups was judged by a videotaped home behavioural assessment, whereas baseline intelligence, memory and speech ability did not differ (Crapper McLachlan *et al.*, 1991, 1993; Nieboer *et al.*, 1995).

Amyotrophic lateral sclerosis is a disease characterized by progressive muscular wasting and weakness, spasticity and hyper-reflexia, with little or no effect on the intellect or oculomotor and sensory functions. A form of this disease unique to the Western Pacific region (e.g., Guam, Kii Peninsula of Japan, West New Guinea) has been linked to aluminum exposure. Although amyotrophic lateral sclerosis is primarily a motor neuron disease, hippocampal neurons from individuals with the Western Pacific form and individuals from the same region with parkinsonism-dementia contain diffuse NFTs that are ultrastructurally and biochemically similar to those of Alzheimer's disease. However, the characteristic neuritic plaques of Alzheimer's disease appear to be absent in these individuals (Strong, 1995). Elevated levels of aluminum and calcium have been measured in NFT-bearing neurons from amyotrophic lateral sclerosis-parkinsonism-dementia patients (Perl *et al.*, 1982; Garruto *et al.*, 1984); within the neurons, aluminum and calcium are co-localized in the perikarya and dendritic processes (Gajdusek, 1985; Garruto and Yase, 1986). Soil and drinking water from the Western Pacific region contain low levels of calcium and magnesium and elevated levels of aluminum (Gajdusek and Salazar, 1982). It has been postulated that in affected individuals, a defect in mineral metabolism combined with chronic dietary deficiencies of calcium and magnesium produce a form of secondary hyperparathyroidism associated with greatly increased gastrointestinal absorption of aluminum (Strong, 1995).

2.4.6 Mode of action

There is evidence that ingested and absorbed aluminum are distributed to the potential target site, the brain, from studies in both laboratory animals and humans. For example, in a number of the studies of neurological effects of orally administered aluminum described in Tables 6 and 7 the accumulation of aluminum in the brains of mice, rats and monkeys from the treatment groups was reported. More sensitive testing in which of the ²⁶Al radioisotope were administered to rats resulted in elevated levels of aluminum in the brain measured from 48 hours to 30 days after dosing (Fink *et al.*, 1994; Walton *et al.*, 1995; Drüeke *et al.*, 1997; Jouhanneau *et al.*, 1997). In humans, the most consistent evidence for the accumulation of aluminum in the brain is that from a series of studies of patients who died of renal failure and were treated with aluminum-containing phosphate binders and dialysis or no dialysis. In general, the highest levels of aluminum were measured in brains from renal failure patients with dialysis encephalopathy, followed by dialysis patients without the condition, non-dialysed patients and controls (Alfrey *et al.*, 1976; Flendrig *et al.*, 1976; McDermott *et al.*, 1978; Arieff *et al.*, 1979; Alfrey, 1980).

Information related to potential modes of action by which aluminum affects the nervous system has been discussed in a number of recent reviews (Strong *et al.*, 1996; WHO, 1997; ATSDR, 1999, Savory, 2000). Consequently, the presentation of this information is limited to a brief summary consistent with the limited scope and objectives of this report which builds on previous initiatives by Health Canada. Most of this information has been reviewed elsewhere.

As discussed previously (Section 2.4.3), the administration of aluminum by non-traditional routes of exposure (e.g., intrathecal, intracerebral, etc.) to certain species (e.g., rabbit, cat, guinea pig, etc.) can result in neuronal cytoskeletal pathology manifested as hyperphosphorylated neurofilamentous aggregates. These neurofilamentous aggregates may arise from aluminum-induced alterations to neurofilament protein gene expression (e.g., reductions in transcribable DNA, effects on DNA repair processes and suppression of mRNA levels for specific neurofilament proteins) and/or aluminum-induced post-translational modifications to neurofilament proteins (e.g., hyperphosphorylation, inhibition of dephosphorylation, increased resistance to proteolysis and cross-linking of neurofilament protein subunits).

Observations of alterations to the activities of choline acetyltransferase, acetylcholinesterase and the neuronal uptake of choline following the administration of aluminum to immature and adult rodents have led to the hypothesis that the neurotoxicity of aluminum may involve an effect on cholinergic neurotransmission.

An additional potential mechanism of aluminum-induced neurotoxicity involves alterations to second messenger systems in the brain. Decreased levels of inositol triphosphate and cAMP have been recorded in rats consuming aluminum in drinking water. *In vitro*, aluminum decreases agonist-stimulated inositol phosphate accumulation in brain slices. Aluminum may also affect calcium-dependent signalling and processes by inhibiting voltage-sensitive channels for the entry of calcium into neurons and the extrusion of calcium from the neuronal cytosol by Mg²⁺-ATPase.

Administration of aluminum to rodents can result in enhanced lipid peroxidation in the brain. Rather than a direct effect of aluminum, this appears to occur via an acceleration of iron-induced peroxidation. In addition, aluminum can suppress antioxidant systems and alter membrane lipid content and composition in the brain.

Aluminum can inhibit the activities of two enzymes that are important to glucose metabolism in the brain, namely hexokinase and glucose-6-phosphate dehydrogenase. The observation of inhibition of these two enzymes by aluminum coupled with that of reduced glucose metabolism in the brains of rats chronically administered aluminum and Alzheimer's patients have led to the hypothesis that aluminum-induced neurodegeneration may involve selective effects on glucose metabolism.

Alterations to the permeability of the blood-brain barrier may also be relevant in the induction of aluminum-induced neurotoxicity. Increases in the permeability of the blood-brain barrier to sucrose, thyroxine, cortisol, prolactin, growth hormone and luteinizing hormone have resulted from the intravenous or intraperitoneal administration of various aluminum salts to rats

and mice. Studies in mice administered aluminum chloride indicate that the increases in permeability may be due to selective effects on specific transport systems.

While there is evidence, therefore, for the interaction with and impact of aluminum on different components of the neurological system, available data are inadequate to serve as a basis for a hypothesized mode of action of aluminum in inducing specific neurological disorders such as Alzheimer's disease.

3.0 RISK CHARACTERIZATION

3.1 Environment

3.1.1 General Considerations

The aluminum salts considered in this report are produced and used in large quantities in Canada. In many applications, aluminum chloride, aluminum nitrate and aluminum sulfate become part of fabricated products and are not released to the environment. Water treatment uses a large amount of aluminum chloride and aluminum sulfate for the removal of fine suspended or soluble materials and is an important source of aluminum release to the aquatic and terrestrial environments (Germain et al., 1999).

Given its physical properties, most of the aluminum associated with the aluminum salts used in water treatment hydrolyses to aluminum hydroxide and becomes part of the floc structure, which settles in the form of sludge. A small amount of the aluminum added may stay in finished water or sludge in either colloidal particulate ($\text{Al}(\text{OH})_3$) or soluble (e.g., $\text{Al}(\text{OH})_2^+$, $\text{Al}(\text{OH})_4^-$) form and, in jurisdictions where this is permitted, be released to the aquatic environment when filters are backwashed, clarifiers purged or sedimentation basins emptied. Sludge may be released to sewers or spread on agricultural land. When released to aquatic environments, solid aluminum hydroxide present in process wastewater will remain in solid form. Aluminum present in soluble form may react with soluble materials present in water and precipitate, or it may stay in soluble form.

Based on information on the sources and fate of aluminum salts in the ambient environment, biota are expected to be exposed to aluminum resulting from the use of aluminum salts primarily in water and sediment receiving alum sludges discharged from DWTPs and in soil receiving applications of such sludges. The focus of the environmental risk characterization will therefore be sensitive aquatic and terrestrial organisms exposed to these sources of aluminum.

3.1.2 Environmental risk characterization

3.1.2.1 Aquatic organisms

3.1.2.1.1 Pelagic

Environmental exposure to aluminum in water is expected to be greatest in areas near direct releases of process wastewater to the aquatic environment by DWTPs. Unfortunately, measured values in receiving environments following direct releases are available only in the Ottawa River, when RMOC is backwashing filters. However, aluminum levels in effluents were calculated for the 30 DWTPs that reported direct wastewater releases to the receiving environment in a municipal survey (Germain *et al.*, 1999). Table 5 presents estimated total aluminum concentrations in backwash waters for 13 DWTPs, including those with the highest estimated levels. The aluminum level in RMOC's DWTP's wastewater was quite similar to that measured at the beginning of the plume in the river (30 mg/L vs. 36 mg/L). P&P mills also use aluminum salts, but their releases are generally

one order of magnitude lower than those of DWTPs (Germain *et al.*, 1999). Table 5 includes total aluminum levels present in effluent from two typical Canadian mills.

Measurements of total concentrations of a metal can rarely be correlated directly with their biological effects. Metal in particulate form is generally not bioavailable, and the formation of complexes with inorganic (e.g., OH^- , SO_4^{2-}) or organic (e.g., fulvic acid) ligands can reduce the bioavailable fraction of the dissolved form of a metal. In order to estimate the amount of bioavailable aluminum present in rivers, we performed speciation with MINEQL+ and WHAM models. We calculated the level of dissolved inorganic monomeric form of aluminum following the releases of wastewater from selected DWTPs and two P&P plants, using the estimated aluminum level in effluents 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) 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), 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 (Table 5). For the two P&P 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). As noted in Section 2.2.2.2, backwash events last for about 30 minutes and occur every 48–72 hours for each filter at a DWTP. 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 (see Section 2.3.2.2). 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) Estimated Exposure Value (EEV) for waters close to discharge points.

Because aluminum releases reported by DWTPs occur in circumneutral to neutral waters, two Critical Toxicity Values (CTV) 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 $\text{LC}_{50\text{s}}$ (~0.6 mg dissolved Al/L) during several experiments in the pH range 8.0–8.6 and water hardness range 20–100 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. Since the pH in waters for which the EEV was estimated is 8.38, the corresponding CTV is 0.06 mg/L as dissolved inorganic monomeric aluminum.

In determining Estimated No-Effects Values (ENEV) 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 an ENEV from the CTV was 1.0. Aluminum being a natural element, it is also useful to consider whether the ENEV 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. It should be noted that only a portion of this dissolved aluminum is in inorganic monomeric forms (corresponding to the ENEV). 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:

$$\begin{aligned}\text{Quotient} &= \frac{\text{EEV}}{\text{ENEV}} \\ &= \frac{0.055 \text{ mg/L}}{0.06 \text{ mg/L}} \\ &= 0.92\end{aligned}$$

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 large fraction of the aluminum released from DWTPs during backwash events is probably in solid form, while calculations used to estimate the EEV assumed that all of the aluminum was in dissolved form (Germain *et al.*, 1999). This “solid” aluminum would not tend to participate in solution reactions and would precipitate. 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).

In a study done with sludge from Calgary and Edmonton, AEC (1987) concluded that all sludges tested were non-toxic using a microbial test and acutely and subacutely non-toxic to rainbow trout. In addition, as noted previously in Section 2.2.2.2, 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 10 different DWTPs containing up to 2900 mg total Al/L. These results show that the concentration of dissolved aluminum in process wastewaters is less than the ENEV.

3.1.2.1.2 Benthic

Toxic effects due to exposure to high concentrations of aluminum are unlikely, because of the solubility constraints in receiving waters discussed above. However, based on the limited effects data available, alum 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 (George *et al.*, 1991). AEC (1984), for example, reported smothering effects related to settled sludge on sediments following disposal to rivers in Alberta. Usually, however, the influence of sludge deposit is limited in space, typically extending only a few hundred metres downstream. Consequently, population-level impacts are expected to be minimal. Furthermore, it is reported that when the sludge blanket is removed, the systems recover.

3.1.2.2 Terrestrial organisms

Terrestrial organisms are exposed to added aluminum when alum sludges from DWTPs are 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 1.0 was applied to the CTV to derive the ENEV. The conservative ENEV 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 ENEV unless soil pHs were less than about 5.1 (Belanger *et al.*, 1999). Because it is very unlikely that the pHs of soils receiving alum sludge applications will be this low, it is very unlikely that the ENEV of 0.135 mg/L is exceeded in Canadian soils receiving such applications.

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.

3.1.2.3 Uncertainty and Recommendations

There are a number of uncertainties in this risk characterization. Regarding effects of aluminum on pelagic organisms, there are only a few studies conducted at circumneutral pHs (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 1.0 to derive an ENEV 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 form (Fortin and Campbell, 1999). Addition: Measurement and speciation of aluminum following the releases of DWTP's wastewaters would confirm the estimated levels and forms provided by MINEQL+ and WHAM models.

Other uncertainties exist relating to the impact of alum sludge releases on benthic organisms. There are some indications that sludge releases, whatever the flocculant used, may have a smothering effect on benthos. Given the potential for localized impacts on benthic organisms resulting from direct releases of sludge (not only alum sludge) from DWTPs to surface

waters, it is recommended that this practice be discouraged even if the level of total aluminum measured in sediments in one site in Canada influenced by alum sludge is of the same order of magnitude as concentrations measured in unaffected areas elsewhere in Canada. Provisions to manage sludges should be incorporated in the planning stage before construction of new DWTPs and when an old facility is being upgraded.

Because of the increase in aluminum solubility in acidic water, releases of backwash waters, clarifier purge waters or waters from sedimentation basins should be discouraged in lakes and rivers where the pH can be less than 6.

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 ENEV for sensitive vegetation.

3.2 Environment upon which life depends

Based on available information on releases and their physical and chemical properties, aluminum chloride, aluminum nitrate and aluminum sulfate do not deplete stratospheric ozone, contribute to the formation of ozone in the troposphere or influence climate change.

3.3 Human health

3.3.1 Population exposure

3.3.1.1 Estimated population exposure

The average daily intake of aluminum has been estimated based on the levels in air, drinking water, soil and food and the amounts consumed by the various age groups of the general population of Canada (Table 9) (Environmental Health Directorate, 1998), although these intakes should be considered in the context of relative bioavailability from various routes of exposure (Section 3.3.1.2). The total average daily intake for all age groups of the general population of Canada from all sources is estimated to range from 113 to 598 µg/kg bw/ day. Based on the available data, the greatest source of exposure to aluminum for children, teens, adults and seniors of the general population of Canada is food. For infants and toddlers, the greatest source of exposure is the inadvertent ingestion of soil. Inhalation of airborne aluminum contributes only a small amount to the total daily intake, as estimated intakes range from <0.01 to 0.10 µg/kg-bw per day for ambient air and from 0.17 to 1.0 µg/kg-bw per day for indoor air.

For those who regularly use aluminum-containing over-the-counter oral therapeutic products, these products represent the major source of daily aluminum intake. Based on the manufacturers' maximum recommended daily doses, estimated daily intakes of aluminum from these products range from 1.4 to 21 mg/kg-bw per day (Table 10). The highest intakes are for

children, teens, adults and seniors who use antidiarrheal agents and for adults and seniors who use antacids and adsorbents.

The very limited data available indicate that certain aluminum-containing over-the-counter oral therapeutic products may be used regularly by only a small fraction of the Canadian population. In the Statistics Canada National Population Health Survey, 0.2% of a sample population of 17 011 individuals over the age of 12 indicated that they had consumed one aluminum-containing antacid within 2 days of being surveyed. For the same population, 0.7% stated that they had taken one aluminum-containing salicylate (analgesic) within 2 days of being surveyed (Statistics Canada, 1995).

As shown in Table 11, estimated adult dermal exposure to aluminum through the use of aluminum-containing cosmetic products in Canada ranges from 0.01 to 1500 µg/kg-bw per day. The greatest cosmetic sources of daily dermal exposure to aluminum are skin cleansers, hair dye and hair conditioners.

3.3.1.2 Bioavailability

Data on the fractional absorption (bioavailability) of aluminum compounds via the inhalation, oral or dermal routes of exposure have been reviewed by Yokel and McNamara (2000). Estimates of bioavailability from various routes and media of exposure are necessarily crude owing to the limitations of the data on which they are based and the considerable number of influencing factors (Section 3.3.1.3). Generally, the bioavailability of aluminum via inhalation, ingestion and dermal exposure appears to be relatively low — in the range of tenths of a percent to a few percent.

There are no data available on the bioavailability to humans of aluminum from ambient or indoor air. An estimate of 1–2% bioavailability (Yokel and McNamara, 2000) can be derived from the occupational exposure studies of Gitelman *et al.* (1995) in which pre- and post-work shift serum and urinary aluminum levels were measured in aluminum industry workers exposed to respirable particles containing aluminum at a median concentration of 25 µg/m³ and Pierre *et al.* (1995) in which 24-hour urine samples were collected from workers occupationally exposed to approximately 200–500 µg soluble aluminum/m³. However, whether the airborne aluminum was absorbed from the lungs following inhalation, from the gastrointestinal tract following mucociliary clearance of the lungs or from the olfactory tract was not investigated in the identified occupational studies of populations for which exposure would be considerably greater than that expected in the general environment.

The oral bioavailability of aluminum in drinking water has been assessed using a variety of ²⁷Al- and ²⁶Al-radiolabelled aluminum salts (e.g., aluminum hydroxide, aluminum chloride, aluminum sulfate, aluminum citrate, etc.) in water administered to rats, rabbits and humans. Yokel and McNamara (2000) estimated a range of 0.1–0.5% based on the more recent studies in which 1) doses (0.13–3.2 µg/kg-bw per day) were similar in magnitude to estimated daily intakes from drinking water, 2) the form of aluminum used (aluminum hydroxide, aluminum chloride or aluminum in municipal tapwater) is likely to have speciation similar to that of aluminum in drinking water, and 3) fractional absorption was based on urinary excretion, serum levels or

plasma aluminum versus time curves for oral versus intravenous administration (Hohl *et al.*, 1994; Drüeke *et al.*, 1997; Jouhanneau *et al.*, 1997; Schönholzer *et al.*, 1997; Priest *et al.*, 1998; Stauber *et al.*, 1999).

Estimates of bioavailability from the limited number of studies that have examined aluminum in food and beverages are within a range similar to that for drinking water (Yokel and McNamara, 2000). Priest (1993) estimated 0.1% bioavailability of aluminum from food based on previously published estimates of daily intake from food (15 mg), urinary excretion rate (25 µg/day) and the percentage of aluminum retained in the body of a human volunteer (5%) following intravenous injection with ²⁶Al-citrate. More recently, Stauber *et al.* (1999) measured the 24-hour urinary aluminum excretion in 29 male and female volunteers who consumed low-aluminum water and meals and instant tea with known amounts of aluminum and estimated the bioavailability from food to be 0.53%.

Data on the oral bioavailability of aluminum from drugs are restricted mainly to studies of aluminum-containing compounds (e.g., sucralfate, aluminum lactate, Zeolite A[®] and aluminum hydroxide) used as active ingredients in antacids, phosphate binders, toothpastes and other products (Yokel and McNamara, 2000). Estimates for sucralfate (basic aluminum sucrose sulfate), an antacid, range from 0.005% based on measurements of urinary aluminum in human volunteers (Haram *et al.*, 1987) to 0.60% calculated from plasma aluminum versus time curves for oral versus intravenous administration in rabbits (Yokel and McNamara, 1988). For aluminum lactate, estimates of bioavailability range from 0.02% in rats (Wilhelm *et al.*, 1992) to as high as 1.9% for rabbits administered high doses of the compound (540 mg/kg-bw) and fasted before administration (Yokel and McNamara, 1985). Cefali *et al.* (1996) reported the bioavailability of Zeolite A[®], an aluminum silicate inducer of osteoblast proliferation, as 0.023–0.032% based on plasma aluminum versus time curves for oral versus intravenous dosing in dogs. However, in the controls, there were large variations in plasma aluminum, while only small increments were observed following Zeolite A[®] treatment. Moreover, the pharmacokinetic parameters for aluminum did not incorporate baseline adjustments (Yokel and McNamara, 2000). Although a wide range of estimates of bioavailability have been obtained for aluminum hydroxide, which is commonly used as an antacid and phosphate binder, they are generally less than those for other aluminum salts. Estimates range from 0.001%, determined from urinary aluminum measurements in humans administered 28 mg Al(OH)₃/kg-bw (Weberg and Berstad, 1986), to as high as 0.45% in fasted rabbits dosed with 270 mg/kg-bw of the compound (Yokel and McNamara, 1988).

There is no information available on the bioavailability of aluminum from the inadvertent ingestion of soil (Yokel and McNamara, 2000).

Limited data on the bioavailability of aluminum from dermal exposure are available from a study of an aluminum-containing underarm antiperspirant in male and female volunteers (Flarend *et al.*, in press). Based on measurements of urinary ²⁶Al levels with corrections for the amount of aluminum retained on the skin and the duration of monitoring, the estimated bioavailability is 0.02%.

3.3.1.3 Factors influencing oral bioavailability

There is evidence that certain factors related to the speciation or forms of aluminum and their solubilities can influence the oral bioavailability of aluminum. A number of these factors have been reviewed by Yokel and McNamara (2000) and Greger and Sutherland (1997), including pH, citrate and other organic acids, silicates, phosphate and fluoride.

As discussed previously (Section 2.3.1.2), the forms or species of aluminum present in solutions and their solubilities vary considerably depending upon pH. Evidence that these pH-related changes in the form and solubility of aluminum can alter oral bioavailability includes observations of decreased aluminum absorption in humans administered ranitidine to increase gastric pH (Rodger *et al.*, 1991) and a report of enhanced aluminum absorption at pH 4 compared with pH 7 in an *in situ* rat intestine model (van der Voet and de Wolff, 1986). In contrast, Beynon and Cassidy (1990) reported no difference in aluminum absorption between uremic patients with achlorhydria and normal subjects.

Citrate, commonly found in fruit juices and other foods, can enhance the oral bioavailability of aluminum through the formation of an aluminum citrate complex. The absorption of aluminum hydroxide has been shown to be increased in the presence of citric acid in humans (Slanina *et al.*, 1986; Weberg and Berstad, 1986; Nolan *et al.*, 1990; Walker *et al.*, 1990; Coburn *et al.*, 1991; Rudy *et al.*, 1991; Lindberg *et al.*, 1993; Gomez *et al.*, 1994; Nestel *et al.*, 1994; Priest *et al.*, 1996) and in animals (van der Voet *et al.*, 1989; Partridge *et al.*, 1989, 1992; Schönholzer *et al.*, 1997). Similarly, aluminum citrate was absorbed to a greater degree than other forms of aluminum when administered to rats or rabbits (Yokel and McNamara, 1988; Froment *et al.*, 1989a; Schönholzer *et al.*, 1997). In contrast, Jouhannau *et al.* (1993, 1997) reported no difference in the amount of aluminum absorbed by rats in the presence of added citrate; in human volunteers, Stauber *et al.* (1999) found no significant difference in the bioavailability of aluminum from alum-treated tapwater with or without citrate added. It has been proposed that citrate increases aluminum absorption by promoting the opening of tight junctions between gastrointestinal mucosal cells (Froment *et al.*, 1989b; Taylor *et al.*, 1998). Other hypotheses include increased solubility of aluminum at low pHs in the presence of citrate and chelation and transport of aluminum into gut mucosal cells by citrate (Greger and Sutherland, 1997).

Other organic acids present in food (ascorbic, gluconic, lactic, malic, oxalic and tartaric acids) can also increase the solubility and tissue retention of aluminum in rats (Partridge *et al.*, 1989; Domingo *et al.*, 1991, 1994).

Silicates can reduce the oral bioavailability of aluminum by the formation of hydroxyaluminosilicates (Harris *et al.*, 1996). Plasma ^{26}Al concentrations were reduced by 85% in five men who consumed ^{26}Al and silicon in orange juice compared with orange juice and ^{26}Al without silicon (Edwardson *et al.*, 1993). Silicic acid administered prior to and during the dosing of rats with aluminum citrate resulted in reduced tissue aluminum accumulation (Quarterly *et al.*,

1993). However, the bioavailability of aluminum was not significantly altered in rats that were administered both aluminum and silicon after eating (Drüeke *et al.*, 1997).

Aluminum hydroxide has been used as a phosphate binder to treat uremic patients with hyperphosphatemia. The basis for this treatment is the ability of aluminum to form insoluble complexes with phosphates in the gastrointestinal tract, thus preventing phosphorus absorption. Greger and Sutherland (1997) proposed that in the presence of sufficient quantities of phosphate, the formation of insoluble aluminum phosphate complexes could produce a similar effect on aluminum absorption. It has been suggested that phosphate-containing substances in the diet (e.g., phytate and casein) may reduce the absorption of aluminum (Glynn *et al.*, 1995).

Aluminum salts can reduce the absorption of fluoride from the gastrointestinal tract (Spencer *et al.*, 1981; Greger and Sutherland, 1997), and, similar to phosphate, it has been hypothesized that sufficient concentrations of fluoride should reduce the absorption of aluminum (Greger and Sutherland, 1997). However, Allain *et al.* (1996) observed increased plasma aluminum levels in rats administered aluminum fluoride versus aluminum chloride.

It has been suggested that certain species or forms of aluminum in drinking water may have a greater relative bioavailability than the forms present in food and consequently make a greater contribution to daily intake and potential adverse effects (Martyn *et al.*, 1989). This is based in part on the increased levels of low molecular weight, dissolved, labile and presumably bioavailable species of aluminum observed after treatment of drinking water with aluminum-containing coagulants (Driscoll and Letterman, 1988; Van Benschoten and Edzwald, 1990; Gardner and Gunn, 1995). A comparison of aluminum levels in raw water and drinking water treated with alum from four provincial sites revealed that total recoverable aluminum levels decreased, while levels of total dissolved and dissolved extractable aluminum increased. The extractable aluminum is a labile fraction that includes free aluminum and all inorganic and organic forms exchangeable with a chelating resin (Bérubé and Brulé, 1996, 1999).

There is limited evidence from studies with animals and humans that other factors that are not directly related to the form of ingested aluminum may enhance aluminum absorption, including iron deficiency (Cannata *et al.*, 1991, 1993; Brown and Schwartz, 1992; Florence *et al.*, 1994), dietary calcium deficiency (Taneda, 1984; Provan and Yokel, 1990), vitamin D (Adler and Berlyne, 1985; Ittel *et al.*, 1988; Long *et al.*, 1991, 1994) and uremia (Ittel *et al.*, 1987, 1988, 1991; Olaizola *et al.*, 1989).

Administration of aluminum hydroxide and citrate resulted in a significantly greater increase in aluminum levels in blood in Alzheimer's patients aged 65–76, but not in those aged 77–89, compared with normal controls (Taylor *et al.*, 1992). However, within the control groups, there was a significant correlation between age and increase in blood aluminum. Day *et al.* (1994) reported that patients with Down's syndrome, a disease that may be genetically linked to Alzheimer's disease, absorbed significantly greater amounts of aluminum (5–6 times) than controls when both groups were given ²⁶Al in the presence of citrate (i.e., orange juice).

3.3.2 Hazard characterization

As described in Section 2.4.4 and Table 8, in epidemiological studies in a range of populations the hypothesis that aluminum in the general environment (primarily drinking water) is a risk factor in the development or acceleration of Alzheimer's disease or impaired cognitive function in the elderly has been investigated. It is this potential association with Alzheimer's disease or impaired cognitive function in the elderly that has greatest implications for public health resulting from exposure in the general environment. Hence, the weight of evidence for these associations primarily from the studies of greatest inherent sensitivity — i.e., analytical epidemiological investigations — is considered here in the context of traditional criteria for causality, principally as a basis for characterizing additional relevant study.

The criteria against which the weight of evidence of causality for such associations are judged are outlined in Health Canada (1994) and subsequent updates included on the Environmental Substances Division website (www.hc-sc.gc.ca/ehp/ehd/bch/env_contaminants/psap/psap.htm). They include consistency and specificity, strength, dose–response, temporality, biological plausibility and coherence of the observed association.

As discussed previously, the majority of epidemiological studies of the potential association between aluminum in the general environment and Alzheimer's disease or impaired cognitive function have focused on drinking water as the source of exposure. Among these are studies of the inherently more sensitive analytical type (i.e., cohort, case–control and cross-sectional) conducted in populations from Ontario, Quebec, France, England and Switzerland (Table 8). However, it should be noted that variations in exposure of individuals in these analytical studies have been assessed to only a very limited extent, with information on concentrations of aluminum in drinking water being distinguished only by location of residence. In general, the quality of the studies has been sufficient in terms of assessment of outcomes and consideration of confounders to make them relevant to an assessment of causality.

A direct association between Alzheimer's disease or Alzheimer's-type presenile dementia and exposure to aluminum in drinking water was investigated in studies on populations from Ontario, France, England and Quebec (Michel *et al.*, 1991; Neri and Hewitt, 1991; Neri *et al.*, 1992; Forbes *et al.*, 1995b; Forster *et al.*, 1995; Forbes and McLachlan, 1996; McLachlan *et al.*, 1996; Martyn *et al.*, 1997; Gauthier *et al.*, in press). The potential association between dementia or cognitive impairment and aluminum in drinking water was investigated in studies from Ontario, France, England and Switzerland (Wood *et al.*, 1988c; Wettstein *et al.*, 1991; Forbes *et al.*, 1992; 1994; 1995a; Forbes and Agwani, 1994; Jacqmin *et al.*, 1994; Jacqmin-Gadda *et al.*, 1996). A positive association was reported in all of the studies from Ontario, France and Quebec (Michel *et al.*, 1991; Neri and Hewitt, 1991; Neri *et al.*, 1992; Forbes *et al.*, 1992; 1994; 1995a; 1995b; Forbes and Agwani, 1994; Jacqmin *et al.*, 1994; Jacqmin-Gadda *et al.*, 1996; Forbes and McLachlan, 1996; McLachlan *et al.*, 1996; Gauthier *et al.*, in press), and no association was observed in those from England and Switzerland (Wood *et al.*, 1988c; Wettstein *et al.*, 1991; Forster *et al.*, 1995; Martyn *et al.*, 1997). The results of one of the French studies (Michel *et al.*,

1991) have been discounted due to a reliance on outdated information on aluminum concentrations in drinking water (Jacqmin *et al.*, 1994; Smith, 1995; WHO, 1997).

With respect to the assessment of outcomes, the diagnostic criteria for selection of cases were generally more stringent and specific to Alzheimer's disease among the studies and populations in which there was a positive outcome. In the positive study from Quebec, cases were ascertained based on a three step process that included a modified mini-mental state exam (MMS) and standardized diagnostic criteria (DSM, NINCDS-ADRDA and ICD⁶) (Gauthier *et al.*, in press). ICD criteria were also used in two positive studies from Ontario (Neri and Hewitt, 1991; Neri *et al.*, 1992; Forbes *et al.*, 1995b; Forbes and McLachlan, 1996). In an additional positive study from Ontario, McLachlan *et al.* (1996) obtained autopsy-confirmed cases of Alzheimer's disease with clinical histories of dementia from brains donated to the Canadian Brain Tissue Bank. In the fourth study from Ontario, Forbes and colleagues (Forbes and Agwani, 1994; Forbes *et al.*, 1992; 1994; 1995a) assessed impaired mental functioning by a questionnaire that included a modified mental status test. Cognitive impairment was determined by MMS score in the positive study from France conducted by Jacqmin-Gadda and colleagues (Jacqmin *et al.*, 1994; Jacqmin-Gadda *et al.*, 1996). Among the studies from England in which no association was observed, only Forster *et al.* (1995) used a diagnostic algorithm incorporating NINCDS-ADRDA and DSM criteria, and an MMS examination to identify cases. Martyn *et al.* (1997) relied on a diagnosis of Alzheimer's disease from hospital notes or computerized tomographic scans to classify demented patients as cases, but standardized diagnostic criteria were not specified in the study. In the third negative study from England, Wood *et al.* (1988c) identified subjects with dementia using an unspecified mental test. Finally, in the negative study from Switzerland (Wettstein *et al.*, 1991) dementia was diagnosed using the MMS.

There is somewhat less consistency in the control of potential confounders and other factors among the studies from Ontario, Quebec and France in which a positive association was reported compared to the studies on populations from England and Switzerland in which no association was observed. The study from Quebec (Gauthier *et al.*, in press) and selected analyses from the Ontario study of cognitive impairment (Forbes *et al.*, 1994; 1995a) involved control of a range of factors (e.g., age, sex, education, family history, genotype, occupation, etc.), and age and sex were accounted for in the Ontario study by Neri and colleagues (Neri and Hewitt, 1991; Neri *et al.*, 1992). However, these factors were generally not addressed in the Ontario death certificate study (Forbes *et al.*, 1995b; Forbes and McLachlan, 1996), in the study by McLachlan *et al.* (1996) or in some of analyses included in the Ontario study of cognitive impairment (Forbes *et al.*, 1992; Forbes and Agwani, 1994). In the positive study from France by Jacqmin and colleagues (Jacqmin *et al.*, 1994; Jacqmin-Gadda *et al.*, 1996) analyses of cognitive impairment included control for age, sex, education and occupation. All of the studies from England had some form of adjustment for age. Forster *et al.* (1995) also controlled for a range of other factors including family history, disease history, head injuries, physical activity and smoking and the study of Martyn *et al.* (1997) included control for diagnostic centre and distance from residence to diagnostic centre. The other study from England, Wood *et al.* (1988), controlled for both age and sex, while the Swiss study, Wettstein *et al.* (1991) accounted for age, education and socioeconomic status. There is also some evidence that other characteristics of water quality such

⁶ International Classification of Diseases, World Health Organization.

as pH are co-factors for the purported association, consistent with what might be expected, if the association was causal (Forbes *et al.*, 1992; 1994; 1995a; 1995b; Jacqmin *et al.*, 1994; Jacqmin-Gadda *et al.*, 1996).

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. This lack of consistency may be a function in part, of variations in sensitivity between the studies. For example, in the study from Quebec (Gauthier *et al.*, in press), the classification of subjects was restricted to exposed (upper quartile of subjects) versus unexposed due to the limited number of cases and controls. There is evidence for a statistically significant increasing risk of Alzheimer’s disease with increasing concentration of aluminum in drinking water (i.e., dose-response) only in the Ontario study by Neri and colleagues (Neri and Hewitt, 1991; Neri *et al.*, 1992). In another Ontario study (McLachlan *et al.*, 1996), the risks of Alzheimer’s disease increased (3.6–7.6) as concentrations of aluminum increased from 125 to 175 µg/L, but the confidence intervals for the higher risk estimates were wide and included 1.

There are also inconsistencies in the dose–response trend across the studies from Ontario, Quebec and France in which positive outcomes were reported. Among the studies conducted in Ontario, Neri and Hewitt (1991) and Neri *et al.* (1992) determined relative risks (RRs) of 1.3–1.5 for concentrations of 100 to >200 µg Al/L, whereas McLachlan *et al.* (1996) reported odds ratios (ORs) of 1.7–2.5 for the composite exposure level of ≥100 µg Al/L and ORs of 3.6–7.6 for individual exposure levels from 125 to 175 µg Al/L. Using a cut point of 84.7 µg/L to define low versus high concentrations of aluminum, Forbes *et al.* (1992, 1994, 1995a) and Forbes and Agwani (1994) reported ORs for cognitive impairment ranging from 0.67 to 4.0 for exposure to high concentrations of aluminum in the presence of varying levels of pH, fluoride and/or silica. In general, the higher ORs corresponded to exposure scenarios when pH levels were high or fluoride and silica levels were low. When more complex multivariate analyses were conducted on the same dataset with control for a range of factors, the ORs ranged from 1.72 to 2.35 (Forbes and Agwani, 1994; Forbes *et al.*, 1994; 1995a). In a death certificate study from Ontario, Forbes *et al.* (199b) analysed the risks of Alzheimer’s disease from exposure to concentrations of aluminum ≥ 336 µg/L combined with high or low levels of pH, fluoride or silica and estimated RRs⁷ ranging from 0.88 to 4.0 with the higher RRs generally observed when pH was high or fluoride and silica were low. In the same study, the RRs for exposure to lower concentrations of aluminum (68-200 µg/L) were ≤ 1.0. The follow-up analysis by Forbes and McLachlan (1996) produced even higher RRs (4.8–10) for concentrations above 250 µg Al/L. Based on these results, Forbes and McLachlan (1996) hypothesized a J-shaped dose-response curve for the relationship between Alzheimer’s disease and aluminum in drinking water with a minimum around 100 µg Al/L. In the positive study from Quebec, an OR of 2.67 was observed for exposure to 12 µg/L of monomeric organic aluminum in drinking water with lower ORs reported for exposures to other aluminum fractions in drinking water. In their study on a French population, Jacqmin *et al.* (1994) initially reported odds ratios (ORs) for cognitive impairment of 1.3-1.4 for 50 to 100 µg Al/L at pH 7,

⁷ In the studies of Forbes *et al.* (1995b) and Forbes and McLachlan (1996) the relative risks (RRs) were estimated by rate ratios.

while in their follow-up analysis an OR of 4.0 was estimated for exposure to concentrations of aluminum higher than the first quartile of the distribution ($\geq 3.5 \mu\text{g/L}$) combined with low pH and silica levels. ORs for higher quartiles of the aluminum distribution (≥ 9.0 to $\geq 16.0 \mu\text{g/L}$) were less than 1.2 (Jacqmin-Gadda *et al.*, 1996). Adding to these inconsistencies is the fact that the highest concentrations of aluminum reported in negative studies from England and Switzerland (98–250 $\mu\text{g/L}$) were similar to those in the positive studies (Wood *et al.*, 1988c; Wettstein *et al.*, 1991; Forster *et al.*, 1995; Martyn *et al.*, 1997). There is additional evidence (albeit less reliable) for a dose–response trend in two of the four ecological epidemiological studies in which a positive association between Alzheimer’s disease and aluminum in drinking water was observed (i.e., Martyn *et al.*, 1989: RR = 1.4–1.7 for 20 to $>110 \mu\text{g Al/L}$; and Flaten, 1990: RR = 1.2–1.3 for 50 to $>200 \mu\text{g Al/L}$).

For the analytical epidemiological studies from Ontario, Quebec and France in which there was a positive association between Alzheimer’s disease and exposure to aluminum, the strength of the observed association was generally moderate, with statistically significant RRs or ORs as high as 1.5–4.0 reported for the highest exposure groups (Neri and Hewitt, 1991; Neri *et al.*, 1992; Forbes *et al.*, 1992; 1994; 1995a; 1995b; Forbes and Agwani, 1994; Jacqmin *et al.*, 1994; Jacqmin-Gadda *et al.*, 1996; McLachlan *et al.*, 1996; Gauthier *et al.*, in press). An exception is the Ontario study of Forbes and McLachlan (1996), in which RRs for Alzheimer’s disease in subjects 85 years of age or older exposed to aluminum concentrations of $>250 \mu\text{g/L}$ ranged from 4.8 ($p < 0.05$) with no control for water quality parameters to 10 ($p < 0.05$) with control for water source, pH, turbidity and concentrations of silica, iron and fluoride.

The analytical epidemiological studies in which there was a positive association provide only limited evidence to satisfy the criterion of temporality of exposure and disease, since in few of these studies have the effects of the duration of exposure on the occurrence of Alzheimer’s disease or cognitive dysfunction been assessed. In one of the studies conducted in Ontario (McLachlan *et al.*, 1996) an OR of 1.7 was reported for exposure to $\geq 100 \mu\text{g Al/L}$ in drinking water, increasing to 2.5 when a 10-year weighted residential history prior to onset of the disease was taken into account. In their study of cognitive impairment, Forbes *et al.* (1994) indicated that they observed greater ORs when their analyses were restricted to subjects who had lived at their current addresses for more than 5 years. In the death certificate study of Alzheimer’s disease from Ontario, Forbes and McLachlan (1996) noted that the death certificates for their cases did not state how long subjects had resided in the areas where their deaths occurred thus limiting the assessment of exposure duration. However, the risk of Alzheimer’s disease and/or presenile dementia was greater for individuals > 75 compared to < 75 years of age and > 85 versus > 75 years of age (Forbes *et al.*, 1995b; Forbes and McLachlan, 1996). According to the authors, these results may be attributed to a greater cumulative exposure to aluminum over a lifetime for individuals in the older age groupings. In the study from Quebec (Gauthier *et al.*, in press) individual exposures were weighted for duration of residence at a given location. However, a significant relationship between organic monomeric aluminum in drinking water and Alzheimer’s disease was reported only for the onset period of the disease. The authors suggested that the onset period may have actually represented long-term exposure, as the cases lived an average of 44 years at their residences prior to onset of the disease. In contrast to this limited evidence of increasing risk with increasing duration of exposure, the exclusion of patients greater than 65

years of age strengthened the relationship between Alzheimer's disease and aluminum in the ecological study of Martyn *et al.* (1989). However, the authors attributed this result to greater case ascertainment for the younger age group due to more aggressive clinical investigation.

The evidence for biological plausibility of the association between exposure to aluminum in drinking water and Alzheimer's disease is, at the very most, limited. Indeed, it is restricted primarily to observations, based on the limited available data, that effects observed consistently at lowest doses in experimental animals are those on the neurological system, the induction of Alzheimer's-like neuropathology in the brains of certain species of experimental animals following aluminum administration, and the observation of aluminum-induced neurological disorders in humans, such as dialysis encephalopathy (Section 2.4.5).

In relation to biological plausibility, four essential criteria that must be met in order to assign a role for aluminum as a definitive factor in the pathogenesis of Alzheimer's disease are commonly cited (Kruck and McLachlan, 1989). These are as follows:

- 1) It must be located at the site of toxic action without exception and be significantly diminished or absent in controls.
- 2) It must be present in and available from the environment.
- 3) There must be a demonstrable route of access to the site of toxic action.
- 4) Removal of aluminum from this site must be followed by retardation or arrest of the induced process.

In relation to these criteria, evidence of the presence of elevated levels of aluminum in bulk brain tissue and in NFTs and neuritic plaques from Alzheimer's patients is conflicting. There is, however, evidence that aluminum is accessible to the site of toxic action (i.e., central nervous system), and, based on data on speciation, more bioavailable forms of aluminum may be present in the media for which associations with Alzheimer's disease have been observed (i.e., drinking water). Variations in results are also consistent with what might be expected, when co-factors that influence the bioavailability of aluminum are taken into account.

However, these criteria fall far short of those considered appropriate for assessment of weight of evidence for mode of action as a basis for assessment of biological plausibility for risk assessment. Indeed, as outlined in Section 2.4.6, no plausible pathway for induction of Alzheimer's disease by aluminum has been proposed with measurable key events, for which sufficient investigation has been conducted to assess weight of evidence against traditional criteria of causality as outlined below.

Overall, then, 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.

3.4 Uncertainties and recommendations

While the evidence of an association between exposure to aluminum and Alzheimer's disease is weak, it cannot be dismissed completely in view of the consistency of some results with several lines of circumstantial evidence and the paucity of data to serve as a basis for consideration of biological plausibility. These include reported associations being for the medium for which bioavailability may be the greatest and the documented accumulation and interaction of aluminum with the central nervous system. In view of the potentially significant public health implications if the association were causal, this area is considered a priority for research.

Health Canada initiatives related to development of appropriate research protocols for investigation in this area are described in the Introduction of this report. Specific recommendations of an international workshop regarding the design and conduct of the study included the use of mice (wild-type and transgenic for human genes associated with Alzheimer's disease) and rabbits as the appropriate species; exposure commencing *in utero* and continuing throughout the lifetime of the animals; use of an organo-aluminum compound; administration of a purified, low aluminum content diet; assessment of behavioural endpoints in the U.S. EPA neurotoxicity testing guidelines; appropriate brain histopathology, biochemical and hematological analyses; kinetic studies of aluminum accumulation in the brain; control of aluminum contamination; and Good Laboratory Practice.

As follow-up, an Expert Steering Committee developed an RFP for a study or studies based on the recommendations from the international workshop. The Steering Committee developed designs for a 2-year two-generation study in wild-type mice and a 1-year two-generation study in transgenic mice carrying copies of human genes rendering them predisposed to Alzheimer's-type neuritic plaques. Because of their susceptibility to Alzheimer's-type pathology, the transgenic mice could be a population of animals highly sensitive to any potential effect of aluminum on the development of the disease. Both studies were to involve exposure to aluminum maltolate in drinking water, a purified low-aluminum diet, a repeated battery of behavioural tests, and biochemical and morphological tests at sacrifice.

The Steering Committee also discussed the option of conducting a full-scale case–control epidemiological study of aluminum in drinking water and Alzheimer's disease and recommended that a subcommittee be struck at a later date to design such a study.

It was determined that any RFPs developed for either the mouse or epidemiological studies should not proceed without secured funding, which has not yet been acquired.

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APPENDIX A: Search strategies for identification of relevant data

Environmental evaluation

Data relevant to the risk characterization of aluminum chloride, aluminum nitrate and aluminum sulfate to the environment were identified from existing review documents, published reference texts up to 1996 and on-line searches conducted between January and May 1996 of the following databases: Aqualine, ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts; 1996), BIOSIS (Biosciences Information Services; 1990–1996), CAB (Commonwealth Agriculture 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). Following the initial research, Current Contents was used to maintain an ongoing record of the current scientific literature pertaining to the potential environmental effects of aluminum salts. Data obtained after January 1999 were not considered in the report.

In addition, a survey of Canadian industry was carried out under authority of Section 16 of the *Canadian Environmental Protection Act* (CEPA) (Environment Canada, 1997b). 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

Health evaluation

Data relevant to the characterization of potential effects on human health were identified on the basis of a review prepared in 1997 by BIBRA Toxicology International, a Toxicological Profile for aluminum prepared by the Agency for Toxic Substances and Disease Registry (ATSDR, 1999) and an assessment report on aluminum prepared in 1997 by a Task Group of the

International Programme on Chemical Safety (WHO, 1997). In addition, critical reviews updating the information in the WHO (1997) assessment were prepared in the areas of epidemiology (Smiargiassi, 1999), mode of neurotoxicity of aluminum (Savory, 2000) and the bioavailability of aluminum (Yokel and McNamara, 2000).

To identify data relevant to the estimation of exposure of the general population to aluminum chloride, aluminum nitrate or aluminum sulfate, literature searches were conducted using the strategy of searching by their names, CAS registry numbers and major synonyms in the following databases: Amicus (National Library of Canada), BIOSIS, CAB Abstracts, CISTIMON (Canadian Institute for Scientific and Technical Information list of monographs, National Research Council of Canada), ELIAS, Enviroline, Environmental Bibliography, Food Science and Technology Abstracts, Microlog (Canadian Research Index, Government Publications, Micromedia Ltd.) and Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine).

In addition to the above sources of information, officials of provincial and territorial governments as well as the Food Directorate, the Product Safety Bureau, the Therapeutic Products Programme and the Laboratory Centre for Disease Control of Health Canada were contacted to obtain information relevant to this characterization. Data obtained after January 2000 were not considered in the characterization.

Table 1: Physicochemical properties of aluminum chloride, aluminum nitrate and aluminum sulfate¹

Property	AlCl ₃	Al(NO ₃) ₃	Al ₂ (SO ₄) ₃
Melting point	194°C at 527 kPa	73°C	decomposes at 770°C
Boiling point	n.a.	n.a.	n.a.
Sublimation	181°C	n.a.	n.a.
Decomposition	–	135°C	770°C
Solubility in water	reacts explosively with water 69.86 g/100 mL at 15°C ²	63.7 g/100 mL at 25°C	36.4 g/100 mL at 20°C

¹ Taken from Perry and Green (1984); Budavari *et al.* (1989); ATSDR (1992); Lewis (1992).

² For AlCl₃·6H₂O.

Table 2: Production, importation, exportation and apparent consumption of aluminum chloride and aluminum sulfate in Canada for 1995 and 1996

	Amount (tonnes)			
	AlCl ₃ ¹		Al ₂ (SO ₄) ₃ ·14H ₂ O	
	1995	1996	1995	1996
Production	13 420	13 500	241 400	252 355
Importation	1 570	1 670	12 675	15 500
Exportation	5 890	5 900	7 500	7 060
Apparent consumption	9 100	9 270	246 575	260 795

¹ Includes PAC.

Table 3: Aluminum salts and aluminum (mixed results) releases reported by Canadian industries for 1996

Releases to	Amount (tonnes)
Air	38
Watercourses	8124
Wastewater treatment plants	305
Landfarming	317
Soil conditioning	70

Table 4: Sludge disposal practices for drinking water treatment plants using aluminum-based coagulants (mean for 1995 and 1996)

Disposal practice	Coagulant used (tonnes)	Number of responses	Sludge ¹ reported (tonnes)	% of total release
Agricultural spreading (landfarming)	4 839	5	1 691	0.3
Landfill	4 843	11	8 153	1.4
Lagoon	1 056	8	47 226	8.2
River	29 423	30	332 006	57.8
Sewer	5 750	31	184 755	32.2
Not specified	8 832	17	0	0
Total	54 741	103	574 000²	100.0

¹ Many DWTPs have reported equal amounts for sludge and coagulant used.

² Rounded to the closest thousand.

Table 5: Estimated total and dissolved inorganic aluminum concentrations in receiving waters and effluents from selected drinking water treatment plants and pulp and paper mills

Province and location	Receiving environment (river)	Sector	Amount of alum used (1996)	Amount of treated water	Estimated total Al level (including solid phase) in “backwash” water or in effluent	Estimated ¹ dissolved inorganic Al level in receiving environment		Background concentration of Al in receiving environment	
						Micro-crystalline gibbsite mg/L	Boehmite mg/L	Total mg/L	Dissolved mg/L
			tonnes/year	m ³ /day	mg/L				
Alberta									
Edmonton									
Rossdale	North Saskatchewan	DWTP	4 527	135 900	80.5	0.151	0.025	0.35	0.01
E.L. Smith	North Saskatchewan	DWTP	6 567	176 600	89.9	n.a. ²	n.a.		
Lethbridge	Oldman	DWTP	750 ³	36 670	155.0	0.183	0.032	1.75	0.04
Medicine Hat	South Saskatchewan	DWTP	1 300	44 100	71.2	n.a.	n.a.	0.92	0.02
Peace River	Peace	DWTP	110	4 502	58.8	0.132	0.022	n.a.	n.a.
Red Deer	Red Deer	DWTP	956	30 800	75.0	0.165	0.027	0.07	0.01
Ontario									
RM of Ottawa-Carleton									
Britannia	Ottawa	DWTP	2 421	194 000	30.1	0.027	0.005	0.11	n.a.
Lemieux	Ottawa	DWTP	1 870	151 000	29.9	n.a.	n.a.	0.11	n.a.
Thunder Bay	Kaministiquia	P&P mill	Confid. ⁴	160 000	4.8 ⁵	0.040	0.007	n.a.	n.a.

Manitoba									
Brandon	Assiniboine	DWTP	40	17 252	5.6	n.a.	n.a.	0.45	n.a.
Quebec									
La Tuque	St. Maurice	P&P mill	Confid. ⁴	94 000	0.76 ⁶	0.011	0.002	0.10	n.a.
New Brunswick									
Oromocto	St. John	DWTP	89	4 565	97.1	0.038	0.007	0.07	n.a.
Saskatchewan									
Prince Albert	North Saskatchewan	DWTP	499	17 105	70.4	0.229	0.038	2.15	n.a.
Saskatoon	South Saskatchewan	DWTP	1 455	101 905	34.5	n.a.	n.a.	0.32	n.a.
Swift Current	Swift Current	DWTP	335	7 174	94.1	0.348	0.059	n.a.	n.a.

¹ Assuming 1:10 dilution.

² n.a. = not available.

³ Mixture of alum and PAC.

⁴ Confidential.

⁵ Source: MISA (1990).

⁶ Source: Quebec P&P Database (1999).

Table 6: Neurological effects of orally administered aluminum salts on rats, mice and monkeys

Study	Species	Exposure	Exposure duration	Results
Hermenegildo <i>et al.</i> , 1999	rat	2.5% Al sulfate in drinking water (0.2% Al)	3–5 weeks	<ul style="list-style-type: none"> - altered cerebellar glutamate–nitric oxide–cGMP pathway: - decreased N-methyl-D-aspartate-induced extracellular cGMP increase - increased s-nitroso-N-acetyl penicillamine-induced extracellular cGMP increase - reduced cerebellar calmodulin and nitric oxide synthase levels - reduced basal activity of guanylate cyclase - decreased basal extracellular cGMP levels
Kumar, 1998	rat	gavage: 320 mg Al/kg-bw per day (as AlCl ₃)	4 and 14 days or 60 days	<ul style="list-style-type: none"> - increased acetylcholinesterase activity in olfactory bulb, striatum and hypothalamus (4 and 14 days) - decreased acetylcholinesterase activity (60 days)
Abd El-Fattah <i>et al.</i> , 1998	mouse	<p>purified diet + 2000, 4000 or 6000 µg Al/g diet (as Al acetate)</p> <p>purified diet + 2000 or 4000 µg Al/g diet (as Al acetate)</p>	<p>2 weeks</p> <p>8 weeks</p>	<ul style="list-style-type: none"> - decreased glutathione levels in brain (2 weeks — high exposure, 8 weeks — high exposure) - thiobarbituric acid reactive substances (TBARs) increased (lipid peroxidation) (8 weeks — both exposures) - effects ameliorated by co-administration of vitamin E
Zheng and Liang, 1998	rat	1600 mg Al/L in drinking water (as AlCl ₃)	90 days	<ul style="list-style-type: none"> - impaired step-down test performance (passive avoidance) - impaired Morris water maze performance - no effect on acetylcholinesterase activity
Varner <i>et al.</i> , 1998	rat	0.5 ppm AlF ₃ in drinking water	52 weeks	<ul style="list-style-type: none"> - damaged and abnormal neurons and decreased neuronal density in hippocampus and neocortex
Katyal <i>et al.</i> , 1997	rat	standard diet + 250 mg AlCl ₃ ·6H ₂ O/kg-bw per day	6 weeks	<ul style="list-style-type: none"> - decreased thiol levels in brain - decreased brain glutathione reductase and ATPase activities - no significant effect on TBARs or glutathione-S-transferase
Somova <i>et al.</i> , 1997	rat	5 or 20 mg AlCl ₃ /kg-bw per day in drinking water	6 months	<ul style="list-style-type: none"> - temporal cortex — reduced cell density in ganglionic layer and spongiform changes (high exposure) - hippocampus — neurofilaments, deformity and vacuolization of nuclei (high exposure)

Study	Species	Exposure	Exposure duration	Results
Sánchez <i>et al.</i> , 1997	rat	50 or 100 mg Al/kg-bw per day (as Al(NO ₃) ₃ ·9H ₂ O in drinking water) + 355 and 710 mg citrate/kg-bw per day, respectively	6.5 months	<ul style="list-style-type: none"> - decreased calcium concentrations in brains of old rats (16 months) (high exposure) - decreased manganese concentrations in brains of young (21 days) and adult (8 months) rats (high exposure) - decreased copper and zinc concentrations in brains of young (21 days) rats (high and low exposure) - decreased iron concentrations in brains of young (21 days) rats (high exposure) - no effect on brain magnesium concentrations
Sarin <i>et al.</i> , 1998	monkey	gavage: 25 mg Al/kg-bw every second day (as Al lactate)	52 weeks	<ul style="list-style-type: none"> - decreased total lipid, glycolipid and phospholipid content of brain - increased cholesterol levels and phospholipid to cholesterol ratio in brain - increased lipid peroxidation (hippocampus > cerebral cortex > corpus striatum) and decreased ganglioside levels - decreased Na⁺K⁺-ATPase, acetylcholinesterase and 2',3'-cyclic nucleotide phosphohydrolase activities in brain
Domingo <i>et al.</i> , 1996	rat	50 or 100 mg Al/kg-bw per day (as Al(NO ₃) ₃ ·9H ₂ O in drinking water) + 355 and 710 mg citrate/kg-bw per day, respectively	6.5 months	<ul style="list-style-type: none"> - no effects on open field activity - no effects on shuttle box performance (passive avoidance)
Gupta and Shukla, 1995	rat	500 mg Al/L in drinking water (as AlCl ₃)	12 months	<ul style="list-style-type: none"> - increased lipid peroxidation in brain (hippocampus and whole brain) - decreased activities of superoxide dismutase, glutathione peroxidase and catalase
Şahin <i>et al.</i> , 1995	mouse	drinking water + 4.4 µg Al/L (as AlCl ₃)	90 days	<ul style="list-style-type: none"> - decreased motor coordination (rota-rod)
Florence <i>et al.</i> , 1994	rat	standard diet + 1 g Al/kg diet (as Al citrate)	6 months	<ul style="list-style-type: none"> - vacuolated astrocytes (cell body and processes) - swollen astrocytic processes - vacuolization of neuronal cytoplasm - neuronal nuclear membrane indentations, vacuoles and inclusions
Varner <i>et al.</i> , 1994	rat	0.5, 5 or 50 ppm AlF ₃ in drinking water	45 weeks	<ul style="list-style-type: none"> - no effects on open field analysis and walking patterns (locomotor activity) - no effects on balance beam test (motor coordination) - no effects on T-maze performance (spontaneous alternation) - no effects on water maze performance - altered olfactory performance (medium and high exposure)
Oteiza <i>et al.</i> , 1993	mouse	purified diet + 1000 µg Al/g diet (as AlCl ₃) + 3.5% citrate	5–7 weeks	<ul style="list-style-type: none"> - decreased forelimb and hindlimb grip strength - increased air puff startle response - no effect on thermal sensitivity, negative geotaxis and auditory startle - no change in brain TBARs or glutamine synthetase and alkaline phosphatase activities

Study	Species	Exposure	Exposure duration	Results
Bilkei-Gorzó, 1993	rat	gavage: 30 or 100 mg AlCl ₃ /kg-bw per day, 300 mg Al(OH) ₃ /kg-bw per day or 100 mg Al(OH) ₃ /kg-bw per day + 30 mg citrate/kg-bw per day	90 days	- impaired maze performance (all exposures) - increased brain acetylcholinesterase activity (high exposure AlCl ₃ and low exposure Al(OH) ₃) - decreased choline acetyltransferase activity (low exposure AlCl ₃)
Lal <i>et al.</i> , 1993	rat	500 mg Al/L in drinking water (as AlCl ₃) (12 mg Al/day per rat)	180 days	- reduced spontaneous locomotor activity - impaired acquisition, extinction and reacquisition of an active avoidance task (shuttle box) - impaired maze relearning ability - increased brain lipid peroxidation - reduced brain Mg ²⁺ - and Na ⁺ K ⁺ -ATPase activities
Varner <i>et al.</i> , 1993	rat	0.5, 5 or 50 ppm AlF ₃ in drinking water	45 weeks	- reduced numbers of neurons in hippocampus (all exposures) - neurons in hippocampus disorganized (all exposures)
Johnson <i>et al.</i> , 1992	rat	adults: 0.3% Al ₂ (SO ₄) ₃ ·18H ₂ O in drinking water weanlings: 0.1–0.3% Al ₂ (SO ₄) ₃ ·18H ₂ O in drinking water	3 months 8 weeks	- adults: decreased levels of microtubule associated protein-2 (MAP-2) (hippocampus and brain stem) and spectrin (hippocampus) - weanlings: decreased MAP-2 levels in cortex and brainstem, increased cAMP levels and decreased inositol triphosphate levels in hippocampus
Golub <i>et al.</i> , 1992a	mouse	semi-purified diet + 1000 µg Al/g diet (as Al lactate)	90 days	- decreased motor activity, hindlimb grip strength and auditory and air puff startle responsiveness - no effects on temperature sensitivity or foot splay - no effect on lipid peroxidation (TBARS)
Roy <i>et al.</i> , 1991	mouse	gavage: 17–172 mg Al/kg-bw per day (as Al ₂ (SO ₄) ₃ ·18H ₂ O or KAl(SO ₄) ₂ ·12H ₂ O)	21 days	- multifocal, dose- and duration-dependent degeneration of nerve cells in cerebral cortex, subcortical region and base of brain (≥2.86 mg Al/kg-bw per day as Al ₂ (SO ₄) ₃ ·18H ₂ O or ≥4.86 mg Al/kg-bw per day as KAl(SO ₄) ₂ ·12H ₂ O)
Flora <i>et al.</i> , 1991	rat	gavage: 25 mg Al/kg-bw per day (as Al(NO ₃) ₃)	6 weeks	- brain dopamine and 5-hydroxytryptamine levels decreased, norepinephrine levels increased
Fraga <i>et al.</i> , 1990	mouse	purified diet + 500 or 1000 µg Al/g diet (as Al lactate)	10 weeks	- increased lipid peroxidation in brain (TBARS production) (high exposure)
Golub <i>et al.</i> , 1989	rat	purified diet + 500 or 1000 µg Al/g diet (as Al lactate) (62 or 130 mg Al/kg-bw per day)	6 weeks	- decreased motor activity (high exposure)
Connor <i>et al.</i> , 1989	rat	3.7% Al ₂ (SO ₄) ₃ ·18H ₂ O in drinking water (0.3% Al; 2.0 mmol Al/day per rat)	30 days	- decreased retention of passive avoidance response - no effect on open field activity
Connor <i>et al.</i> , 1988	rat	3.7% Al ₂ (SO ₄) ₃ ·18H ₂ O in drinking water (0.3% Al; 2.0 mmol Al/day per rat)	30 days	- impaired acquisition and retention of a passive avoidance learned response - no effect on active avoidance response, radial arm maze or open field activity - increased hippocampal muscarinic receptors - no effect on choline acetyltransferase activity

Study	Species	Exposure	Exposure duration	Results
Johnson and Jope, 1987	rat	0.3% Al in drinking water (2.4% Al citrate [5.6 mmol Al/day per rat] or 3.7% Al ₂ (SO ₄) ₃ ·18H ₂ O [1.8 mmol Al/day per rat])	4 weeks	<ul style="list-style-type: none"> - increased cAMP levels in cerebellum, cortex, hippocampus and striatum - increased cGMP levels in cerebellum and striatum (Al sulfate) and hippocampus (Al sulfate + citrate) - choline levels decreased in cortex, hippocampus and striatum (Al citrate)
Fleming and Joshi, 1987	rat	100 µM AlCl ₃ in drinking water	1 year	<ul style="list-style-type: none"> - impaired T-maze performance
Thorne <i>et al.</i> , 1987	rat - weanling	2400 mg Al(OH) ₃ /kg-bw per day in drinking water	60 days	<ul style="list-style-type: none"> - no effect on open field activity (horizontal or vertical movement) - no effect on passive avoidance test - no effect on radial maze performance - some correlations between activity and brain aluminum levels
Thorne <i>et al.</i> , 1986	rat – adult	1513, 2697 or 3617 mg Al/kg-bw per day (as Al(OH) ₃ in diet)	30 days	<ul style="list-style-type: none"> - no effect on open field activity (horizontal or vertical movement) - no effect on passive avoidance test - no effect on visual discrimination performance - some correlations between test performance and brain aluminum levels
Commissaris <i>et al.</i> , 1982	rat	standard diet + 0.2% Al (as AlCl ₃)	12 weeks or 11 months	<ul style="list-style-type: none"> - no effects on motor coordination (rota-rod) (12 weeks) - reduced motor activity (both exposure durations) - slowed acquisition of passive avoidance behaviour (shuttle box) (11 months) - impaired retention of passive avoidance behaviour (12 weeks)
Bowdler <i>et al.</i> , 1979	rat	gavage: 200, 400 or 600 mg AlCl ₃ ·6H ₂ O/kg-bw per day or 195 mg Al(OH) ₃ /kg-bw per day	28 days	<ul style="list-style-type: none"> - increased general activity (open field maze) - decreased motor coordination (rota-rod) - increased sensitivity to flicker - no effect on shuttle box performance (passive avoidance)
Krasovskii <i>et al.</i> , 1979	rat	gavage: 0.0025, 0.25 or 2.5 mg Al/kg-bw per day	6–12 months	<ul style="list-style-type: none"> - slowdown in development and reinforcement of conditioned reflexes - high value of index of latent stage of conditioned reflexes - altered small movements

Table 7: Neurological effects of aluminum salts administered orally to rats and mice during gestation, weaning and/or post-weaning

Study	Species	Exposure	Exposure period ¹	Effects in offspring
Llansola <i>et al.</i> , 1999	rat	dams: 3% Al sulfate in drinking water	dams: G1–PN7	<ul style="list-style-type: none"> - decreased glutamate-induced proteolysis of microtubule associated protein-2 (MAP-2), disaggregation of microtubules and neuronal death in cerebellar neuron cultures - decreased nitric oxide synthase and guanylate cyclase, and increased calmodulin contents of whole cerebellum and cultured cerebellar neurons
Verstraeten <i>et al.</i> , 1998	mouse	dams and pups: purified diet + 1000 µg Al/g diet (as Al lactate)	dams: G0–PN21 + pups: PN21–40	<ul style="list-style-type: none"> - increased brain myelin phospho- and galactolipid contents, and increased thiobarbituric acid reactive substances (TBARs) (lipid peroxidation) in myelin fraction
Golub and Germann, 1998	mouse	<p>dams: purified diet + 500 or 1000 µg Al/g diet (as Al lactate) (50 and 100 mg/kg-bw per day)</p> <p>pups: purified diet + 1000 µg Al/g diet (as Al lactate)</p>	<p>dams: G0–PN21 + pups: PN21–35 (D)</p> <p>pups: PN 35- end (P)</p> <p>training and testing: PN50 – end</p>	<p>operant tasks:</p> <ul style="list-style-type: none"> - no effect on delayed spatial alternation test (D) - enhanced responses in the differential reinforcement of high rates test (motor learning and ability) (D or P) - enhanced performance on progressive ratio test (food motivation) (P)
Poulos <i>et al.</i> , 1996	rat	dams: 120 mM Al lactate in drinking water	dams: G0–weaning	<ul style="list-style-type: none"> - delayed expression of phosphorylated high molecular weight neurofilament protein in tracts in diencephalon
Golub <i>et al.</i> , 1995	mouse	<p>dams: purified diet + 500 or 1000 µg Al/g diet (as Al lactate) (100 and 200 mg/kg-bw per day)</p> <p>pups: purified diet + 500 or 1000 µg Al/g diet (as Al lactate)</p>	<p>dams: G0–weaning (D)</p> <p>dams: G0–weaning + pups: weaning–PN50 (D + P)</p> <p>training and testing: PN50 – end</p>	<p>operant tasks:</p> <ul style="list-style-type: none"> - increased cagemate aggression (D or D + P) (high exposure level) - enhanced attainment of training criteria for delayed spatial alternation and discrimination reversal testing, but no effect on actual performance (D or D + P) (both exposure levels) - decreased grip strength (forelimb and hindlimb) (D or D + P) (both exposure levels) - no effects on temperature sensitivity, negative geotaxis and auditory startle - decreased levels of iron in brain and spinal cord (D) (both exposure levels)

Study	Species	Exposure	Exposure period ¹	Effects in offspring
Golub <i>et al.</i> , 1994	mouse	dams: purified diet + 1000 µg Al/g diet (as Al lactate) (pregnant: 200 mg/kg-bw per day, lactating: 420 mg/kg-bw per day) pups: purified diet + 1000 µg Al/g diet (as Al lactate) (130 mg/kg-bw per day)	dams: G0–weaning (PN21) (D) dams: G0–weaning + pups: weaning–PN52 (D + P) testing: PN22 and PN52	- reduced auditory startle response (D or D + P)
Golub <i>et al.</i> , 1993	mouse	dams: purified diet + 1000 µg Al/g diet (as Al lactate) pups: purified diet + 1000 µg Al/g diet (as Al lactate)	dams: G0–weaning + pups: weaning–PN24	- decreased brain manganese concentration - no effect on brain iron concentration
Misawa and Shigeta, 1993	rat	dams: gavage with 900 or 1800 mg AlCl ₃ /kg-bw	dams: G15 (acute) testing: 4 weeks of age	- delayed development of auditory startle (both exposure levels) - decreased activity (open field) (high exposure level) - no significant effect on shock avoidance rates
Clayton <i>et al.</i> , 1992	mouse	dams: drinking water + 750 mg Al sulfate/L	dams: G10–17 testing: PN3–44 weeks of age	- differential effects (+/–) on choline acetyltransferase activity in various brain regions - no effects on righting, cliff aversion, grasping, climbing, radial maze
Golub <i>et al.</i> , 1992b	mouse	dams: purified diet + 1000 µg Al/g diet (as Al lactate) (250 mg Al/kg-bw per day)	dams: G0–parturition (gestation), parturition–weaning (lactation), G0–weaning (gestation + lactation) testing: weaning	- decreased forelimb grip strength (gestation) - increased hindlimb grip strength (gestation, lactation) - increased negative geotaxis latency (lactation) - decreased temperature sensitivity (lactation) - decreased manganese concentrations in brain (lactation) - no effects on Fe concentrations in brain
Cherroret <i>et al.</i> , 1992	rat	pups: gavage with 100 or 200 mg Al/kg-bw per day (as Al lactate)	pups: PN5–14 testing: PN50 and PN100	- inhibition of cerebral choline acetyltransferase activity (high exposure level) - no effects on operant conditioning learning abilities (light avoidance or food motivation and pressing on a lever or running in a maze) - decrease in general activity (radial maze test) (high exposure level)

Study	Species	Exposure	Exposure period ¹	Effects in offspring
Muller <i>et al.</i> , 1990	rat	dams: standard diet + 400 mg Al/kg-bw per day (as Al lactate)	dams: G1–7, G1–14, G1–20 testing: PN4-65	<ul style="list-style-type: none"> - no effects on righting or grasping reflexes - impaired negative geotaxis (G1–14 and G1–20) - no effect on suspension test outcomes - impaired locomotor coordination (G1–7, G1–14 and G1–20) - impaired operant conditioning (adverse light stimulus and lever pressing) (G1–7, G1–14 and G1–20)
Bernuzzi <i>et al.</i> , 1989a	rat	pups: gavage with 100, 200 or 300 mg Al/kg-bw per day as Al lactate	pups: PN5–14 testing: PN6-20	<ul style="list-style-type: none"> - no effects on grasping reflex - impaired negative geotaxis (medium and high exposure) - impaired suspension test performance (high exposure) - impaired locomotor coordination test performance (high exposure)
Bernuzzi <i>et al.</i> , 1989b	rat	dams: standard diet + 100, 300 or 400 mg Al/kg-bw per day (as AlCl ₃) or standard diet + 100, 200 or 400 mg Al/kg-bw per day (as Al lactate)	dams: G1–parturition testing: PN4-20	<ul style="list-style-type: none"> - impaired righting reflex (medium and high exposure for both salts) - no effects on grasping reflex - impaired negative geotaxis (all exposure levels for AlCl₃) - no effects on suspension test outcome - decreased locomotor coordination (high exposure for both salts)
Donald <i>et al.</i> , 1989	mouse	dams: purified diet + 500 or 1000 µg Al/g diet (as Al lactate) (100–210 and 200–420 mg Al/kg-bw per day)	dams: G0–weaning testing: PN21-39	<ul style="list-style-type: none"> - no effects on air puff or auditory startle response - increased forelimb and hindlimb grip strength (both exposure levels) - decreased temperature sensitivity (high exposure level) - no effects on negative geotaxis latency - increased foot splay (both exposure levels)
Golub <i>et al.</i> , 1987	mouse	dams: purified diet + 500 or 1000 µg Al/g diet (as Al lactate)	dams: G0–PN21 testing: PN8-18	<ul style="list-style-type: none"> - dams: ataxia, splaying and dragging of hindlimbs, paralysis, dyspnea - pups: delayed neuromotor development (Wahlsten neurobehavioural test battery)
Bernuzzi <i>et al.</i> , 1986	rat	dams: standard diet + 160 or 200 mg Al/kg-bw per day (AlCl ₃)	dams: G8–parturition testing: PN4-20	<ul style="list-style-type: none"> - impaired righting reflex (low and high exposure) - no effects on grasping reflex - increased negative geotaxis latency (low and high exposure) - no effects on suspension test outcome - no effects on locomotor coordination

¹ G is gestation day; PN is postnatal day.

Table 8: Analytical epidemiological studies of exposure to aluminum in drinking water and Alzheimer’s disease or dementia

Location	Reference/ study type	Study population	Exposure measure	Results	Comments
Ontario	McLachlan <i>et al.</i> , 1996 Case-control	cases and controls based on brains donated to Canadian Brain Tissue Bank cases: A1 — 296 AD based on clinical history of dementia and neuropathology criteria (neuritic plaques and NFTs in specific brain regions); A2 — 89 AD as above coexisting with other neurological disease controls: C1 — 125 with no brain neuropathology; C2 — 170 with other neurodegenerative diseases	total Al in drinking water based on Ontario Drinking Water Surveillance Program (DWSP) data for municipal supplies serving place of residence and residential history	no weighting of residential history: A1 vs. C1 + C2 for Al \geq 100 $\mu\text{g/L}$, OR = 1.7 (95% CI 1.2–2.6) 125 $\mu\text{g/L}$, OR = 3.6 (95% CI 1.4–9.9) 150 $\mu\text{g/L}$, OR = 4.4 (95% CI 0.98–20) 175 $\mu\text{g/L}$, OR = 7.6 (95% CI 0.98–61) A1 + A2 vs. C1 + C2 for Al =100 $\mu\text{g/L}$, OR = 1.7 (95% CI 1.2–2.5) weighted 10-year residential history: A1 vs. C1 + C2 for Al \geq 100 $\mu\text{g/L}$, OR = 2.6 (95% CI 1.2–5.7) A1 + A2 vs. C1 + C2 for Al \geq 100 $\mu\text{g/L}$, OR = 2.5 (95% CI 1.2–5.3)	no control for age, sex, education, occupation, etc. exposure weighted for 10-year residential history

Location	Reference/ study type	Study population	Exposure measure	Results	Comments
Ontario	Forbes <i>et al.</i> , 1995b and Forbes and McLachlan, 1996 (follow-up analysis)	AD based on death certificate data indicating presenile dementia or AD as underlying cause of death according to ICD ¹ criteria Forbes <i>et al.</i> , 1995b: > 3000 death certificates Forbes and McLachlan, 1996: 1041 death certificates	total Al in drinking water based on Ontario DWSP data for areas of residence at time of death	Forbes <i>et al.</i> , 1995b: analyses for AD in individuals ≥ 75 years of age (ORs were smaller for similar analyses of AD and presenile dementia, presenile dementia alone and individuals of all ages) : for Al alone: Al ≤ 67 $\mu\text{g/L}$, RR = 1.00 Al = 68-200 $\mu\text{g/L}$, RR = 0.91 (95% CI 0.82-1.01) Al ≥ 336 $\mu\text{g/L}$, RR = 3.15 (95% CI 1.85-5.36) for pH: Al ≤ 67 $\mu\text{g/L}$, pH < 7.85, RR = 1.00 Al = 68-200 $\mu\text{g/L}$, pH = 7.85-7.95, RR = 0.91 (95% CI 0.82-1.00) Al ≥ 336 $\mu\text{g/L}$, pH ≥ 7.95 , RR = 3.27 (95% CI 1.92-5.57) for F : Al ≤ 67 $\mu\text{g/L}$, RR = 1.00 Al = 68-200 $\mu\text{g/L}$, F < 300 $\mu\text{g/L}$, RR = 0.95 (95% CI 0.84-1.06) Al ≥ 336 $\mu\text{g/L}$, F ≥ 860 $\mu\text{g/L}$, RR = 3.10 (95% CI 1.81-5.27) for F < 300 $\mu\text{g/L}$ and including Al/F interaction term: Al ≤ 67 $\mu\text{g/L}$, RR = 1.00 Al = 68-200 $\mu\text{g/L}$, RR = 1.11 (95% CI 0.92-1.33) Al ≥ 336 $\mu\text{g/L}$, RR = 3.88 (95% CI 2.22-6.77) for F ≥ 860 $\mu\text{g/L}$ and including Al/F interaction term: Al ≤ 67 $\mu\text{g/L}$, RR = 1.00 Al = 68-200 $\mu\text{g/L}$, RR = 0.85 (95% CI 0.74-0.98) Al ≥ 336 $\mu\text{g/L}$, RR = 0.98 (95% CI 0.14-6.97) for silica: Al ≤ 67 $\mu\text{g/L}$, RR = 1.00 Al = 68-200 $\mu\text{g/L}$, silica < 1500 $\mu\text{g/L}$, RR = 0.90 (95% CI 0.81-1.00) Al ≥ 336 $\mu\text{g/L}$, silica ≥ 1500 $\mu\text{g/L}$, RR = 3.14 (95%CI 1.84-5.34)	no control for sex, education, occupation, etc. possible inaccuracies in death certificate data no information on duration of exposure

Location	Reference/ study type	Study population	Exposure measure	Results	Comments
				<p>for silica < 1500 µg/L and including Al/silica interaction term: Al ≤ 67 µg/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)</p> <p>for silica ≥ 1500 µg/L and including Al/silica interaction term: Al ≤ 67 µg/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)</p> <p>analysis adjusting for pH, F, silica and water source: Al ≤ 67 µg/L, RR = 1.00 Al = 68-200 µg/L, RR = 0.99 (95% CI 0.86-1.13) Al ≥ 336 µg/L, RR = 3.54 (95% CI 2.06-6.10)</p> <p>Forbes and McLachlan, 1996:</p> <p>follow-up analyses for aluminum alone for individuals ≥ 85 years of age: Al ≤ 67 µg/L, RR = 1.00 68–250 µg/L, RR = 0.85, p < 0.05 >250 µg/L, RR = 4.76, p < 0.05</p> <p>for individuals ≥ 85 years of age, taking into account water source, pH, turbidity and concentrations of silicic acid, iron, fluoride: Al ≤ 67 µg/L, rate ratio = 1.00 68–250 µg/L, rate ratio = 0.89 (not significant) >250 µg/L, rate ratio = 9.95, p < 0.05</p>	

Location	Reference/ study type	Study population	Exposure measure	Results	Comments
Ontario	Forbes and Agwani, 1994; Forbes <i>et al.</i> , 1992; 1994; 1995a Longitudinal cohort	males with cognitive impairment based on interview/questionnaire with modified mental status test for subjects from the Ontario Longitudinal Study of Aging (LSA) Forbes <i>et al.</i> , 1992: 485 males for each analysis Forbes and Agwani, 1994: 530 males Forbes <i>et al.</i> , 1994: 290-485 males for each analysis Forbes <i>et al.</i> , 1995a: 494-541 males for each analysis	median total Al in drinking water based on Ontario DWSP data for municipal supplies serving place of residence and residential history	Forbes <i>et al.</i> , 1992: analysis for Al alone: Al < 84.7 µg/L, OR = 1.00 Al ≥ 84.7 µg/L, OR = 1.14 (not significant) analysis for F (only those series including significant ORs): Al < 84.7 µg/L, F > 880 µg/L, OR = 1.00 Al ≥ 84.7 µg/L, F > 880 µg/L, OR = 1.69 (not significant) 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 = 1.00 all other combinations of Al and F, OR = 1.95 (p < 0.05) Forbes <i>et al.</i> , 1994: analysis for Al alone restricted to surface water sources: Al < 84.7 µg/L, OR = 1.00 Al ≥ 84.7 µg/L, OR = 1.53 (95% CI 0.94-2.51) analysis for F restricted to surface water sources: 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 and Agwani, 1994; Forbes <i>et al.</i> , 1992; 1994; 1995a: exposure not weighted for duration Forbes and Agwani, 1994; Forbes <i>et al.</i> , 1992: no control for age, education, occupation, etc. Forbes <i>et al.</i> , 1994; 1995a: selected analyses included control for education, health status, income, no. of moves and age Forbes <i>et al.</i> , 1994: increased ORs when analysis restricted to subjects residing at current address > 5 years

Location	Reference/ study type	Study population	Exposure measure	Results	Comments
				<p>analysis for pH :</p> <p>Al < 84.7 µg/L, all pHs, OR = 1.00 Al ≥ 84.7 µg/L, pH < 7.85, OR = 0.76 (95%CI 0.28-2.06) Al ≥ 84.7 µg/L, pH = 7.85-8.05, OR = 0.68 (95% CI 0.21-2.19) Al ≥ 84.7 µg/L, pH > 8.05, OR = 1.30 (95% CI 0.85-2.04)</p> <p>analysis for pH and F :</p> <p>Al < 84.7 µg/L, F < 880 µg/L, all pHs, OR = 1.00 Al ≥ 84.7 µg/L, F < 880 µg/L, pH < 7.85, OR = 0.91 (95% CI 0.30-2.74) Al ≥ 84.7 µg/L, F < 880 µg/L, pH = 7.85-8.05, OR = 0.67 (95% CI 0.30-2.74) Al ≥ 84.7 µg/L, F < 880 µg/L, pH > 8.05, OR = 1.36 (95% CI 0.55-3.39) Al ≥ 84.7 µg/L, F ≥ 880 µg/L, pH > 8.05, OR = 0.87 (95% CI 0.50-1.52) Al < 84.7 µg/L, F ≥ 880 µg/L, pH > 8.05, OR = 0.47 (95%CI 0.23-0.97)</p> <p>analysis adjusting for F, pH, water source, age, education, health, income and no. of moves:</p> <p>Al < 84.7 µg/L, OR = 1.00 Al ≥ 84.7 µg/L, OR = 1.72 (95% CI 1.08-2.75)</p> <p>Forbes and Agwani, 1994:</p> <p>analysis adjusting for F, pH, turbidity, dissolved organic carbon and water source:</p> <p>Al < 84.7 µg/L, OR = 1.00 Al ≥ 84.7 µg/L, OR = 1.97 (95% CI 1.21-3.22) analysis above with adjustment for detailed information on water source Al ≥ 84.7 µg/L, OR = 2.27 (95% CI 1.27-4.07)</p> <p>Forbes <i>et al.</i>, 1995a:</p> <p>analysis adjusting for F, pH, turbidity, dissolved organic carbon, silica, iron, water source, education, health status, income, no. of moves and including age term:</p> <p>Al < 84.7 µg/L, OR = 1.00 Al ≥ 84.7 µg/L, OR = 2.19 (95% CI 1.29-3.71)</p>	

Location	Reference/ study type	Study population	Exposure measure	Results	Comments
				<p>analysis adjusting for F, pH, turbidity, dissolved organic carbon, silica, iron, water source, education health status, income, no. of moves and including term for Al/silica interaction: Al < 84.7 µg/L, OR = 1.00 Al ≥ 84.7 µg/L, OR = 2.35 (95% CI 1.32-4.18)</p> <p>analysis for silica: Al < 84.7 µg/L, OR = 1.00 Al ≥ 84.7 µg/L, OR = 1.47 (95% CI 0.99-2.20)</p> <p>Al < 84.7 µg/L, silica < 790 µg/L, OR = 1.00 Al < 84.7 µg/L, silica ≥ 790 µg/L, OR = 2.20 (95% CI 1.02-4.74)</p> <p>Al ≥ 84.7 µg/L, silica < 790 µg/L, OR = 1.00 Al ≥ 84.7 µg/L, silica ≥ 790 µg/L, OR = 0.89 (95% CI 0.54-1.47)</p>	
Ontario	<p>Neri and Hewitt, 1991 and Neri <i>et al.</i>, 1992 (follow-up analysis)</p> <p>Case-control</p>	<p>cases: AD and presenile dementia based on ICD criteria from hospital discharge data on individuals ≥ 55 years of age</p> <p>controls: other diagnoses (not psychiatric or neurological), matched to cases for age/sex</p> <p>Neri and Hewitt, 1991: 2232 cases/2232 controls</p> <p>follow-up analysis by Neri <i>et al.</i>, 1992: 2258 cases/2258 controls</p>	<p>total Al in drinking water based on Ontario DWSP data for area of current place of residence</p>	<p>Neri and Hewitt, 1991: significant dose-response between AD and concentrations ≥ 10 µg/L <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</p> <p>Neri <i>et al.</i>, 1992: significant dose-response between AD and concentrations ≥ 10 µg/L <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</p>	<p>dose-response</p> <p>control for age and sex</p> <p>stronger dose-response upon reanalysis restricted to age >75 years (Smith, 1995)</p> <p>no information on duration of exposure</p>

Location	Reference/ study type	Study population	Exposure measure	Results	Comments
Quebec (Saguenay- Lac-Saint- Jean)	Gauthier <i>et al.</i> , in press Case-control	cases: 68 probable and possible AD based on a 3 step process including testing/interview/exam and utilizing MMS ² results and standardized criteria (DSM, NINCDS-ADRDA, ICD) ¹ controls: 68 free of cognitive impairment — paired for age/sex	various Al species in drinking water based on data from treatment plant serving place of residence and residential history for each Al species, upper quartile of subjects considered as “exposed”	no significant relationship between long-term exposure (1945 to onset) to any Al species and AD risk of AD for exposure during onset of disease: monomeric organic Al: OR = 2.67 (95% CI 1.04–6.90) (exposed, 12.2 µg/L vs. non-exposed, 0–12.2 µg/L) total Al: OR = 2.10 (95% CI 0.83–5.35) total dissolved Al: OR = 1.93 (95% CI 0.79–4.67) monomeric inorganic Al: OR = 0.71 (95% CI 0.29–1.72) polymeric Al: OR = 1.98 (95% CI 0.79–4.98)	only study examining speciation of Al in drinking water control for age, sex, education level, family history, ApoE ε4 allele, occupational exposure exposure weighted for residential history
England (and Wales)	Martyn <i>et al.</i> , 1997 Case-control	cases: 106 with clinical diagnosis of AD or normal computer tomography (CT) scan or cerebral atrophy and progressive deterioration of cognition in the absence of other causes controls: 99 cases of other dementia (no CT abnormality), 226 brain cancer patients, 441 cases of other neurological disorders cases and controls were all males	total Al in drinking water based on data from treatment plant or distribution system serving place of residence and residential history	no significant relationship between AD and drinking water concentrations <200 µg/L highest ORs (based on Al concentrations averaged over 10 years before diagnosis and using brain cancer cases as controls): Al <15 µg/L, OR = 1.0 15–44 µg/L, OR = 1.63 (95% CI 0.64–4.18) 45–109 µg/L, OR = 1.08 (95% CI 0.45–2.60) ≥110 µg/L, OR = 0.32 (95% CI 0.11–0.90) no significant relationship between AD and Al in drinking water when silica < 6 mg/L	control for age, neuroradiology centre where diagnosis made, distance of residence from neuroradiology centre AD diagnostic criteria not stated exposure not weighted for duration
England (Northern)	Forster <i>et al.</i> , 1995 Case-control	cases: 109 AD-type presenile dementia diagnosed before age 65 based on hospital case notes (NINCDS-ADRDA and DSM criteria), MMS score and examination controls: 109 from general population paired for age/sex	total 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, tea consumption and antacid use based on interview data	no significant relationship between AD and Al in drinking water: e.g., Al in drinking water 10 years before onset: <50 µg/L, OR = 1.2 (95% CI 0.67–2.37) >50 µg/L, OR = 0.8 (95% CI 0.42–1.50) >99 µg/L, OR = 0.8 (95% CI 0.44–1.49) >149 µg/L, OR = 1.0 (95% CI 0.41–2.43) no significant relationship between AD and consumption of tea or antacid use: >4 cups tea/day, OR = 1.4 (95% CI 0.81–2.63) antacids, OR = 1.6 (95% CI 0.77–3.51)	control for age, sex, family history, disease history, head injuries, physical activity, smoking no information on presence or absence of Al in antacids

Location	Reference/ study type	Study population	Exposure measure	Results	Comments
England (Northern)	Wood <i>et al.</i> , 1988c Cross- sectional	dementia (unspecified mental test) in 386 hip fracture patients > 55 years of age in two health districts	total Al in drinking water based on treatment plant data and place of residence 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)	no significant difference in mental test scores between high-Al (180–250 µg/L) and low-Al (≤ 50 µg/L) districts	control for age and sex primary focus of study was bone mass/hip fracture no information on duration of exposure details of mental test score not provided

Location	Reference/ study type	Study population	Exposure measure	Results	Comments
France (South- western)	Jacqmin <i>et al.</i> , 1994 and Jacqmin-Gadda <i>et al.</i> , 1996 (follow- up analysis) Cohort	cognitive impairment assessed by MMS in individuals ≥ 65 years of age from Principle Lifetime Occupation and Cognitive Impairment in a French Elderly Cohort (PAQUID) study Jacqmin <i>et al.</i> , 1994: 3,469 individuals Jacqmin-Gadda <i>et al.</i> , 1996: 3,430	total Al in drinking water based on data from treatment plant or distribution system serving place of residence	Jacqmin <i>et al.</i> , 1994: association with Al non-significant without adjustment for pH; association positive for pH ≤ 7.3 , negative for pH \geq 7.3: for pH = 7.0 Al = 5 $\mu\text{g/L}$, OR = 1.0 50 $\mu\text{g/L}$, OR = 1.26 100 $\mu\text{g/L}$, OR = 1.35 for pH = 8.5 Al = 5 $\mu\text{g/L}$, OR = 1.0 50 $\mu\text{g/L}$, OR = 0.59 100 $\mu\text{g/L}$, OR = 0.50 Jacqmin-Gadda <i>et al.</i> , 1996: logistic regression adjusted for age, sex, education and occupation: only significant association with Al and highest OR reported for first quartiles of Al, pH and silica including term for Al/silica interaction: pH = 7.35, silica = 10.4 mg/L, Al ≥ 3.5 $\mu\text{g/L}$ OR = 1.65 (95% CI 0.80-3.39) analysis including term for Al/silica interaction OR = 3.94 (95% CI 1.39-11.2) logistic regression with adjustment for personal characteristics and calcium: Al < 3.5 $\mu\text{g/L}$, pH < 7.35, silica < 10.4 mg/L, OR = 1.00 Al ≥ 3.5 $\mu\text{g/L}$, pH ≥ 7.35 , silica ≥ 10.4 mg/L, OR = 0.75 (95%CI 0.59- 0.96) Al ≥ 3.5 $\mu\text{g/L}$, pH < 7.35, silica < 10.4 mg/L, OR = 1.30 (95%CI 0.75- 2.24)	control for age, sex, education, occupation exposure not weighted for duration

Location	Reference/ study type	Study population	Exposure measure	Results	Comments
France (South- western)	Michel <i>et al.</i> , 1991 Cross- sectional	possible and probable AD based on testing, interview and clinical exam (DSM, NINCDS- ADRDA criteria) in 2792 residents \geq 65 years of age from the PAQUID study	total Al in drinking water based on data from water authorities on wells serving place of residence	increase of 10 $\mu\text{g/L}$, RR = 1.16, p = 0.0014 increase of 100 $\mu\text{g/L}$, RR = 4.53 (95% CI 3.36–6.10)	control for age, education, rural or urban residence relationship between Al and AD discounted based on updated analyses of water Al levels post-publication (Smith, 1995; WHO, 1997)
Switzerland (Zurich)	Wettstein <i>et al.</i> , 1991 Cross- sectional	dementia MMS in 800 residents of two districts aged 81–85 (400/district) and residing in each district > 15 years	total Al in drinking water based on treatment plant data and place of residence 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)	no significant difference in test scores between low-Al (4 $\mu\text{g/L}$) and high- Al (98 $\mu\text{g/L}$) districts	control for socioeconomic status, age, education no significant differences in serum Al, urine Al or urine Al/creatinine ratio in AD patients from both districts

¹ Criteria for Alzheimer's disease (AD) diagnosis: DSM: Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association; ICD: International Classification of Diseases, World Health Organization, Geneva; NINCDS: National Institute of Neurological and Communicative Disorders and Stroke; ADRDA: Alzheimer's Disease and Related Disorders Associations.

² MMS is Mini Mental Status test.

Table 9: Estimated daily intake of total aluminum by the general population of Canada

Route of exposure	Estimated daily intake by age group (µg/kg-bw per day)							
	Infants (0–0.5 years)			Toddlers (0.5–4 years) ⁴	Children (5–11 years) ⁵	Teens (12–19 years) ⁶	Adults (20–59 years) ⁷	Seniors (60+ years) ⁸
	Breastfed ¹ (exclusive)	Formula-fed ² (exclusive)	Other foods ³					
Drinking water ⁹	na	na	0.80–8.3	0.90–9.4	0.71–7.4	0.40–4.2	0.42–4.4	0.44–4.6
Food ¹⁰	0.90–37	7.0–100	82	194	218	173	105	87
Ambient air ¹¹	<0.01–0.05	<0.01–0.05	<0.01–0.05	<0.01–0.10	<0.01–0.08	<0.01–0.04	<0.01–0.04	<0.01–0.03
Indoor air ¹²	0.24–0.47	0.24–0.47	0.24–0.47	0.52–1.0	0.41–0.78	0.23–0.44	0.20–0.38	0.17–0.33
Soil ¹³	244	244	244	394	128	31	26	25
Total intake	245–281	251–345	327–335	589–598	347–354	204–209	131–135	113–117

¹ Assumed to weigh 7.5 kg, breathe 2.1 m³ air, drink 750 g of breast milk and consume 30 mg soil per day (Environmental Health Directorate, 1998).

² Assumed to weigh 7.5 kg, breathe 2.1 m³ air, drink 0.8 L of infant formula and consume 30 mg soil per day (Environmental Health Directorate, 1998).

³ Assumed to weigh 7.5 kg, breathe 2.1 m³ air, drink 0.3 L of water and consume 30 mg soil per day (Environmental Health Directorate, 1998).

⁴ Assumed to weigh 15.5 kg, breathe 9.3 m³ air, drink 0.7 L of water and consume 100 mg soil per day (Environmental Health Directorate, 1998).

⁵ Assumed to weigh 31.0 kg, breathe 14.5 m³ air, drink 1.1 L of water and consume 65 mg soil per day (Environmental Health Directorate, 1998).

⁶ Assumed to weigh 59.4 kg, breathe 15.8 m³ air, drink 1.2 L of water and consume 30 mg soil per day (Environmental Health Directorate, 1998).

⁷ Assumed to weigh 70.9 kg, breathe 16.2 m³ air, drink 1.5 L of water and consume 30 mg soil per day (Environmental Health Directorate, 1998).

⁸ Assumed to weigh 72 kg, breathe 14.3 m³ air, drink 1.6 L of water and consume 30 mg soil per day (Environmental Health Directorate, 1998).

⁹ Based on a range of mean concentrations of total aluminum in drinking water of 20 µg/L for New Brunswick (New Brunswick Department of the Environment, 1996, 1998a,b) to 208 µg/L for Alberta (Alberta Environmental Protection, 1998). na is not applicable.

¹⁰ *Exclusively breast-fed infants:* Food intake estimates for exclusively breast-fed infants are based on a range of mean concentrations of total aluminum in breast milk of 9.2 µg/L (0.009 µg/g) (Hawkins *et al.*, 1994) to 380 µg/L (0.37 µg/g) (Mandić *et al.*, 1995). Density of breast milk was assumed to be 1.03 g/mL (Environmental Health Directorate, 1998). *Exclusively formula-fed infants:* Food intake estimates for exclusively formula-fed infants are based on a range of mean concentrations of aluminum of 0.06 µg/g for ready-to-use milk-based formula to 0.85 µg/g for ready-to-use soya-based

formula (Dabeka *et al.*, 1999). Density of milk- and soya-based formula was assumed to be 1.1 g/mL (Dabeka, 1999). *Infants fed other foods and all other age groups*: Food intakes based on mean levels of aluminum determined (Dabeka *et al.*, 1999) for 124 individual food items from Canada in the following food groups: 0.27 µg/g in eggs, 0.34–1.1 µg/g in mixed dishes and soups, 0.02–1.3 µg/g in vegetables, 0.07–1.5 µg/g in dairy products, 1.8–4.0 µg/g in nuts and seeds, 0.09–4.4 µg/g in beverages (including soft drinks and alcohol), 0.02–4.2 µg/g in fruit, 0.08–5.6 µg/g in foods containing primarily sugar, 0.43–7.0 µg/g in meat and poultry, 0.14–7.2 µg/g in fats, 0.53–12 µg/g in fish and 0.15–165 µg/g in cereal products; and the daily intake of each food item by the various age groups of the general population of Canada (Environmental Health Directorate, 1998).

¹¹ Based on a range of mean concentrations of total aluminum measured in PM₁₀ samples of 0.05 µg/m³ for Sutton, Quebec, to 1.3 µg/m³ for Vancouver, B.C. (Germain *et al.*, 1999), and on the assumption that 3 hours per day are spent outdoors (Environmental Health Directorate, 1998).

¹² Based on a range of median concentrations of total aluminum measured in PM₁₀ samples of 0.99 µg/m³ for indoor air at night to 1.9 µg/m³ for indoor air during the day (Clayton *et al.*, 1993) and on the assumption that 21 hours per day are spent indoors (Environmental Health Directorate, 1998).

¹³ Based on a mean concentration of aluminum of 61 µg/mg (6.1%) measured in surface soils (0–20 cm) in southern Ontario in 1994 (Garrett, 1998).

Table 10: Estimated daily intake of total aluminum from orally administered over-the-counter therapeutic products for those who use products sold in Canada containing aluminum compounds as active ingredients^{1,2}

Product type	Estimated daily oral intake (mg/kg-bw per day) ³				
	Toddlers (0.5–4 years)	Children (5–11 years)	Teens (12–19 years)	Adults (20–59 years)	Seniors (60+ years)
Antacids and adsorbents	ni	ni	ni	7.8–18	7.7–18
Cathartics and laxatives	ni	ni	ni	12	12
Antidiarrheal agents	16-19	16-20	12-19	14-18	14-17
Local mucosal anesthetics (heartburn medication)	ni	ni	ni	12	12
Analgesics (buffered aspirin)	ni	ni	ni	1.5	1.4–1.5

¹ Daily intakes were estimated from the manufacturers' maximum recommended daily dose for a representative sample of products from each of the product types listed. Aluminum-containing products were identified from the Drug Products Database, and the ranges of concentrations of elemental aluminum in the product types listed were as follows: 6900–90 000 ppm for antacids and adsorbents, 11 000 ppm for cathartics and laxatives, 5500–110 000 ppm for antidiarrheal agents, 21 000 ppm for local mucosal anesthetics and 16 000 ppm for analgesics (Health Canada, 1999a).

² Available data from the National Population Health Survey indicate that 0.2% of the population (over the age of 12) surveyed stated that they had taken one antacid containing aluminum in the 2 days prior to being surveyed; 0.7% of the same population stated that they had taken one salicylate containing aluminum (i.e., buffered aspirin) in the 2 days prior to being surveyed (Statistics Canada, 1995).

³ ni is not indicated for use in the age group listed as per manufacturer's instructions.

Table 11: Estimated daily dermal exposure to total aluminum from cosmetic products for those adults (20–59 years) who use products sold in Canada containing aluminum compounds as active ingredients

Product	Aluminum concentration ($\mu\text{g/g}$) ¹	Average amount of product per application (g) ²	Average frequency of use (times/day) ²	Estimated adult exposure to aluminum ($\mu\text{g/kg-bw per day}$) ³
Antiwrinkle preparations	346–330 000	0.38	0.02	0.04–37
Barrier creams	235–3300	0.53–1.3	0.18–0.98	0.79–24
Dentifrice ⁴	1600–10 000	0.04 ⁵	2 ⁵	1.8–12
Deodorants and antiperspirants	2000–93 000	0.52	1.0	15–689
Eye makeup	40 – 1.0×10^6	0.005–0.5 ⁶	1–2 ⁶	0.01–282
Face makeup	42–35 000	0.01–0.27	0.35–1.2	0.01–59
Fragrances	210–700	0.65	0.68	1.3–4.4
Hair conditioner	1600–16 000	12	0.4	109–1100
Hair dye	442–30 000	12–50 ⁶	0.02–0.29 ⁶	3.7–1500
Lipstick	158–52 000	0.01 ⁶	2–6 ⁶	0.04–44
Manicure preparation	1000–100 000	0.28	0.16	0.63–63
Powders	3500–13 000	2	0.18	18–65
Skin cleansers	78–100 000	1.3–3.7	0.18–0.63	0.26–1500
Skin moisturizers	235–100 000	0.53	0.98	1.7–732

¹ The ranges of concentrations of aluminum are based on selected products from the Cosmetic Notification System database for which information was available on the aluminum content of active ingredients (Health Canada, 1999b).

² CTFA (1983).

³ Assumed to weigh 70.9 kg (Environmental Health Directorate, 1998).

⁴ Exposure to aluminum from dentifrice is based on ingestion rather than dermal exposure.

⁵ Assumed to ingest 0.04 g of dentifrice per day based on two brushings per day (Levy *et al.*, 1995).

⁶ European Commission (1996).

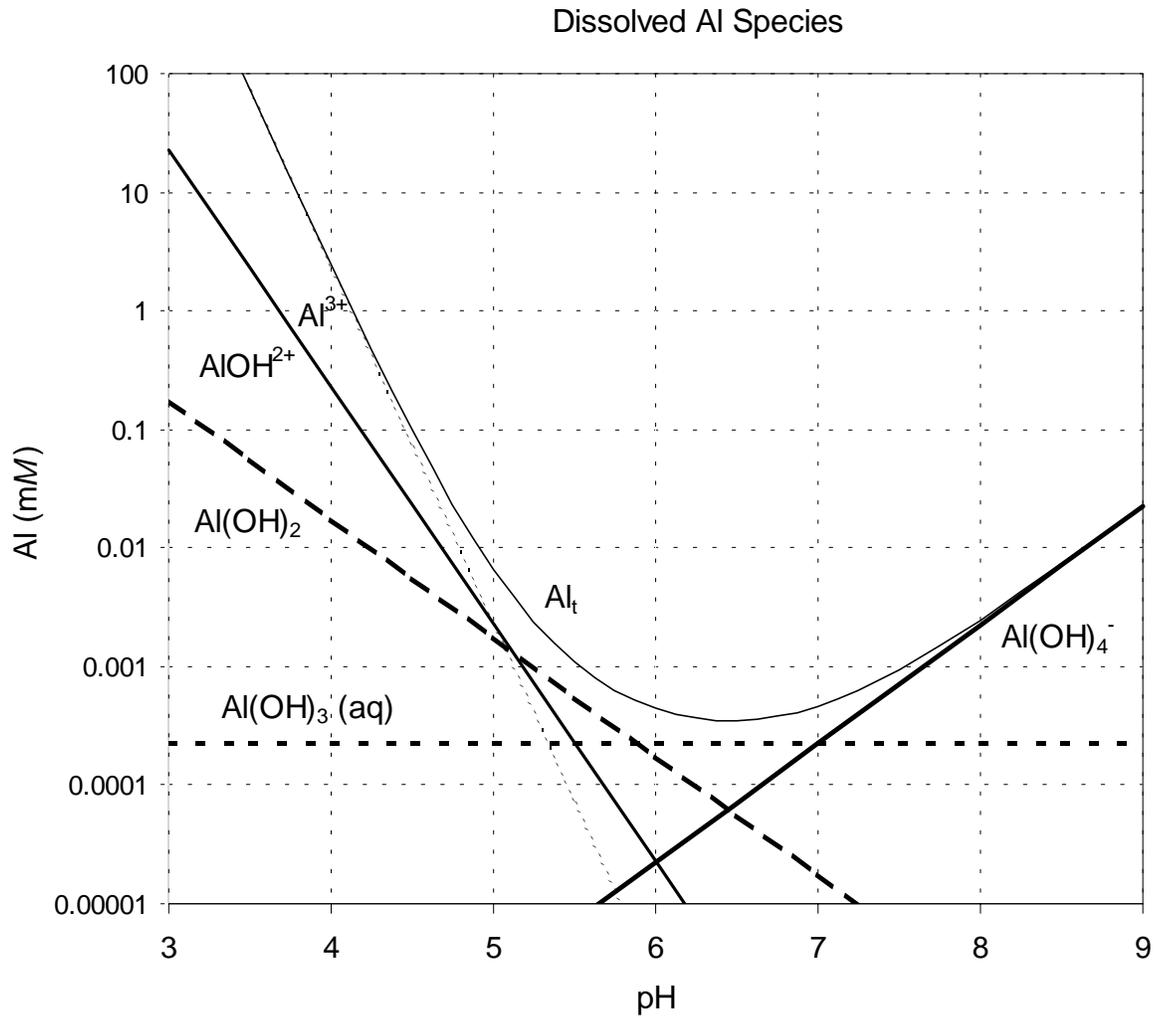


Figure 1. Solubility of aluminum species (and total aluminum, Al_t) in relation to pH in a system in equilibrium with microcrystalline gibbsite (0.001 mM = 0.027 mg/L).