A Systematic Review of Potential Human Health Risks of Aluminum

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15th BfR Consumer Protection Forum
November 26, 2014

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Preliminary Remarks

- The Next Generation of Risk Science
  - New Science
  - New Methods
  - A Population Health Approach

- US NRC Review of US EPA IRIS Program
  - Systematic Review to Summarize Evidence
  - Weight of Evidence Approaches
  - Combining Data from Different Sources

Review

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A Framework for the Next Generation of Risk Science

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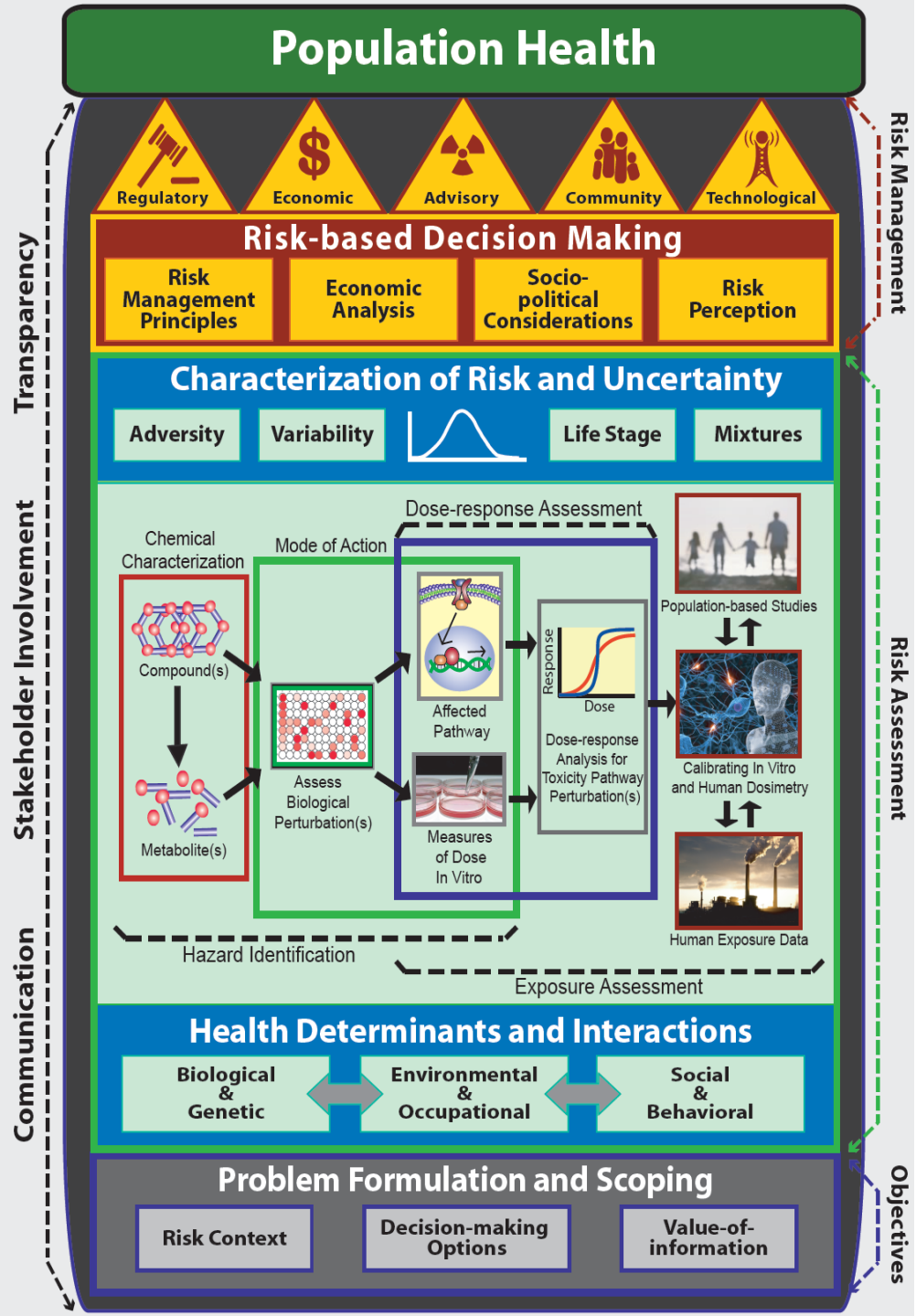
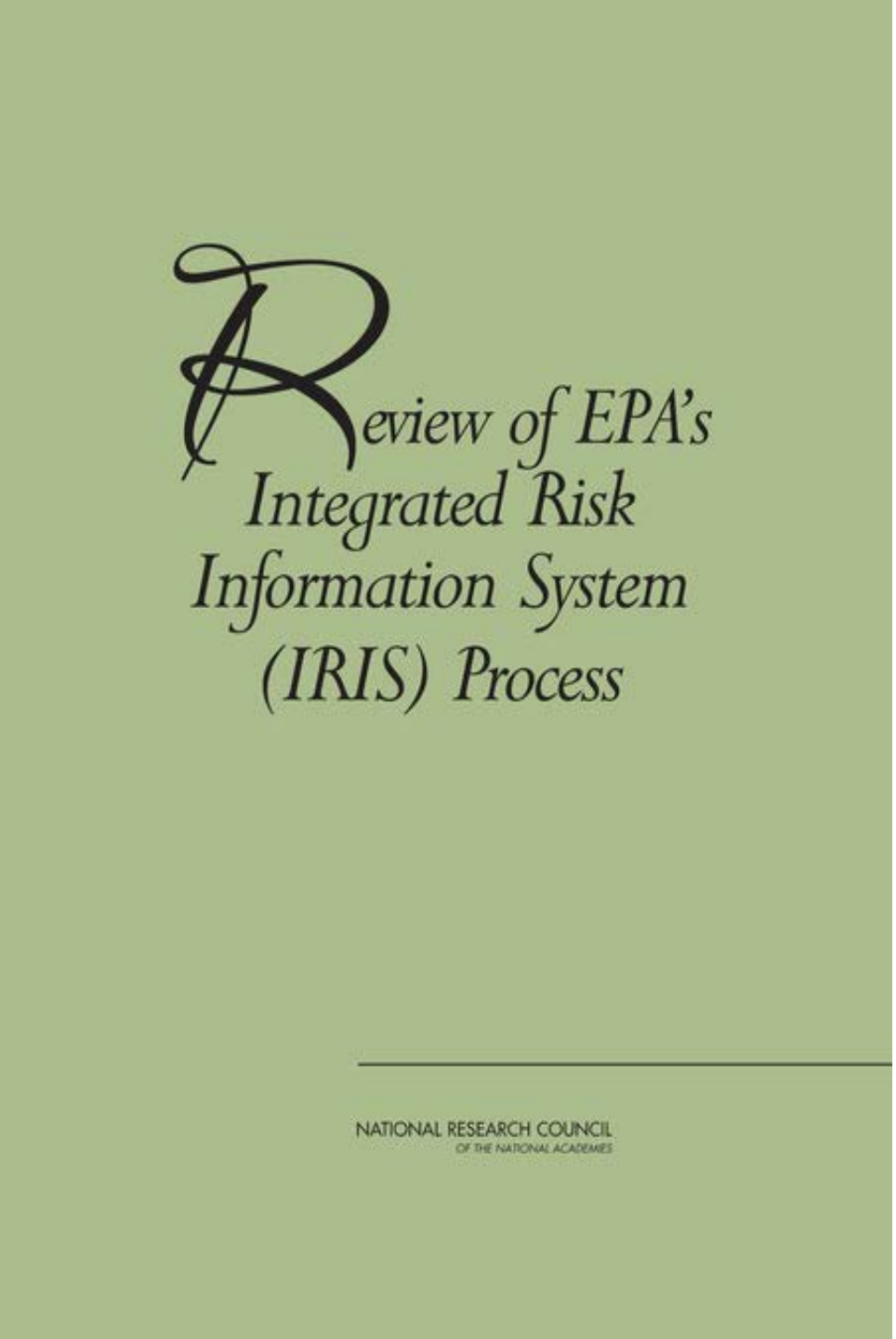
RESULTS: The NexGen framework has three phases. Phase I (objectives) focuses on problem formulation and scoping, taking into account the risk context and the range of available risk management decision-making options. Phase II (risk assessment) seeks to identify critical toxicity pathway perturbations using new toxicity testing tools and technologies, and to better characterize risks and uncertainties using advanced risk assessment methodologies. Phase III (risk management) involves the development of evidence-based population health risk management strategies of a regulatory, economic, advisory, community-based, or technological nature, using sound principles of risk management decision making.



Three Cornerstones

- New paradigm for toxicity testing *(TT21C)*, based on perturbation of toxicity pathways (US NRC, 2007)
- Advanced risk assessment methodologies, including those addressed in *Science and Decisions* (US NRC, 2009)
- Population health approach: multiple health determinants and multiple interventions (Krewski et al., 2007)

NexGen



Key Directions

- **Evidence identification** *(systematic review)*
- **Evidence evaluation** *(weight of evidence)*
- **Evidence integration** *(combining data)*
- **Calculation of toxicity values** *(reference doses, unit risks)*

Systematic Review

Critical Reviews in Toxicology

http://informahealthcare.com/txc
ISSN: 1040-8444 (print), 1547-6898 (electronic)

Crit Rev Toxicol, 2014; Early Online: 1–81
 DOI: 10.3109/10408444.2014.934439

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REVIEW ARTICLE

Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide and its soluble salts

Calvin C. Willhite[1,2], Nataliya A. Karyakina[1], Robert A. Yokel[3], Nagarajkumar Yenugadhati[2], Thomas M. Wisniewski[4], Ian M.F. Arnold[5], Franco Momoli[6,7,8], and Daniel Krewski[1,2,7]

Comprehensive and reproducible

Systematic Review

Tables of contents

Consider all available evidence

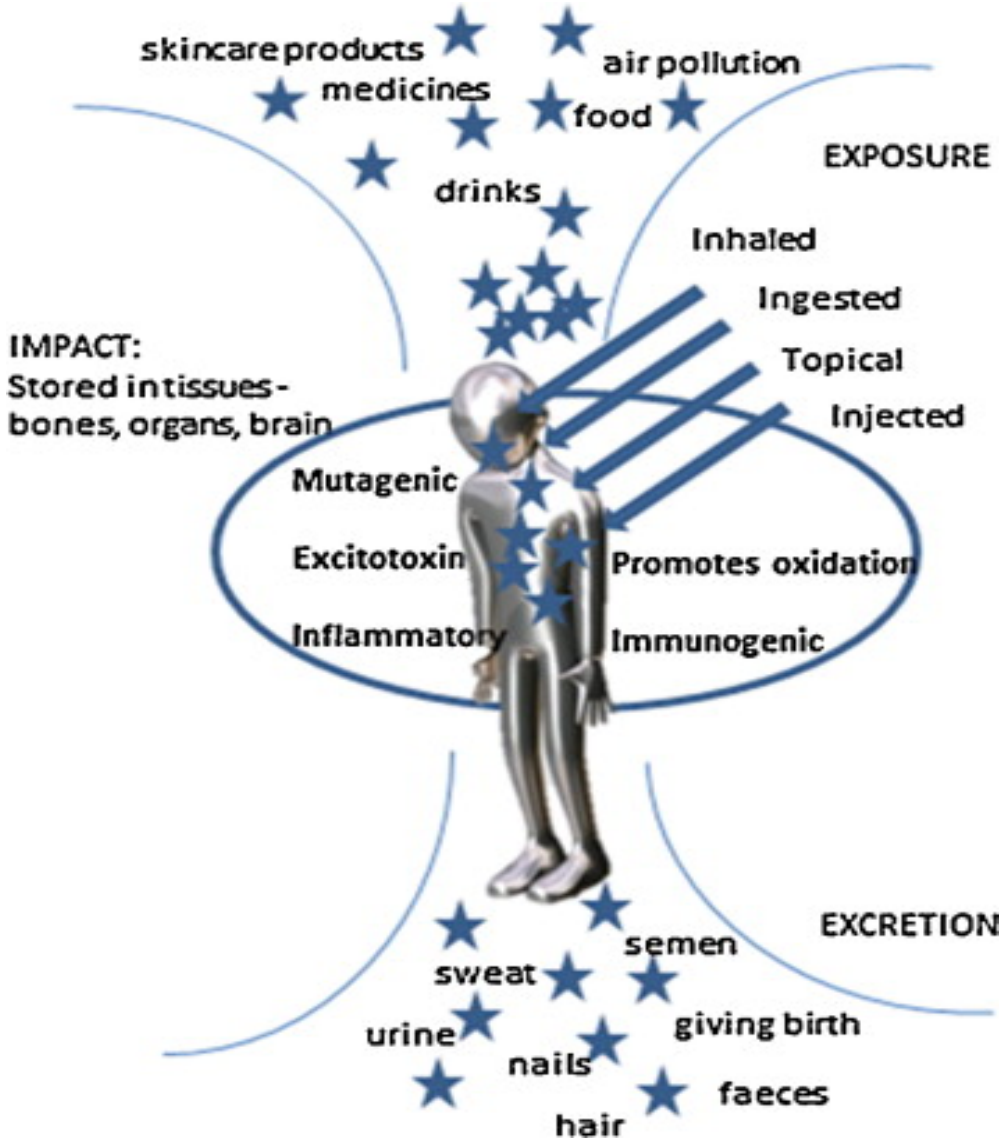
Outline

- Overview
- Literature search methods
- Key findings:
  - absorption and bioavailability
  - neurotoxicity
  - respiratory effects
  - developmental toxicity
  - carcinogenicity
- Conclusions
- Future research

Aluminum in Brief

- Essentiality: not essential, lack of homeostatic control
- Low solubility and bioavailability
- Main routes of exposure: inhalation (occupational exposure), drinking water and diet (natural sources of Al , food additives)
- Main route of elimination: excretion into urine
- Critical health effect : neurotoxicity
- Biomonitoring: blood, plasma and urine Al may not reflect Al body burdens due to rapid excretion of Al from the body

Human Exposure to Aluminum



Source: Kramer & Heath (2014), Vaccine 32, 4140–4148

Previous Review of Aluminum and Health

HUMAN HEALTH RISK ASSESSMENT FOR ALUMINIUM, ALUMINIUM OXIDE, AND ALUMINIUM HYDROXIDE

Daniel Krewski[1,2], Robert A Yokel[3], Evert Nieboer[4], David Borchelt[5], Joshua Cohen[6], Jean Harry[7], Sam Kacew[2,8], Joan Lindsay[9], Amal M Mahfouz[10], Virginie Rondeau[11]

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Journal of Toxicology and Environmental Health, Part B, 10:1–269, 2007

Summary of Previous Review of Aluminum and Health

TABLE 25. Strength of evidence for health effects

		Exposure Pathway[a]			
Health Endpoint[b]		Inhalation	Oral	Dermal	Injection
1	Acute toxicity				
2	Irritation	Strong	Limited	Limited	Strong
3	Corrosivity				
4	Sensitization				
5	Repeated dose toxicity				
6	Mutagenicity	Limited	Limited		
7	Carcinogenicity	No clear evidence	No clear evidence		
8	Reproductive toxicity	Limited	Modest		No clear evidence
9a	Other – Neurological Toxicity	Limited	Modest		Modest
9b	Other – Bone Toxicity		No clear evidence		Modest
9c	Other – Metabolism		Limited		Limited

[a]The absence of an entry indicates that, effectively, there are no data for the exposure pathway / toxicity endpoint combination.

[b]Health endpoint categories are taken from European Commission (2003).

Journal of Toxicology and Environmental Health, Part B, 10:1–269, 2007

Objectives of Updated Review (2007 – 2012)

- Summarize the new scientific evidence for potential health effects from aluminium and aluminum compounds under typical conditions of exposure

- Identify data gaps that need to be filled to strengthen the scientific basis on which assessment of the potential health risk of Al compounds should be based

Exposure Patterns and Health Endpoints

Populations	Exposure Routes	Effects	Types of Effects
➢ Worker	➢ Oral	➢ Acute Toxicity	➢ Systemic
➢ Consumer	➢ Inhalation	➢ Irritation	➢ Local
➢ Humans via the Environment	➢ Dermal	➢ Corrosivity ➢ Sensitisation	
➢ Sensitive Subpopulations		➢ Repeated Dose Toxicity ➢ Mutagenicity ➢ Carcinogenicity ➢ Reproductive Toxicity (Fertility/ Developmental)	

Systematic Review (1/2)

- Focus on aluminium, aluminium oxide, and aluminium hydroxide
- Identify studies published since our previous review in 2007 examining the health effects associated with exposure to aluminium compounds via different routes of exposure:
  - inhalation (occupational exposure, environmental exposure through air),
  - oral (drinking water, natural food sources, food additives, or Al leached from utensils or food packaging; aluminium-containing antacids)
  - dermal (vaccines, antiperspirants, cosmetics)

Systematic Review (2/2)

- Three population groups considered:
  - general population (environmental exposures)
  - workers (occupational exposures)
  - sensitive population groups (children, pregnant women, patients with impaired kidney function)

- Three bibliographic databases (Ovid/MEDLINE, EMBASE, and TOXLINE) searched from June 2006 to May 2012 for relevant eligible published studies

- 3,820 studies were identified, of which 469 were included in the review

Major Findings: Exposure (1/2)

- Aluminium is the third most abundant element in the Earth's crust, and one of the most widely used and distributed metals on the planet

- Food, drinking water, air and medicines are considered to be the major sources of the aluminium burden for humans

- In 1950, aluminium exposure was approximately to be 1 mg per day; it is projected to be 100 mg in 2050 (Exley, 2013)

Major Findings: Exposure (2/2)

- Exposure to Al (dust, bulk powder) at occupational settings has been decreasing over the last 10 years
- Inhalation exposure to Al nanomaterials in occupational settings is increasing
- Diverse range of aluminium (Al) nanoscale products and processes have emerged in the last decade, with applications in medicine, plastics, energy, electronics, and aerospace

Major Findings: Absorption and Bioavailability

- Bioavailability of ingested Al depends on the aqueous solubility of the particular physical and chemical form
- Oral absorption of aluminium from food can vary at least 10-fold, depending on chemical form (EFSA, 2011)
- Animal (EFSA, 2011) and human (Yokel and Florence, 2008) data support the use of bioavailability as a relevant parameter for the assessment of Al toxicity, with aluminium–ligand interactions influencing aluminium bioavailability, metabolism and toxicity.
- New findings confirm that gastrointestinal bioavailability of insoluble Al compounds is low

Bioavailability of Ingested Al-26 Labelled Al Compounds in the Rat

Mean Fractional Absorption of Aluminium-containing Compounds (EFSA, 2011)

Compound name	Administered form	Fraction of dose absorbed (mean % ± SD)
Aluminium citrate	Solution	0.079 ± 0.006
Aluminium chloride	Solution	0.054 ± 0.015
Aluminium nitrate	Solution	0.045 ± 0.013
Aluminium sulphate	Solution	0.210 ± 0.079
Aluminium hydroxide	Suspension[5]	0.025 ± 0.041
Aluminium oxide	Suspension[5]	0.018 ± 0.038
Aluminium metal	Suspension[6]	<0.015[7]
Powdered pot electrolyte	Suspension[6]	0.042 ± 0.004
FD&C red 40 aluminium lake[1]	Suspension[6]	0.093 ± 0.020
Sodium aluminium phosphate, acidic[2]	Suspension[5]	<0.024[7]
Sodium aluminium phosphate,basic[3]	Suspension[5]	<0.015[7]
Sodium aluminium silicate[4]	Suspension[5]	0.120 ± 0.011

[1] Synonym: Allura Red AC aluminium Lake
[2] Synonym: SALP, acidic
[3] Synonyms: SALP, basic; KASAL
[4] Synonym: Sodium aluminosilicate
[5] Administered as a suspension in carboxymethylcellulose
[6] Administered mixed with honey for administration to the back of the rat tongue.
[7] Reported as 50% of the mean detection limit.

Major Findings: Absorption and Bioavailability

- Recently published studies support low bioavailability of Al compounds following dermal exposure
- Recently, BfR calculated the daily systemic absorption of aluminium through the healthy skin to constitute 10.5 µg, which is above the amount considered safe for an adult (8.6 µg per day) (Mathias & Health, 2014)
- Nanomaterials are adsorbed to a higher extent from the GI tract compared to bulk particulates
- Monitoring Al levels /accumulation in biological fluids in humans is challenging: urine and plasma are not reliable biomarkers of exposure, or potential for systemic effects

Major Findings: Neurotoxicity (1/4)

- Some epidemiology studies suggest the possibility of an association of Alzheimer disease with aluminium in water, but other studies have not confirmed this association
- Recent studies investigating whether there is a link between aluminium levels in drinking water and Alzheimer's Disease have provided inconclusive results (Rondeau et al., 2009, Boom, 2008)
- Epidemiological studies lack information on ingestion of aluminium from food and how concentrations of aluminium in food may affect the association between aluminium in water and Alzheimer disease (FAO/WHO, 2012)

Aluminum and Silica in Drinking Water and the Risk of Alzheimer's Disease or Cognitive Decline: Findings From 15-Year Follow-up of the PAQUID Cohort

Virginie Rondeau, Hélène Jacqmin-Gadda, Daniel Commenges, Catherine Helmer, and Jean-François Dartigues

Table 4. Daily Aluminum or Silica Consumption From Drinking Water and Risk of Dementia or Alzheimer's Disease, PAQUID Cohort, France, 1988–2003

Daily Consumption, mg/day	Dementia (461 Cases)			Alzheimer's Disease (364 Cases)		
	RR	95% CI	*P* Value	RR	95% CI	*P* Value
Model 1[a]						
Aluminum (≥0.1 vs. <0.1)	2.59	1.15, 5.80	0.021	3.35	1.49, 7.52	0.003
Model 2[a]						
Aluminum (continuous)[b]	1.29	1.05, 1.58	0.014	1.36	1.11, 1.67	<0.001

Am J Epidemiol 2009;169:489–496

Major Findings: Neurotoxicity (2/4)

- The relevance of transgenic mouse models to human sporadic AD is unclear: *it is not known if the mechanisms underlying the production of AD lesions in transgenic mice is similar to that of sporadic AD in humans*

- Aluminium is a neurotoxicant following long-term exposure to high doses in animals: *however, it is not clear that such effects are to be expected at the much lower levels of aluminium to which the general public is typically exposed.*

Major Findings: Neurotoxicity (3/4)

- At present, there is no clear evidence regarding the potential role of aluminium in neurodegenerative diseases involving cognitive decline: *it is not clear whether aluminium is a trigger for dementia, or simply accumulates in brain tissue as a consequence of degenerative processes in the aging brain*

- The weight of evidence data from recent occupational studies does not support a neurotoxic risk to workers exposed to airborne aluminium, or aluminium oxide and aluminium hydroxide dusts *in workplaces which conform to regulatory standards*

Major Findings: Neurotoxicity (4/4)

- Results of numerous mechanistic studies, usually administration of high doses by oral gavage, suggest that there is no single unifying mechanism by which Al may lead to neurotoxicity (ATSDR, 2008; Health Canada, 2010)

- More recently, Al exposure has been linked to biochemical changes in the brain indicative of oxidative stress in animals exposed to high doses *(poorly soluble, low toxicity Al compounds promote an inflammatory response in different cell types, possibly due to production of reactive oxygen species)*

Major Findings: Respiratory Effects

- There is no evidence for a chemical-specific fibrogenic effect due to aluminium metal powder; such effects were not seen in experimental animals even at high levels of exposure

- The available evidence suggests that aluminium oxide and aluminium hydroxide behave as ‘nuisance dusts’ under current controlled occupational exposure conditions

- When not appropriately controlled, several airborne substances in pot-rooms may contribute to an irritation effect in the lungs *(the available evidence suggests a role for fluoride-containing substances or sulphur dioxide)*

Major Findings: Reproductive and Developmental Toxicity

- The available evidence does not indicate reproductive or teratogenic effects of soluble Al compounds (Poirier et al., 2011; Hirata-Koizumi et al., 2011 a,b)

- Neurodevelopmental effects in rodents were reported by Poirier et al. (2011) at doses of 100 mg/kg bw/day and above, with a NOAEL of 30 mg/kg bw/day

Reproductive and Developmental Toxicity Studies

Species, strain and number of animals per group	Study design	Exposure period	LOAEL/NOAEL	Reference
Rat (Crl:CD (SD); F/M/n=24) Oral, drinking water (free access)	Aluminium sulfate Dose: 0, 120, 600, and 3000 mg/L	*F0 :* M.: PMD 35+MD F.: PMD35+MD+GD0-21+PND26; *F1/F2 generations:* F/M: PMD35+MD+GD0-21+PND26	NOAEL – 8.06 mg/kg bw/day (600 mg/L) (lack of treatment – related effects on developmental endpoints) LOAEL - 41.3 mg/kg bw/day (3000 mg/L) (*decreased body weight gain in the F1 and F2 males and female)*	GLP, OECD TG 416 – compliant 2 generation reproductive toxicity study *Hirata-Koizumi et al., 2011a*
Rat (Crl:CD (SD); F/M/n=24) Oral, drinking water (free access)	Aluminium ammonium sulfate Dose: 0, 50, 500, and 5000 mg/L	*F0* : M.: PMD 35+MD F.: PMD35+MD+GD0-21+PND26; *F1/F2 generations:* F/M: PMD35+MD+GD0-21+PND26	NOAEL – 5.35 mg/kg bw/day (500 mg/L) (lack of treatment – related effects on developmental endpoints) LOAEL – 33.5 mg/kg bw/day (5000 mg/L) (*decreased body weight gain in the F1 and F2 males and females)*	*GLP, OECD TG 416 – compliant 2 generation reproductive toxicity study* *Hirata-Koizumi et al., 2011b*
Rat (SD; F/n=20) Oral, drinking water (free access)	Al citrate Dose: 30, 100 and 300 mg Al/kg bw/day	F: GD 6-21; LD 0-21	NOAEL – 30 mg/kg bw/day LOAEL – 100 mg/kg bw/day (neuromuscular effects, specifically hind limb and fore limb grip strength)	GLP-compliant neurodevelopmental toxicity study Poirier et al., 2011

Major Findings: Carcinogenicity

- The weight of evidence from animal, human and in-vitro studies does not support a cancer hazard in humans exposed to Al by the oral, inhalation, or dermal routes

- Although ‘aluminum production’ has been classified by the International Agency for Research on Cancer (IARC) as ‘carcinogenic to humans’, the epidemiological evidence supports a role for polycyclic aromatic hydrocarbons (PAHs) in the workplace in this finding

- IARC (2012) did not implicate aluminium itself as a human carcinogen

Major Findings: Carcinogenicity

ORIGINAL ARTICLE

Breast Cancer Risk Associated With Residential Proximity to Industrial Plants in Canada

Sai Yi Pan, MD, Howard Morrison, PhD, Laurie Gibbons, MSc, Jia Zhou, MSc, Shi Wu Wen, PhD, Marie DesMeules, MSc, and Yang Mao, PhD, and the Canadian Cancer Registries Epidemiology Research Group

JOEM • Volume 53, Number 5, May 2011

Major Findings: Carcinogenicity

TABLE 2. Odds Ratio of Breast Cancer Associated With Residential Proximity to Major Industries by Type of Industrial Plant

	Distance From	Premenopausal			Postmenopausal			Both		
Thermal power plants										
	>3.2 or no plant	606	628		1,064	1,232	1	1,670	1,883	1
	0.8–3.2	207	177	1.06 (0.83–1.36)	350	311	1.16 (0.97–1.40)	557	493	1.15 (0.99–1.33)
	<0.8	50	30	1.73 (1.06–2.83)	66	61	1.36 (0.92–2.00)	116	91	1.56 (1.16–2.10)
Aluminum smelters										
	>3.2 or no plant	853	821	1	1,455	1,584	1	2,308	2,433	1
	0.8–3.2	8	13	0.52 (0.21–1.31)	19	14	1.06 (0.50–2.23)	27	27	0.84 (0.48–1.49)
	<0.8	2	1	2.08 (0.18–23.72)	6	6	0.97 (0.27–3.41)	8	7	1.10 (0.37–3.25)
Nickel smelters & refinery										
	>3.2 or no plant	859	827	1	1,479	1,598	1	2,338	2,453	1
	0.8–3.2	3	5	0.68 (0.16–2.88)	0	5	. . .	3	10	0.26 (0.07–1.06)
	<0.8	1	3	0.34 (0.03–3.30)	1	1	2.09 (0.13–33.92)	2	4	1.01 (0.10–9.78)

Major Findings: Aluminum Adjuvants

- Contact reactions (delayed hypersensitivity) following Al injections do occur, but they are rare

- No discernable relationship between long-term adverse health outcomes, such as delayed neurodevelopment, and childhood vaccinations were confirmed by the WHO Global Advisory Committee on Vaccine Safety (GACVS, 2012)

PTWI for Al in Food

- The Joint FAO/WHO Expert Committee on Food Additives determined a provisional tolerable weekly intake (PTWI) of 2 mg/kg bw (JECFA, 2012)

- The PWTI is based on a recent GLP-compliant study on developmental and neurobehavioural toxicity of Al in rats (Poirier et al., 2011), using a NOAEL of 30 mg/kg bw/day and an uncertainty factor of 100-fold

- The PTWI (expressed as total Al) applies to all Al compounds in food, including food additives

Neurodevelopmental Toxicity

Neuroscience 193 (2011) 338–362

DOUBLE-BLIND, VEHICLE-CONTROLLED RANDOMIZED TWELVE-MONTH NEURODEVELOPMENTAL TOXICITY STUDY OF COMMON ALUMINUM SALTS IN THE RAT

J. POIRIER,[a,b*] H. SEMPLE,[c] J. DAVIES,[c] R. LAPOINTE,[d] M. DZIWENKA,[c,e] M. HILTZ[c] AND D. MUJIBI[c]

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Neurodevelopmental Toxicity

Table 1. Treatment group allocation of dams

Treatment group	Treatment	No. of animals per group Female	Target dosage level (mg/kg) of elemental aluminum	Target dosage concentration (g/L) of elemental aluminum (assumes average fluid consumption of 120 ml/kg/d)	Dosage concentration (g/L) of aluminum citrate adjusting for 9.3% aluminum by mass[b]
1 (C)[a]	Control (deionized water)	20	0	0	0
2 (A)	Low dose	20	30	0.250	2.69
3 (D)	Mid dose	20	100	0.833	8.96
4 (E)	High dose	20	300	2.499	26.87
5 (B)	Sodium citrate	20	0	0, but dosage concentration of sodium citrate dihydrate equimolar to that of aluminum in Group 4 is 27.2 g/L	0, but dosage concentration of sodium citrate dihydrate equimolar to that of aluminum in Group 4 is 27.2 g/L

LOAEL (neuromuscular effects) = 100 mg/kg bw/day

NOAEL = 30 mg/kg bw/day

PTWI = NOAEL/100 = 0.3 mg/kg bw/day = 2 mg/kg bw/week *(WHO/JECFA, 2012)*

Major Conclusions (1/6)

- Aluminum (Al) is a ubiquitous element encountered in a diverse array of regulated and unregulated circumstances, ranging from its intentional or incidental presence in drinking water, foods, cosmetics and vaccines to ambient and occupational airborne particulates and solutions used in parenteral nutrition

- The current work summarizes recent evidence for adverse health effects after exposure to inorganic Al, with reference, where applicable, to established regulatory guidelines

Major Conclusions (2/6)

- Human health risk assessment for Al is complex, as it depends on the specific Al moiety and its physical and chemical properties, as well as the magnitude, frequency, duration and route of exposure, and exposed subpopulation
- Potential human health hazards posed by occupational, environmental, pharmaceutical, and consumer product Al exposures have been intensely studied: *the existing data underscore the importance of Al chemical and physical forms in relation to uptake, accumulation, and systemic bioavailability of Al*

Major Conclusions (3/6)

- JECFA (2012) recently established a PTWI of 2 mg /kg bw/week: *the PTWI applies to all aluminium compounds in food, including food additives*

- Wide variations in diet result in Al intakes that are often higher than the World Health Organization provisional tolerable Al weekly intake (PTWI)

Major Conclusions (4/6)

- There is no consistent and convincing evidence linking Al found in food and drinking water at the levels and chemical forms presently consumed by people in North America and Western Europe with increased risk of Alzheimer's disease (AD)

- Neither is there consistent epidemiological evidence to show that the use of Al-containing underarm antiperspirants or cosmetics increases the risk of AD or breast cancer

Major Conclusions (5/6)

- Although Al-adsorbed vaccines have an extensive overall safety record, occasional adverse local effects have occurred in some people after injection of Al-containing vaccines

- Al contamination of parenteral nutrition (PN) solutions continues to be of concern, especially for infants and neonates

Major Conclusions (6/6)

- Difficulties in Al human health risk assessment are further confounded by ecological and individual co-factors, including age, kidney function, and diet

- Although exposure to most Al compounds does not appear to pose a significant health risk under common circumstances, *occupational exposures to Al dusts and fumes, handling industrial quantities, and inadvertent medical exposures in people with compromised renal function require careful control*

Data Gaps and Further Research (1/3)

- Clarification of the neurological effects seen at high levels of exposure in laboratory animals
- Clarification of the possible role of oxidative stress in the induction of neurological effects associated with aluminum exposure
- Characterization of occupational and environmental exposure to aluminum nanoparticles and nanomaterials
- Investigation of the comparative toxicity of bulk Al and Al nanoforms

Data Gaps and Further Research (2/3)

- Further Investigation of the effective skin penetration rate of Al, and the long-term effects of chronic dermal aluminum exposure

- Possible development of a full physiologically-based pharmacokinetic (PBPK) model to describe aluminum toxicokinetics *(predict Al concentrations in all body tissues, including different brain areas)*

Data Gaps and Further Research (3/3)

- Large-scale case-control study of the association between antiperspirant use and breast cancer risk

- Despite current knowledge about administration of aluminum adjuvant-containing vaccines, the mechanisms involved in subsequent induction of the immune response warrant further investigation