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Approaches to Exposure Assessment for Metals

Submitted by: McLaughlin Centre for Population Health Risk Assessment

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Workshop on Metals Risk Assessment
Cebu, Philippines
28-29 August 2015

Approaches to Exposure Assessment for Metals

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Professor and Director
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Population Heath Risk Assessment

Outline

1. New directions in risk science
2. Exposomics
   - Biomarkers of exposure
   - Biomonitoring equivalents
   - High throughput techniques
3. Metals-specific exposure assessment
   - Aluminum
   - Manganese
   - Copper
4. Conclusions

Next generation risk assessment

Review

All *EHP* content is accessible to individuals with disabilities. A fully accessible (Section 508–compliant) HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1307260.

A Framework for the Next Generation of Risk Science

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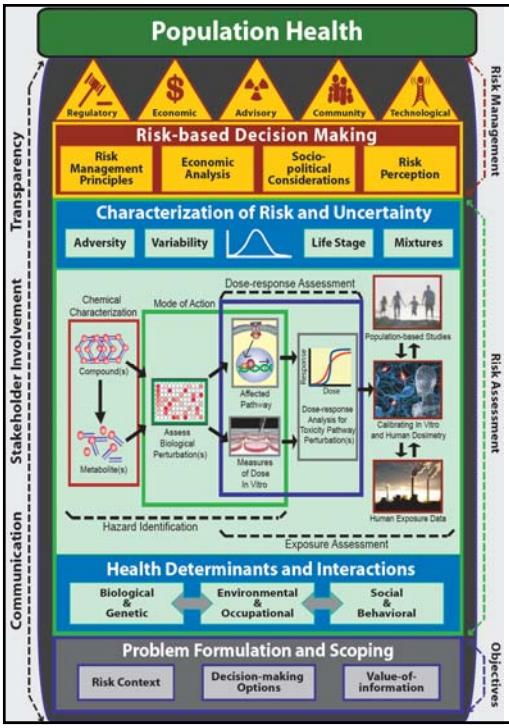

Three Cornerstones

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

NexGen

Exposure Assessment

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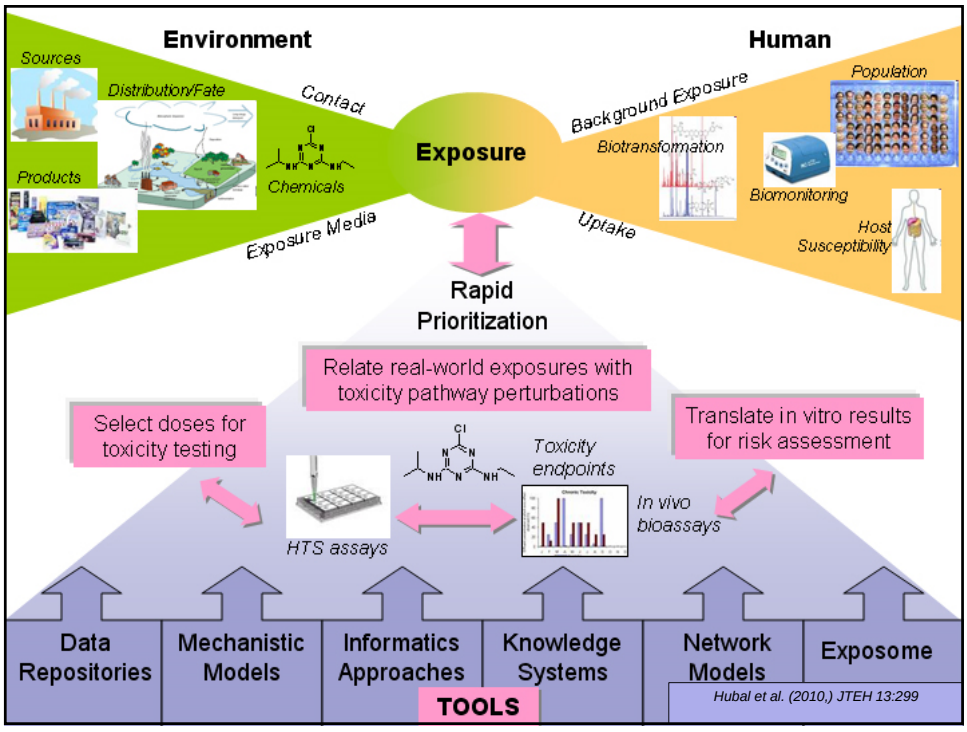
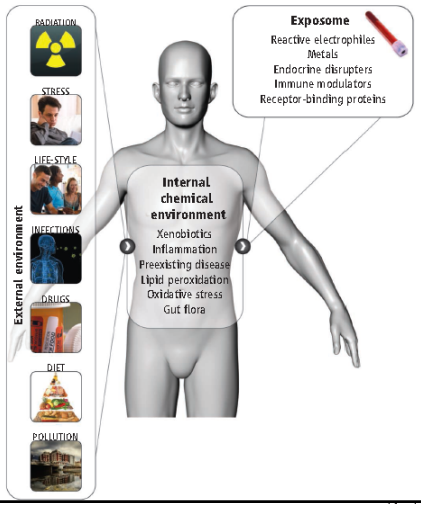


Exposomics

Science

AAAS

Environment and Disease Risks
Stephen M. Rappaport, *et al.*
Science **330**, 460 (2010);
DOI: 10.1126/science.1192603

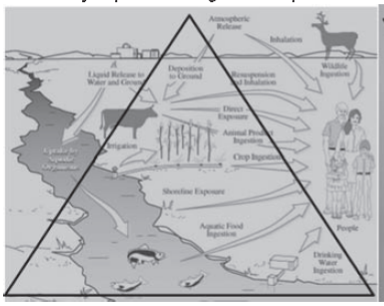


``The exposome represents the combined exposures from all sources that reach the internal chemical environment. Toxicologically important classes of exposome chemicals are shown. Signatures and biomarkers can detect these agents in blood or serum.``

Two Approaches to Exposomics

Bottom-up Exposomics

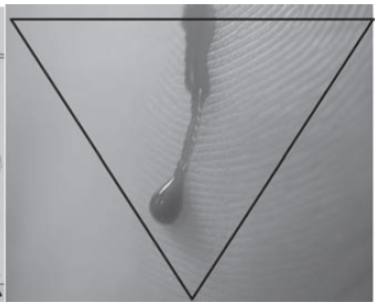
Identify important exogenous exposures



Measure chemicals in air, water & food

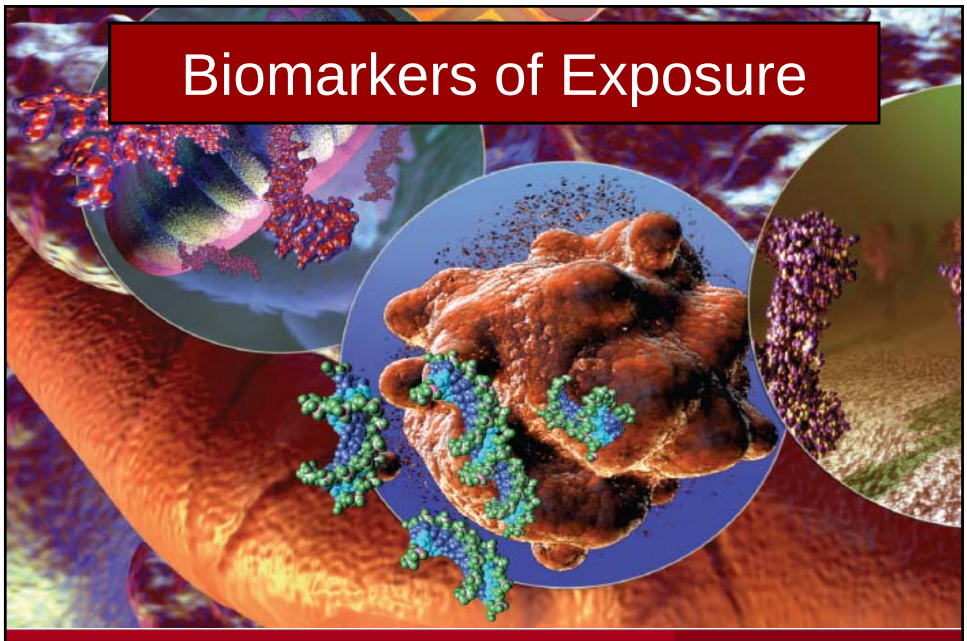
Top-down Exposomics

Measure chemicals in blood



Identify all important exposures

Rappaport et al.. (2011)
J.Exp. Sci. Env. Epi. 21:5



Biomarkers of Exposure

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CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

National Health and Nutrition Examination Survey

Human Biomonitoring Programs

Canadian Health Measures Survey (CHMS)

HEALTH in CANADA

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Health Canada Santé Canada

Your health and safety... our priority. *Votre santé et votre sécurité... notre priorité.*

Report on Human Biomonitoring of Environmental Chemicals in Canada

Results of the Canadian Health Measures Survey Cycle 1 (2007–2009)

Table 8.1.5a

Lead – Arithmetic and geometric means, and selected percentiles of blood concentrations (µg/dL) for the Canadian population aged 6–79 years, Canadian Health Measures Survey Cycle 1, 2007–2009.

	n	%<LOD[a]	A.M. 95%CI	G.M. 95%CI	10th 95%CI	25th 95%CI	50th 95%CI	75th 95%CI	90th 95%CI	95th 95%CI
Total, age 6–79	5319	0.02	1.66 1.52 - 1.79	1.34 1.24 - 1.44	0.60 0.55 - 0.65	0.86 0.79 - 0.93	1.30 1.21 - 1.39	2.03 1.83 - 2.22	3.07 2.77 - 3.37	3.79 3.32 - 4.26
6–11	910	0.00	1.02 0.91 - 1.13	0.90 0.81 - 0.99	0.53 0.49 - 0.57	0.65 0.59 - 0.70	0.87 0.77 - 0.97	1.19 1.05 - 1.34	1.61 1.47 - 1.76	1.95 1.65 - 2.26
12–19	945	0.00	0.89 0.81 - 0.97	0.80 0.74 - 0.85	0.47 0.44 - 0.51	0.57 0.53 - 0.62	0.76 0.70 - 0.83	1.05 0.99 - 1.11	1.34 1.11 - 1.56	1.64 1.47 - 1.82
20–39	1165	0.09	1.37 1.27 - 1.46	1.12 1.04 - 1.21	0.57 0.52 - 0.62	0.76 0.69 - 0.82	1.05 0.99 - 1.11	1.58 1.39 - 1.77	2.35 2.02 - 2.68	3.12 2.75 - 3.49
40–59	1220	0.00	1.87 1.67 - 2.07	1.60 1.45 - 1.75	0.82 0.70 - 0.95	1.15 1.06 - 1.24	1.55 1.43 - 1.67	2.22 1.95 - 2.50	3.17 2.71 - 3.63	3.87 3.16 - 4.57
60–79	1079	0.00	2.49 2.22 - 2.77	2.08 1.90 - 2.29	1.04 0.93 - 1.14	1.44 1.33 - 1.56	2.07 1.90 - 2.24	3.02 2.66 - 3.37	4.17 3.53 - 4.81	5.19 4.20 - 6.16
Males										
Total, age 6–79	2576	0.00	1.86 1.69 - 2.03	1.51 1.40 - 1.63	0.71 0.66 - 0.76	1.01 0.95 - 1.08	1.44 1.34 - 1.54	2.21 2.01 - 2.42	3.26 2.87 - 3.65	4.22 3.71 - 4.72
6–11	459	0.00	1.04 0.94 - 1.14	0.92 0.85 - 0.99	0.54 0.50 - 0.58	0.66 0.61 - 0.72	0.89 0.79 - 1.00	1.21 1.10 - 1.31	1.64 1.44 - 1.83	1.96 1.78 - 2.13
12–19	489	0.00	0.99 0.88 - 1.11	0.88 0.82 - 0.95	0.51 0.46 - 0.55	0.65 0.60 - 0.69	0.87 0.79 - 0.95	1.16 1.05 - 1.27	1.53 1.29 - 1.77	1.79 1.28 - 2.29
20–39	514	0.00	1.70 1.56 - 1.85	1.41 1.28 - 1.55	0.75 0.65 - 0.85	0.97 0.87 - 1.07	1.30 1.15 - 1.46	2.00 1.68 - 2.33	2.94 2.59 - 3.30	3.65 2.88 - 4.42
40–59	577	0.00	2.01 1.75 - 2.27	1.74 1.57 - 1.92	0.98 0.89 - 1.08	1.25 1.15 - 1.35	1.61 1.46 - 1.77	2.35 1.92 - 2.77	3.31 2.77 - 3.85	3.95 3.02 - 4.88
60–79	537	0.00	2.78 2.46 - 3.10	2.31 2.08 - 2.57	1.20 1.07 - 1.34	1.55 1.37 - 1.73	2.24 1.98 - 2.49	3.27 2.86 - 3.68	4.86 3.96 - 5.75	6.17 4.95 - 7.39
Females										
Total, age 6–79	2743	0.04	1.45 1.30 - 1.60	1.18 1.08 - 1.30	0.55 0.50 - 0.60	0.74 0.68 - 0.81	1.14 1.04 - 1.25	1.74 1.51 - 1.97	2.73 2.35 - 3.12	3.50 3.03 - 3.97
6–11	451	0.00	0.99 0.85 - 1.13	0.87 0.77 - 0.99	0.51 0.46 - 0.57	0.64 0.57 - 0.70	0.85 0.73 - 0.97	1.16 0.93 - 1.39	1.61 1.37 - 1.86	1.93 1.26 - 2.60
12–19	456	0.00	0.77 0.72 - 0.83	0.71 0.66 - 0.77	0.43 0.37 - 0.49	0.53 0.48 - 0.58	0.68 0.62 - 0.75	0.91 0.79 - 1.04	1.16 0.98 - 1.33	1.46 1.25 - 1.67
20–39	651	0.15	1.02 0.92 - 1.12	0.89 0.81 - 0.98	0.52 0.46 - 0.57	0.64 0.60 - 0.68	0.86 0.77 - 0.96	1.19 1.08 - 1.30	1.64 1.38 - 1.91	2.05 1.78 - 2.32
40–59	643	0.00	1.72 1.51 - 1.94	1.47 1.31 - 1.65	0.71 0.59 - 0.82	1.05 0.90 - 1.19	1.46 1.27 - 1.64	2.11 1.81 - 2.41	3.11 2.49 - 3.74	3.78 3.05 - 4.52
60–79	542	0.00	2.23 1.92 - 2.54	1.89 1.69 - 2.12	0.94 0.81 - 1.07	1.34 1.15 - 1.52	1.93 1.69 - 2.18	2.67 2.27 - 3.06	3.69 3.20 - 4.17	4.53 3.81 - 5.25

a If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.

Biomonitoring Equivalents

Establishing Biomonitoring Equivalents

Regulatory Toxicology and Pharmacology 51 (2008) S4–S15

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Guidelines for the derivation of Biomonitoring Equivalents: Report from the Biomonitoring Equivalents Expert Workshop

Sean M. Hays [a,*], Lesa L. Aylward [b], Judy S. LaKind [c], Michael J. Bartels [d], Hugh A. Barton [e], Peter J. Boogaard [f], Conrad Brunk [g], Stephen DiZio [h], Michael Dourson [i], Daniel A. Goldstein [j], John Lipscomb [k], Michael E. Kilpatrick [l], Daniel Krewski [m], Kannan Krishnan [n], Monica Nordberg [o], Miles Okino [p], Yu-Mei Tan [q], Claude Viau [n], Janice W. Yager [r]

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Biomonitoring Equivalents

- 2,4-D
- Acrylamide
- Cadmium
- Cyfluthrin
- Di(2-ethylhexyl)phthalate
- Phthalate Esters:
  - Diethyl phthalate
  - Di-n-butyl phthalate
  - Benzylbutyl phthalate
- Polychlorinated dibenzo-p-dioxins and dibenzofurans
- Toluene
- Trihalomethanes:
  - Chloroform
  - Dibromochloromethane
  - Bromodichloromethane
  - Bromoform

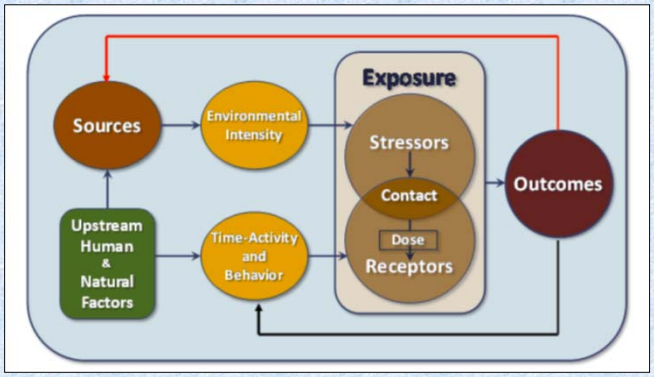
http://www.biomonitoringequivalents.net/html/chemical_specific_bes.html

Exposure Assessment Guidance

BEST

Board on Environmental Studies and Toxicology

Exposure Science in the 21st Century



http://www.nap.edu/openbook.php?record_id=13507

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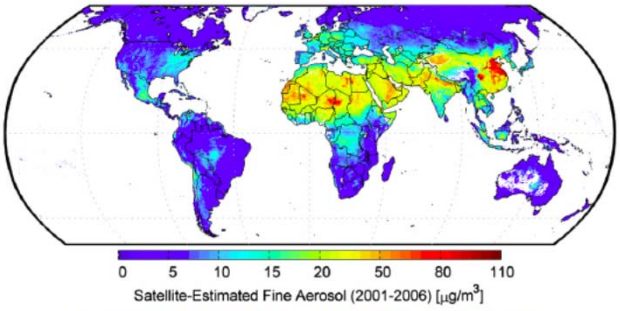
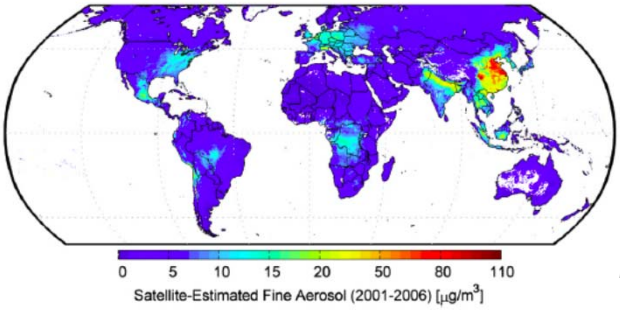
Remote Sensing Techniques: Global PM2.5 Levels

With dust



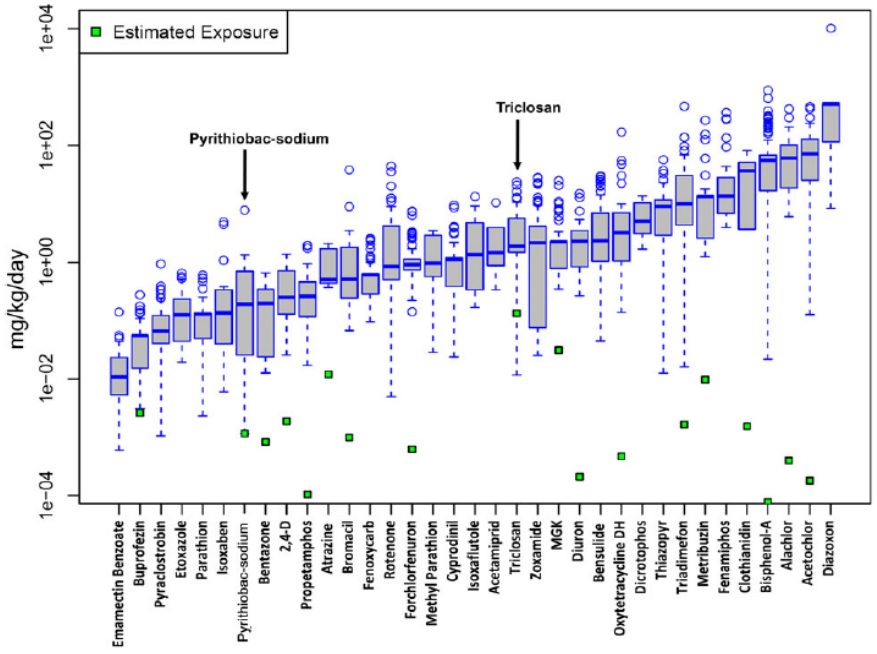
Without dust



Evans et al. (2013) Env. Res. 120:33

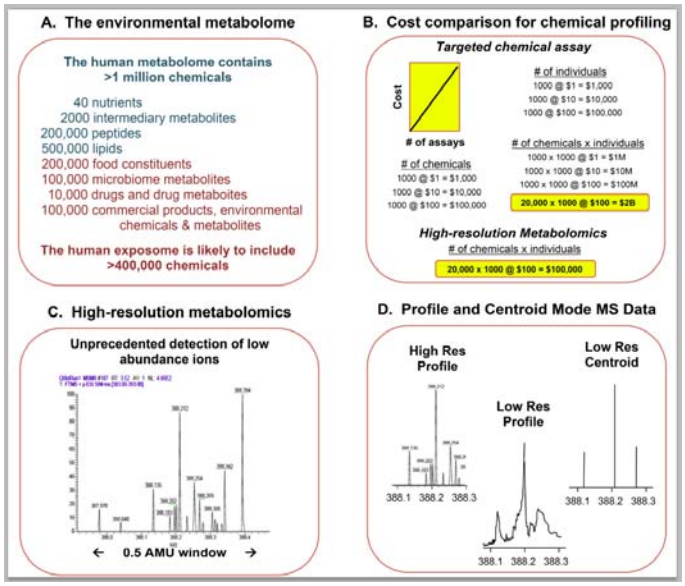
- **ExpoCast** provides high-throughput exposure estimations for thousands of chemicals via multiple routes
- **Farfield exposure models** used to estimate exposure from chemicals that are released into the environment
- **Nearfield exposure models** used to estimate of exposure to chemicals in consumer products and in-home sources
- ***CPCat*** *database catalogs the use of over 40,000 chemicals in different consumer products*

Margins of Exposure based on *In Vitro* Toxicity Testing



Rotroff et al. (2010). Tox. Sci 117:348

High-throughput Biomonitoring



Jones, D.P. (2015), submitted.

Metal Specific Exposure Assessment: Aluminum

Critical Reviews in Toxicology

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

Crit Rev Toxicol, 2014; 44(S4): 1–80
 DOI: 10.3109/10408444.2014.934439

informa healthcare

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]

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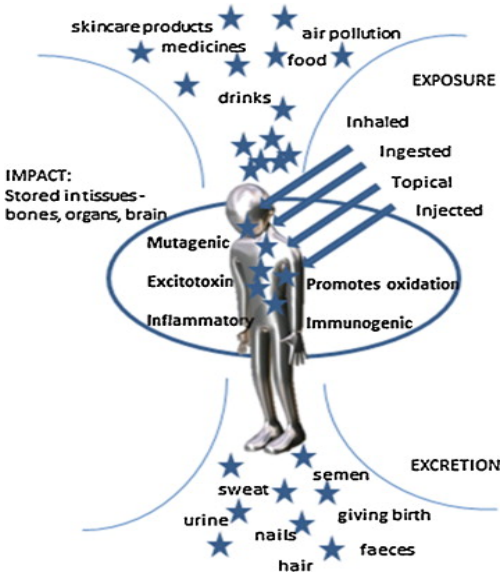
Human Exposure to Aluminum



Kramer & Heath (2014)
Vaccine 32:4140

Main Sources of Exposure to Aluminum

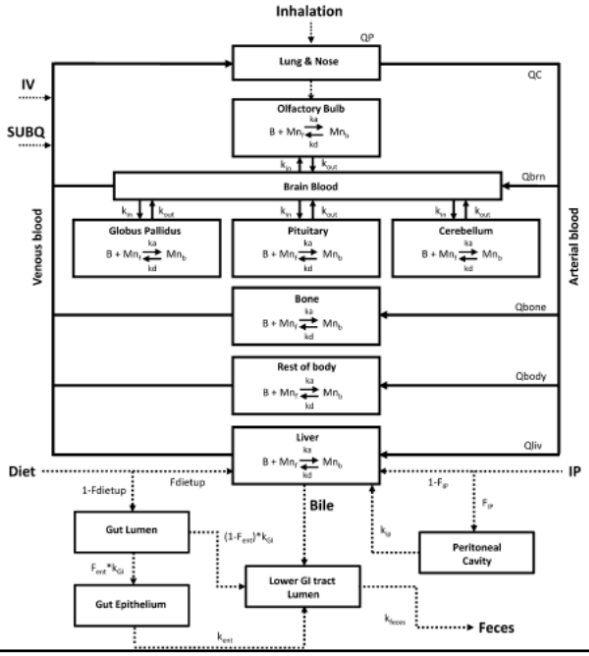
- **Food** is the primary source of aluminum for most healthy people: the typical American diet contributes about 5 mg/d to human exposure
- **Drinking water** contributes much less Al than food: about 0.2 mg/d at the WHO drinking water guideline
- **Non-prescription medicines** can lead to much higher exposures: 120-7,200 mg/d for antacids and 200-1,000 mg/day for buffered aspirin
- **Occupational exposures** can also be appreciable: 3-21 mg/d for Al smelting or welding
- **Other sources**, including cosmetics and anti-perspirants, are comparatively small

Metal Specific Exposure Assessment: Manganese

Main Heath Issues Associated with Manganese Exposure

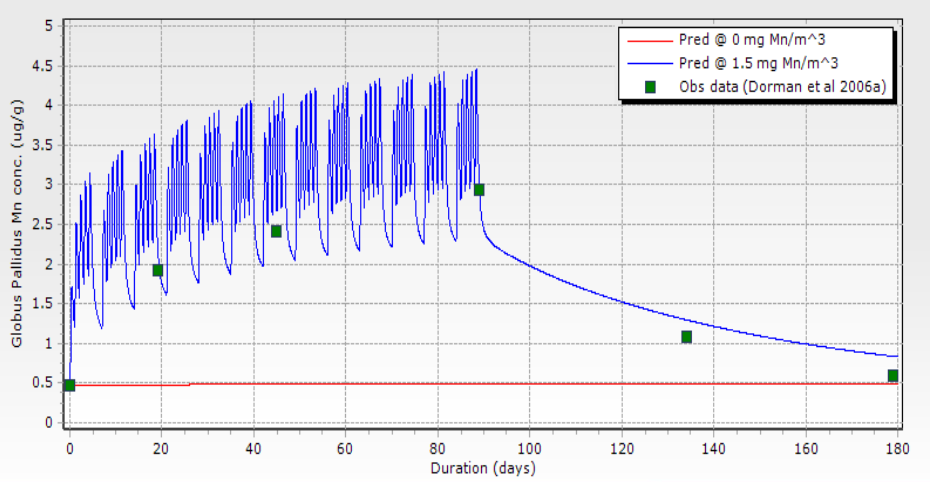
- **Neurotoxicity** (mood changes, tremors, altered gait, facial muscle spasms)
- Lung toxicity (inflammation, pneumonia)
- Effects on reproductive system (loss of libido, impaired fertility in men)
- Developmental toxicity (reduced IQ)

Multi-route PBPK model for Manganese Tissue Kinetics in Adult Monkeys and Humans



Schroeter et al. (2011) Tox. Sci. 20:481

Predicted Mn Concentrations in the Globus Pallidus of Monkeys Exposed to 0 or 1.5 mg Mn/m^3 in air (6 h/d, 5 d/wk) and 133 ppm Mn in diet for 13 weeks (diet-only post-exposure up to 90 days)



Currently Available PBPK Models for Mn

- Rats (adult, pregnant, lactating, and neonatal)
- Nonhuman primates (adult)
- Human (adult, pregnant, lactating, and neonatal)

Metal Specific Exposure Assessment: Copper

Journal of Toxicology and Environmental Health, Part B, 13:546–578, 2010

ISSN: 1093-7404 print / 1521-6950 online
DOI: 10.1080/10937404.2010.538657

Taylor & Francis
Taylor & Francis Group

AN EXPOSURE-RESPONSE CURVE FOR COPPER EXCESS AND DEFICIENCY

Andrea Chambers[1], Daniel Krewski[1], Nicholas Birkett[1,2], Laura Plunkett[3], Richard Hertzberg[4], Ruth Danzeisen[5], Peter J. Aggett[6], Thomas B. Starr[7], Scott Baker[5], Michael Dourson[8], Paul Jones[9], Carl L. Keen[10], Bette Meek[11], Rita Schoeny[12], Wout Slob[13]

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[10]Department of Nutrition, University of California at Davis, Davis, California, USA
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[12]U.S. Environmental Protection Agency, Washington, DC, USA
[13]Dutch National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

Estimates and Assumptions in Assessing Copper Intake

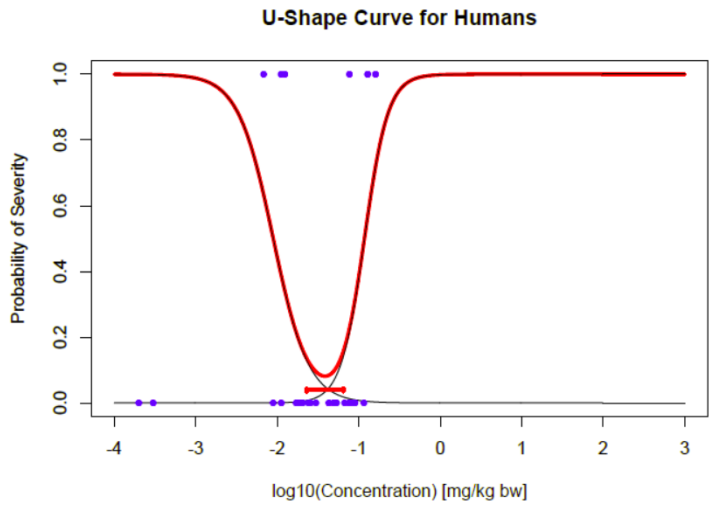
Ref (ID#)	Weight at T1 (kg)	Age at T1 (days)	Exposure T (days)	Weight at T2	Age at T2	Age at Midpoint (days)	Weight at Midpoint (kg)	Consumption Feed (g)	Consumption water (ml)
2	82.2	NA	42	NS/NA	NS	NA	82.2	NA	NA
2	61.3	NA	42	NS/NA	NS	NA	61.3	NA	NA
No need to estimate amount of copper in feed consumed – exposure was given via a capsule with copper content reported in milligrams per day. Weight and age is assumed to be constant.									
6	70	NA	84	NS/NA	NS	NA	70	NA	NA
Weight not given but assumed to be 70kg. No need to estimate amount of copper in feed consume – exposure was given via a capsule with copper content reported in milligrams									
10	0.06	27	30	NS/NA	57	42	0.165	18	NA
Weight reported at onset - age and weight at mid-point estimated from Poiley (1972) based on specie, strain and weight. Consumption of feed based on NAS (1972) estimates by species, sex and weight.									
14	70	NS	28	NS/NA	NA	NS	70	NA	NA
Weight at onset assumed to be 70kg for adult male. Weight and age is assumed to be constant. Amount of copper consumed provided in the article.									
20	NS	21	7	NS/NA	28	24.5	69.26	9	NA
20	NS	21	14	NS/NA	35	28	79.86	12	NA
20	NS	21	21	NS/NA	42	31.5	99.68	15	NA
20	NS	21	28	NS/NA	49	35	119.5	16	NA
20	NS	21	35	NS/NA	56	38.5	139.34	17	NA
20	NS	21	42	NS/NA	63	42	159.17	18	NA
20	NS	21	105	NS/NA	126	73.5	325.84	20	NA
Animals reported as being in the weaning stage. Estimate of 21 days for the age of weaning rats taken from NAS (1969). Weight at midpoint estimated from Poiley (1972) based on specie, strain and age. Consumption of feed based on NAS (1972).									

Chambers (2009), MSc Thesis, University of Ottawa

Seven Level Severity Scoring System for Copper Toxicity due to Excess and Deficiency

	Severity Score (S)	Physiological Response
DEFICIENCY	6	Death
	5	Serious irreversible gross deficiency
	4	Reversible gross deficiency
	3	Metabolic perturbation
	2	Early biological indicators of defient Cu levels
	1	Homeostatic adaptations to low intakes
	0	No effect
	1	Homeostatic adaptation to high intakes
EXCESS	2	Early biological indicators of accumulated Cu
	3	Metabolic perturbation
	4	Reversible gross excess
	5	Serious irreversible gross excess
	6	Death

U-Shaped Dose-response Curve for Copper Toxicity due to Excess and Deficiency



Optimal intake of copper is 2.73 mg/day (95% CI: 1.54 – 4.58 mg/day)

Milton et al (2015), submitted.

Key Issues in Assessing Human Exposure to Metals

- Physical form (insoluble bauxite dust *vs* Al welding fumes)
- Chemical form (insoluble Al silicates *vs* highly soluble Al organics)
- Route of exposure and bioavailability (intravenous Al injection during kidney dialysis *vs* ingested baking powder)
- Target organ (inhaled bauxite particulates and emphysema *vs* systemic Al and adynamic bone disease)
- Substance-specific adjustment factors

Future Directions in Exposure Science

- NRC TT21C/EPA NexGen future risk assessment paradigms built on understanding of toxicity pathways, and HTS assays to detect pathway perturbations: *a concomitant shift in exposure science is needed to complete this transition:*
  - Biomarkers of exposure linked to toxicity pathway perturbations
  - High-throughput exposure assessment (biomonitoring and computational approaches)
  - *In vitro* to *in vivo* extrapolation (IVIVE) for dosimetric calibration of HTS assays
  - Human exposure guidelines based on biomonitoiring equivalents (BEs)

Contributors

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- Natasha Shilnikova, MD, PhD, *RSI and University of Ottawa*
- Calvin Willhite, PhD, *Risk Sciences International (RSI)*