National Toxicology Program Update

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NTP Board of Scientific Counselors
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Overview

- Release of 12th Report on Carcinogens - June 10
- Advancing research on mixtures workshop - September 26-27
- ICCVAM/NICEATM international workshop on alternative methods for rabies vaccine potency tests - October 11-13
- OHAT low-level lead peer review - November 17-18

12th Report on Carcinogens (RoC) – released June 10

- Public Health Service Act, Section 301(b)(4) (1978)
  - Directs HHS Secretary to annually publish a list of carcinogens
  - Changed to a biennial report (1992)
- Preparation delegated to the NTP
  - Dr. Ruth Lunn, Director, Office of the Report on Carcinogens
- RoC is cumulative -- each edition adds newly listed substances to prior list
  - 1st RoC published in 1980 had 26 listings
  - 12th RoC published in 2011 has 240 listings
    - 54 known human carcinogens
    - 186 reasonably anticipated to be human carcinogens

Newly Reviewed Listings in the 12th RoC

Substance	Type of Agent	Listing Status	Public interest
Aristolochic acids	Botanical	KHC	Low to moderate
Captafol	Fungicide	RAHC	Low
Cobalt-tungsten carbide: powders and hard metals	Metal	RAHC	Moderate
Formaldehyde	Industrial chemical	KHC	High
Certain glass wool fibers (inhalable)	Synthetic fibers	RAHC	High
ortho-Nitrotoluene	Industrial chemical	RAHC	Low
Riddelliine	Botanical	RAHC	Low
Styrene	Industrial chemical	RAHC	High

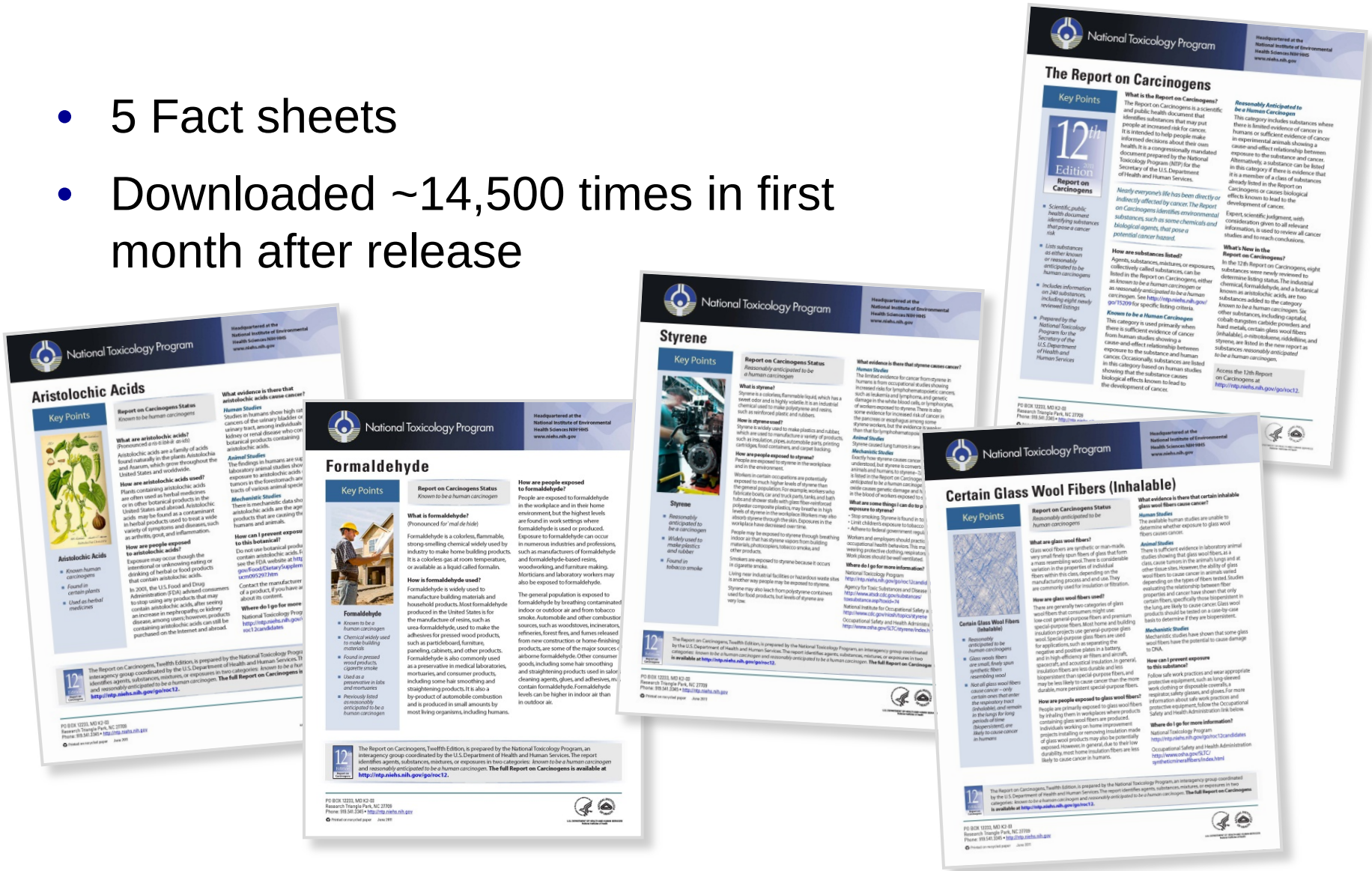
KHC = known human carcinogen; RAHC = reasonably anticipated human carcinogen

RoC Release

- Released June 10, 2011
- Highly coordinated communications plan
- Fact sheets
- Dedicated website
- Media teleconference
- News coverage

RoC Fact Sheets

- 5 Fact sheets
- Downloaded ~14,500 times in first month after release



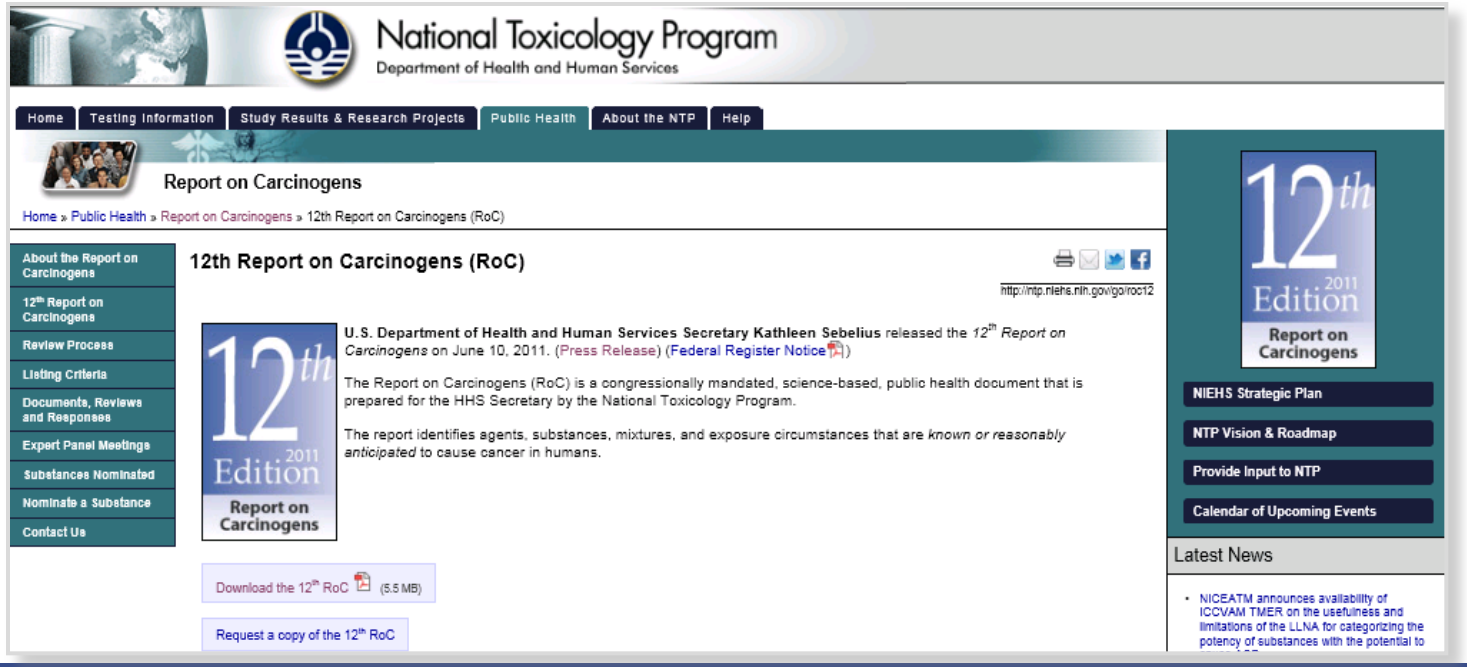
RoC Dedicated Website

- More than 16,000 RoC-related PDF downloads within 2 hours of release
- Within first month after release:

  ~ 49,000 visits to site

  ~ 38,000 views of all web pages

  ~ 45,800 PDF downloads of RoC profiles



RoC News Coverage

- 515 news stories written within first month of release
- 15 Media Interviews arranged, including: **NY Times, Prevention Magazine, Fox Business Week, Associated Press, CBS Radio, ABC,** and **CNN**

"All the News That's Fit to Print"

The New York Times

National Edition

Carolinas: Partly sunny. Scattered thunderstorms north and west. Highs 80s coast and mountains, 90s Piedmont. A storm north and west tonight. Weather map, Page C8.

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GOVERNMENT SAYS 2 MATERIALS POSE A RISK OF CANCER

USED DAILY BY MILLIONS

Formaldehyde, Styrene and 6 Others Named, Despite Lobbying

By GARDINER HARRIS

WASHINGTON — The government issued warnings on Friday about two materials used daily by millions of Americans, saying that one causes cancer and the other might.

Government scientists listed formaldehyde as a carcinogen, and said it is found in worrisome quantities in plywood, particle board, mortuaries and hair salons. They also said that styrene, which is used in boats, bathtubs and Styrofoam, may cause cancer but is generally found in such low levels in consumer products that risks are low.

Frequent and intense exposures in manufacturing plants are far more worrisome than the intermittent contact that most consumers have, but government scientists said that consumers should still avoid contact with formaldehyde and styrene along with six other chemicals that were added Friday to the government's official Report on Carcinogens. Its release was delayed for years because of intense lobbying from the chemical industry,

Formaldehyde Added to List of Carcinogens; Styrene Included but Is a Lesser Risk

From Page A1

contained unacceptable levels of formaldehyde, and salon workers have reported headaches, nosebleeds, burning eyes, vomiting and asthma attacks after using the product and other hair-straighteners.

Studies of workers like embalmers exposed to high levels of formaldehyde have found increased incidences of myeloid leukemia and rare cancers of the nasal passages and upper mouth.

Dr. Otis Brawley, chief medical officer at the American Cancer Society, said that formaldehyde is both worrisome and inescapable. "It's the smell in new houses, and it's in cosmetics like nail polish," he said. "All a reasonable person can do is manage their exposure and decrease it to as little as possible. It's everywhere."

Consumers can reduce their exposure to formaldehyde by avoiding pressed-wood products or buying only those that are labeled as U.L.E.F. (ultra-low-emitting formaldehyde), N.A.F. (no-added formaldehyde) or C.A.R.B. (California Air Resources Board) Phase 1 or Phase 2 compliant.

Styrene is mostly a concern for workers who build boats, car parts, bathtubs and shower stalls. Studies of workers exposed to high levels of styrene have found increased risks of leukemia and lymphoma and genetic damage to white blood cells. There is also some evidence that styrene increases the risks of cancer of the pancreas and esophagus among styrene workers, the report found. Consumers can be exposed to styrene from the fumes of building materials, photocopiers and tobacco smoke.

As for styrene's presence in Styrofoam and other consumer products, Dr. Brawley likened the risk from such products to that of coffee and cellphones — uncertain and slight.

An industry spokesman said the action will hurt small businesses.

"It will unfairly scare workers, plant neighbors and could have a chilling effect on the development of new products," said Tom Dobbins of the American Composites Manufacturers Association. "And our companies are primarily small businesses, and this could hurt jobs and local economies."

Cal Dooley, president and chief executive of the American Chemistry Council, a trade association that represents companies that make and use polystyrene and formaldehyde, rejected the report's conclusions. "We are extremely concerned that politics may have hijacked the scientific process," he said.

Some in the industry have promised to continue fighting the report, and will appeal elements of its findings. But some manufacturers already have begun using alternatives to formaldehyde in their products.

This is the 12th cancer list released by the toxicology program at the National Institutes of Health, and each has been controversial. In 2000, controversy

Consumers told to reduce exposure by avoiding products.

erupted over the ninth report's listing of secondhand smoke and tanning beds. The 11th report's listing in 2005 of naphthalene, which is used in mothballs, caused similar concern.

That this latest report would warn about formaldehyde and styrene has been suspected by industry since shortly after the release of the previous report, and industry groups have fought the process behind its release ever since. As a result, the government added numerous public comment periods to the process, and even after it was written, officials at the Department of Health and Human Services delayed the report's release for months to cope with industry complaints.

"Industry held this report up for four years," said Jennifer Sass, a senior scientist at the Natural Resources Defense Council. "They have tried to create the impression that there was real scientific uncertainty here, but there's not."

The report also lists aristolochic acids, found in plants and sometimes used in herbal medicines, as a known carcinogen and added to the list of probable carcinogens other substances like captafol (a fungicide no longer sold in the United States), finely spun glass wool fibers (used in insulation), cobalt-tungsten carbide (used in manufacturing), riddelliine (plants eaten by cattle, horses and sheep) and ortho-nitrotoluene (used in dyes).

Aristolochic acids are sometimes used in herbal medicines to treat conditions like arthritis and gout. In 2001, the Food and Drug Administration warned against the use of products containing aristolochic acids after seeing an increase in kidney disease among users. Products using the chemical are Rheumixx and BioSlim Doctor's Natural Weight Loss System Slim Tone Formula.

Glass wool fibers are finely spun fibers of glass that form a mass resembling wool. They are commonly used for insulation or filtration, and people can be exposed to them when they install or remove insulation during home improvement projects. Animal studies have shown that glass wool fibers cause lung tumors, but there is little evidence from human studies of a risk.

Opposition Is Split on How to Reshape Yemen

By The New York Times

SANA, Yemen — The protesters, arrayed in the tens of thousands under a blazing sun, pumped their fists in unison as

United States and Yemen's Arab neighbors.

Many are anxious that the president, Ali Abdullah Saleh, will destroy their movement if he is allowed to return.

"This is our chance, now Saleh

numbers were a little low on both sides, perhaps because of the intense heat and the worsening scarcity of gasoline and water.

Most of those who form the original core of the protest movement say they want to preserve

Stocks Plunge Amid Worries Over Growth

mounting budget deficits and simply might not see NATO as worth supporting any longer.

"The blunt reality," Mr. Gates said, "is that there will be dwindling appetite and patience in the U.S. Congress — and in the American body politic writ large — to expend increasingly precious funds on behalf of nations that are apparently unwilling to devote the necessary resources

Advancing Research on Mixtures:

New Perspectives and Approaches for Predicting Adverse Human Health Effects

- September 26-27, 2011, at the Sheraton, Chapel Hill, NC
- Co-organizers: Dr. Danielle Carlin, DERT and Dr. Cynthia Rider, DNTP
- Workshop goals:
  - Identify and focus on key issues that present challenges in mixtures research
  - Inform the development of an intramural and extramural research strategy

http://tools.niehs.nih.gov/conferences/dert/mixtures/

New Tools for Mixtures Toxicology

- Toxicology in the 21st Century
  - HTS, ‘omics
  - Pathway and network analyses
- Exposure sciences
  - Improved monitoring technologies
  - Exposome
- Computational sciences
  - Taking advantage of the available data and computational tools

What's next for NTP?

- Target tissue approach to mixtures - "integrated pathway perturbation"
  - Testing dose additivity for chemicals that target the same pathway/tissue via different mechanisms
  - Moving beyond common biological "receptor" that drives health effects
- Sufficient similarity evaluation
  - Realization that this is a common issue for many NTP test articles
- Use of high density information
  - HTS/MTS/genomics
  - Sufficient similarity in broader biological space
  - Aid linkage of in vitro-in vivo extrapolation
- Cross-disciplinary collaboration
  - Statistical methods development for sufficient similarity determinations
  - Use of toxicologically-derived relative potency factors in epidemiology

International Workshop on Alternative Methods for Human and Veterinary Rabies Vaccine Testing

William Stokes, D.V.M., DACLAM

Conference Organized by NICEATM-ICCVAM

October 11-13, 2011

National Centers for Animal Health, Ames, Iowa

- 80 participants, 12 countries
  - Industry, government, academe
- FDA and USDA requirements for rabies vaccine potency testing: “NIH challenge test”
  - Intracranial injection of live rabies virus
  - Unprotected mice develop clinical rabies and die
- Workshop addressed:
  - Refinement (less pain and distress)
  - Reduction
  - Replacement
- Public health significance
  - 70,000 human deaths annually worldwide
  - 15 million patients treated with post-exposure vaccines annually

Workshop on Rabies Vaccine Potency Testing: Highlights

- Refinement and reduction of the NIH challenge test:
  - Anesthesia: should always be used for IC injections
  - Analgesics: should be provided to all mice
  - Earlier humane endpoints: should be immediately incorporated
  - Reduction: evaluate potential for fewer dilutions, fewer mice per dilution
- Replacement of the NIH Challenge Test

  1) Serological Methods: Serum virus neutralization test (SNT)
     - Eliminates the need for challenge with live rabies virus: complete refinement
     - Sufficiently standardized per recent international study; manufacturers should conduct and submit product-specific validation studies, in consultation with regulators

  2) *In vitro* antigen quantification methods: complete animal replacement
     - Requires use of monoclonal antibodies specific for the trimeric glycoprotein G
     - Validation should proceed once Mab identified; must discriminate sub-potent lots
- Complete workshop report published in *Biologicals*, early 2012

Draft NTP Monograph on Health Effects of Low-level Lead

Andrew A. Rooney, Ph.D.

Office of Health Assessment and Translation

Peer Review Meeting

November 17-18, 2011

Nomination and Scope of the Evaluation

- NIOSH nominated lead at blood levels <10µg/dL for evaluation for adverse reproductive and developmental effects
  - Health effects are well established at higher levels
  - CDC's definition of elevated blood lead is ≥10µg/dL for all ages
- NTP expanded the scope to include:
  - Neurological effects
  - Immune effects
  - Cardiovascular effects
  - Renal effects
  - Reproductive and developmental effects

Key Questions

What is the evidence that adverse health effects are associated with blood lead levels <10µg/dL?

- What neurological, immune, cardiovascular, renal, reproductive, and developmental effect(s) are associated with blood lead levels <10µg/dL?
- What is the blood lead level associated with the health effect (i.e., <10µg/dL or <5µg/dL)?
- At which life stage (childhood or adulthood) is the effect identified?
- Are there data to evaluate the association between bone lead and the health effect and how does the association to this biomarker of lead exposure compare to the association with blood lead?

Organization of the Monograph

- Executive Summary
- Methods
  - Approach to develop health effects conclusions and definitions of levels of evidence for associations
  - Literature search strategy
  - Authoritative sources considered
- Exposure
  - What does blood Pb <10µg/dL mean
- Health Effects Sections
  - Focused narrative
  - Extensive appendix tables

National Toxicology Program
U.S. Department of Health and Human Services

DRAFT NTP MONOGRAPH ON HEALTH EFFECTS OF LOW-LEVEL LEAD

OCTOBER 14, 2011

Office of Health Assessment and Translation
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Peer Review Date: November 17-18, 2011

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Table 1.2: NTP conclusions on health effects of low level Pb by major health effect areas

Health Area	Population Or Exposure window		NTP Conclusion	Principal Health Effects	Blood Pb Evidence	Bone Pb Evidence
Neurological	Prenatal		*Limited*	Decrease in measures of cognitive function	Yes, <5µg/dL	No data
			Limited	Decreased IQ, increased incidence of ADHD and problem behaviors, decreased hearing	Yes, <10µg/dL	No data
	Children		*Sufficient*	Decreased academic achievement and specific cognitive measures, increased incidence of ADHD and problem behaviors	Yes, <5µg/dL	Tibia and dentin Pb are associated with ADHD, behavior, and cognition.
			Sufficient	Decreased IQ, decreased hearing	Yes, <10µg/dL	No data
			Limited	Decreased IQ	Yes, <5µg/dL	No data
	Adults		*Limited*	Psychological effects, decreased hearing, decreased cognitive function, increased incidence of ALS and essential tremor	Yes, <10µg/dL	The association between bone Pb and cognitive decline is stronger than for blood.
Immune	Children		*Sufficient*	Increased IgE*(effect, not a health outcome)	Yes, <10µg/dL	No data
			Limited	Increased hypersensitivity/allergy by skin prick test to common allergens	Yes, <10µg/dL	No data
			Inadequate	Asthma, eczema	Unclear	No data
	Adults		*Inadequate*		Unclear	No data
Cardiovascular	Children		*Inadequate*		Unclear	No data
	Adults		*Sufficient*	Increased blood pressure, increased risk of hypertension, and increased cardiovascular-related mortality	Yes, <10µg/dL	The association between bone Pb and cardiovascular effects is stronger than for blood.
			Limited	Increased ECG abnormalities, heart rate variability	Yes, <10µg/dL	
Renal	Children under age 12		*Inadequate*		Unclear	No data
	Children 12 or older		*Limited*	Decreased glomerular filtration rate	Yes, <5µg/dL	No data
	Adults		*Sufficient*	Decreased glomerular filtration rate	Yes, <5µg/dL	Yes, one study
Reproductive and Developmental	Prenatal		*Limited*	Reduced postnatal growth	Yes, <10µg/dL	No data
	Children		*Sufficient*	Delayed puberty, reduced postnatal growth	Yes, <10µg/dL	One study does not support effects of bone Pb on growth.
			Limited	Delayed puberty	Yes, <5µg/dL	
	Adults	Women	*Sufficient*	Reduced fetal growth	Yes, <10µg/dL	Maternal tibia Pb is associated
			Limited	Increase in spontaneous abortion and preterm birth	Yes, <10µg/dL	No data
		Men	*Sufficient*	Adverse changes in sperm parameters and increased time to pregnancy	Yes, ≥15-20µg/dL	No data
			Limited	Decreased fertility	Yes, ≥10µg/dL	No data
			Limited	Increased spontaneous abortion	Yes, >31µg/dL	No data
		Adults	*Inadequate*	Stillbirth, endocrine effects, birth defects	Unclear	No data

Note: ADHD - attention deficit hyperactivity disorder; IgE – immunoglobulin E; ALS - amyotrophic lateral sclerosis; ECG - electrocardiography

*Increased serum IgE is associated with hypersensitivity; however, as described in **Section 1.4.3**, increased IgE does not equate to disease.

Questions?