April 23, 2014

SCIENCE SPECIFIC COMMENTS FOR THE EPA BI-MONTHLY MEETING HEXABROMOCYCLODODECANE

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APRIL 23, 2014
EPA APRIL BIMONTHLY MEETING

North American Flame Retardant Alliance (NAFRA)
http://flameretardants.americanchemistry.com/

NAFRA's members represent the world's leading producers and users of a variety of flame retardants.

Promotes

- the safe and effective use of flame retardants
- responsible methods for developing/handling flame retardants
- sustainable stewardship for flame retardants
- dialogue with regulators, policymakers, and stakeholders
- expanding existing knowledge about flame retardants

Topics to Be Covered

- Science Issue #1 – Thyroid Endpoints and Relevance
- Science Issue #2 – Liver and Thyroid Effects
- Science Issue # 3 – Mode of Action

SCIENCE ISSUE #1

American Chemistry Council

Biological Endpoints

The Toxicological Review of HBCD will consider:

- Endpoints under consideration: reproductive and developmental toxicity endocrine effects (including thyroid and reproductive hormone), neurotoxicity, neurobehavioral, and immunotoxicity

Considerations for Data Evaluation

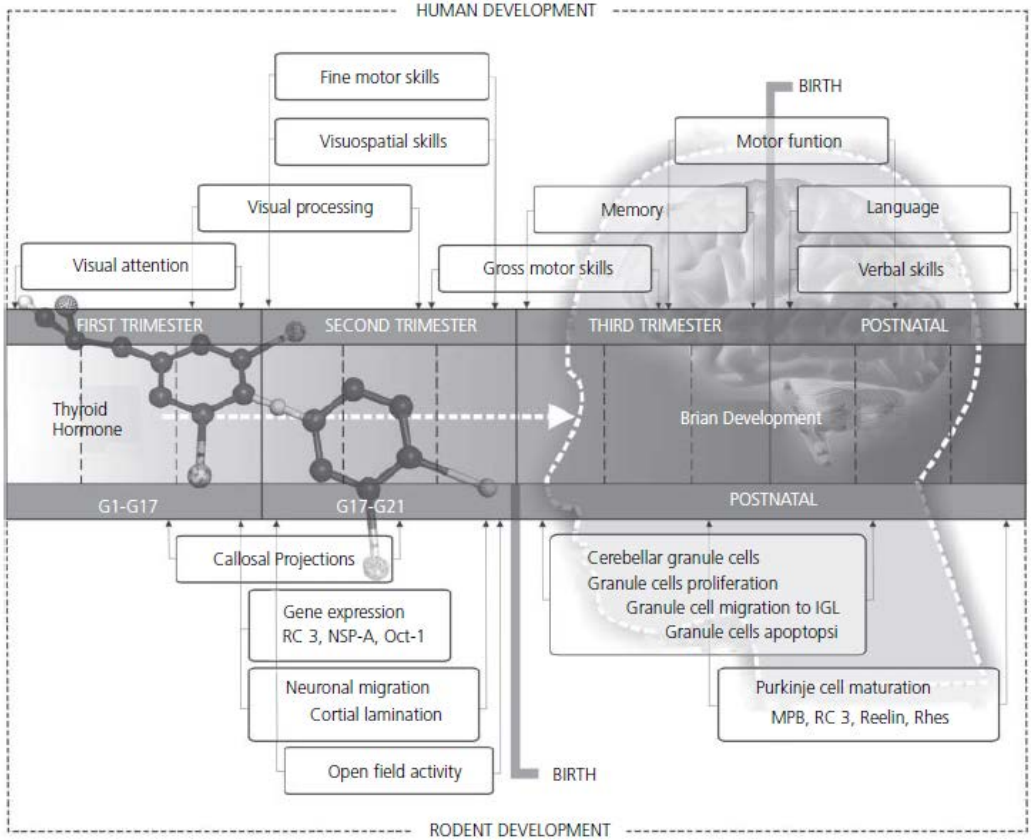
- Time of sampling for thyroid hormones levels
- Correlation of thyroid hormone levels changes to adverse outcomes
- Species and sex specific differences
- Life stages

Biological Relevance of Thyroid Hormone Changes

Science issue 1. Changes in thyroid hormone levels have been reported following HBCD exposure in several rodent toxicity. EPA is seeking public discussion on the levels of change in thyroid hormones that are biologically significant.

Thyroid Hormones

- Protein Synthesis
- Fat and Carbohydrate Metabolism
- Cell Differentiation



Zoeller, R. T., & Rovet, J. (2004). Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. *Journal of neuroendocrinology*, *16*(10), 809-818.

Biological Relevance of Thyroid Hormone Changes

Science issue 1. Changes in thyroid hormone levels have been reported following HBCD exposure in several rodent toxicity. EPA is seeking public discussion on the levels of change in thyroid hormones that are biologically significant.

- Thyroid hormone levels can be impacted by physiological stress, illness, depression and obesity
- There is no consensus on how far thyroid levels must fall for adverse health effect to occur in humans

Thyroid Hormone	Normal Levels
TSH	0.3 – 4mIU/L
T3	80-220 points (Total) 0.2-0.5ng/dL (Free)
T4	4.5 – 12.6ug/dL(Total) 0.7-1.8ng/dL (Free)

National Endocrine and Metabolic Diseases Information Service :
http://www.endocrine.niddk.nih.gov/pubs/thyroidtests/thyroidtests_508.pdf

Species Differences in Thyroid Hormones

Changes in Thyroid Hormone Levels

- Different parts of the brain are sensitive to the level of thyroid hormones at different points in time
- Species and sex differences exist in thyroid development between rodents and humans

Table 2
Selected Parameters of Thyroid System in Humans and Rats (Adapted From U.S. EPA, 1998)

Parameter	Human	Rat
Half-life of T4	5–9 days	0.5–1 day
Half-life of T3	1 day	0.25 day
Thyroxine-binding globulin levels	High	Very low
Amount of T4 required in absence of functional thyroid gland	2.2 μg/kg bw/day	20 μg/kg bw/day
T4 production (rate/kg bw)	1×	10×
Sex difference in serum TSH levels	No difference	Adult males have higher levels than adult females
Follicular cell morphology	Low cuboidal Follicular height is equal in males and females.	Cuboidal Follicular height in males is greater than in females

Reference - Choksi, N. Y., Jahnke, G. D., St Hilaire, C., & Shelby, M. (2003). Role of thyroid hormones in human and laboratory animal reproductive health. Birth Defects Research Part B: Developmental and Reproductive Toxicology, 68(6), 479-491

Exposure to HBCD

Food and dust are considered main sources of human exposure

Media	HBCD Concentrations
Dust	4.5 - 140,000µg/kg dw
Meat	0.86 µg/kg
Dairy	0.261 µg/kg ww
Eggs	0.01 µg/kg ww
Fish and Fish Products	1.46 µg/kg ww
Cereal	0.180 µg/kg ww
Apples	0.022 µg/kg ww
Potatoes	0.018 µg/kg ww

Reference: Environment Canada
Health Canada 2011 Assessment of HBDC

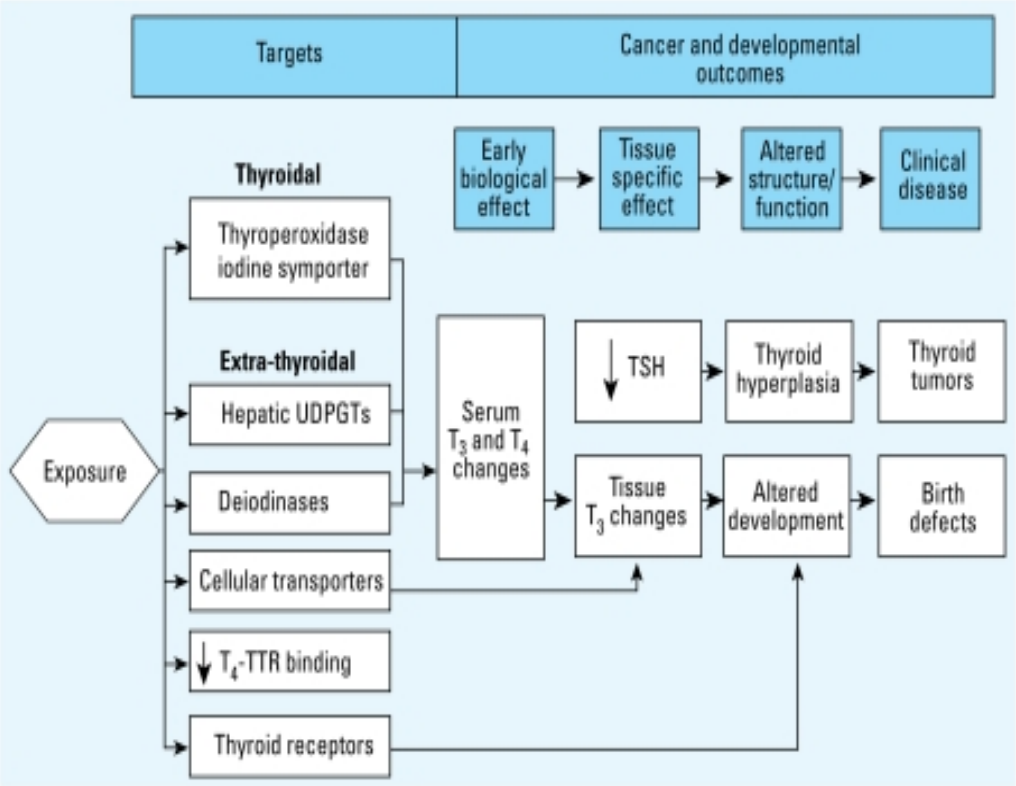
Levels Tested in Animal Studies
10.2- 4,900mg/kg-d

SCIENCE ISSUE #2

American Chemistry Council

Link for Liver and Thyroid Effects

Science issue 2. EPA is seeking public discussion on what sequence(s) of mechanistic events may be hypothesized to link effects in the liver and the thyroid.



Reference: Environ Health Perspect. Jul 2009; 117(7): 1033–1041.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2717126/figure/f3-ehp-117-1033/

Sub-chronic rodent studies suggest:

- liver and thyroid are target organs in HBCD exposed rodents
- some thyroid effects and liver weight changes
- HBCD does not exert the toxicity on the thyroid directly but perhaps acts through liver enzyme induction and consequent metabolism of thyroxin

Liver, Thyroid and Development Effects

Lack of correlation btw HBCD exposure and neurophysical and behavioral effects

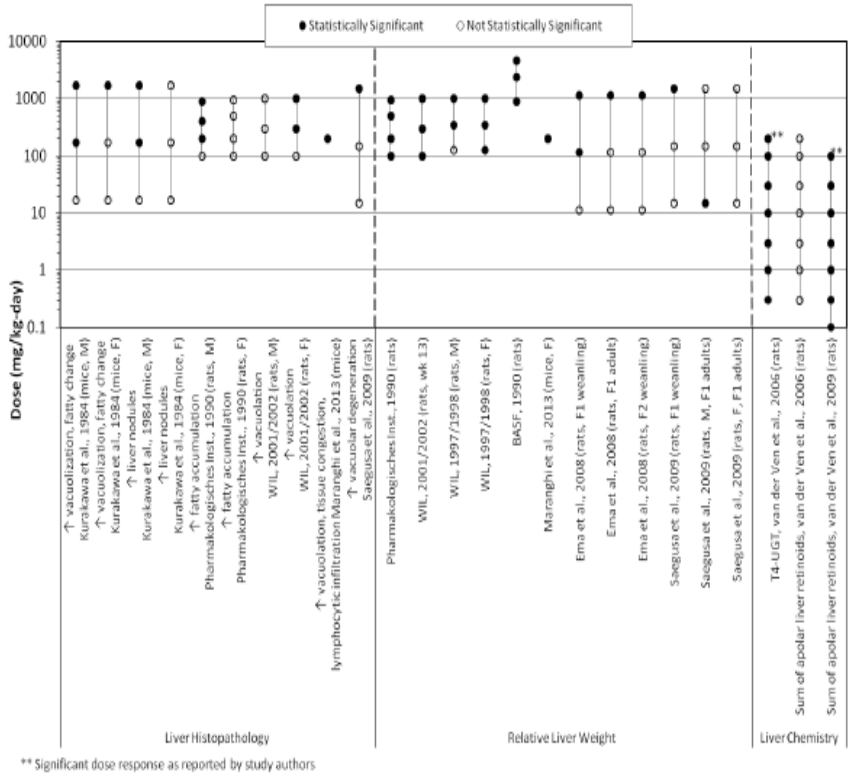


Figure A-2. Exposure-response array of liver effects following oral exposure to HBCD

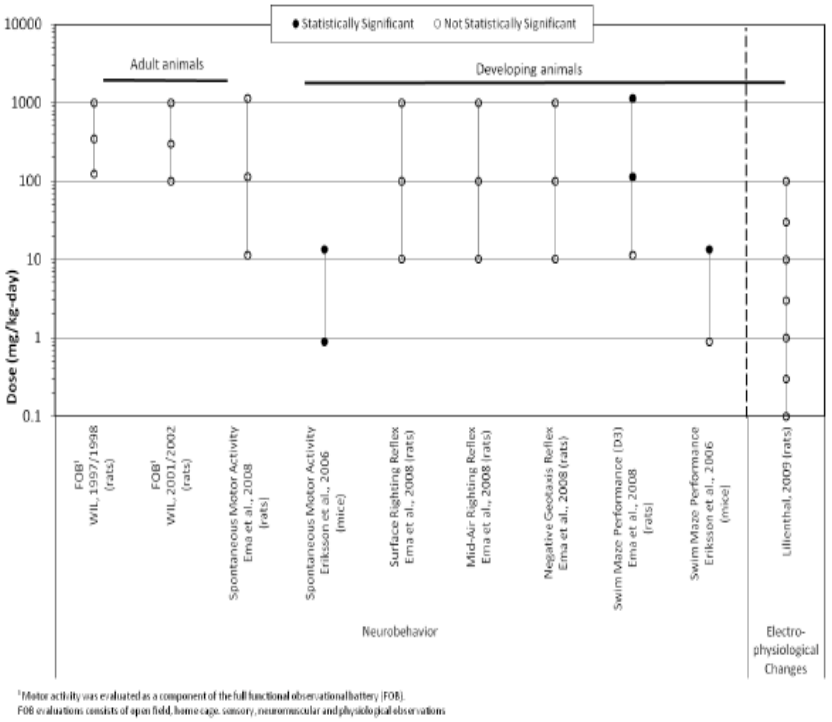


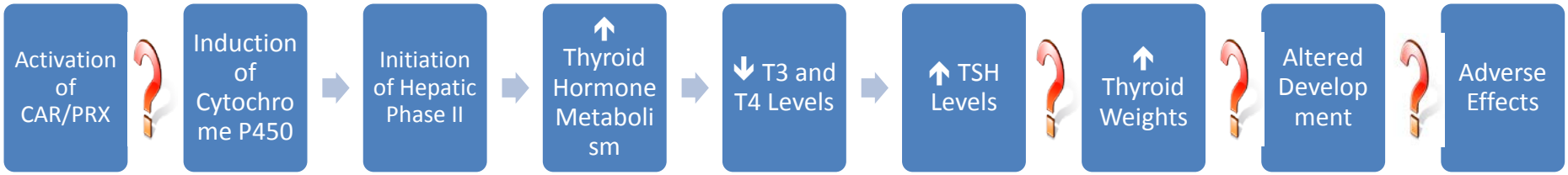
Figure A-3. Exposure-response array of neurological effects following oral exposure to HBCD

SCIENCE ISSUE #3

American Chemistry Council

Possible Modes of Action

Science issue 3. EPA is seeking public discussion about (1) MOAs/AOPs that might be supported by the studies cited in Table B-1 and (2) suggestions for improving the presentation of this type of information at this early stage of draft development.



Possible Supportive Evidence for the MOA

- Induction of CYP3A1/3 (PXR activation)
- Induction of CYP2B1/2B2 (mediated by CAR)
- Induction of CYP3A4 in female rats (PXR mediated)
- Possible sex-specific cytochrome P450 stimulation