

# New Insights in Integrative Medicine To Support Healthy Thyroid Function

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# Causes of Hypothyroidism

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The most common causes of acquired thyroid disorders are:

- Iodine deficiency
- Autoimmune disease
- Iatrogenic (radiation, surgery and drugs)
- Environmental toxicity, such as heavy metals, halides and xenoestrogens
- Nutritional deficiency

Warrell DA, Cox TM, Firth JD (eds). Oxford Textbook of Medicine, Volume 2. Oxford, Oxford University Press, 2003, p 215

# Environmental Toxicity

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## Environmental Hazards:

- PCB's
- Oestrogenic and growth hormones in food consumption
- Xeno oestrogens in cosmetics, personal care products, household cleaning chemicals
- Halide toxicity

Aoki Y. Polychlorinated biphenyls, polychlorinated dibenzo-p-dioxins, and polychlorinated dibenzofurans as endocrine disrupters--what we have learned from Yusho disease. Environ Res. 2001 May;86(1):2-11

# Environmental Medicine Testing

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## Metametrix USA (Diagnostic Insights Australia)

- Organophosphates Profile - Urine
- Bisphenol A Profile
- Phthalates & Parabens Profile
- Chlorinated Pesticides
- PCBs
- Volatile Solvents
- Porphyrins Profile
- Toxic Metals – Whole Blood
- BPA, Phthalates & Parabens, and Organophosphates Combo Profile
- BPA and Phthalates & Parabens Combo Profile
- Urinary Halides

# Effect of Lead on TRH and GRF Binding in Anterior Pituitary Membranes

The low affinity site could be displaced by hGRF (1-44)-NH<sub>2</sub>, hGRF (1-29)-NH<sub>2</sub> and rGRF (1-29)-NH<sub>2</sub>. A synthetic growth hormone releasing peptide (GHRP) also interacted with the low affinity GRF binding site. Lead dose-dependently displaced the binding of [<sup>125</sup>I]GRF to its pituitary receptors. The IC<sub>50</sub> of lead for inhibiting [<sup>125</sup>I]GRF binding was 0.195 mM added lead or 52 pM free lead.

**The data suggest that one mechanism by which lead may affect pituitary function is through inhibition of receptor binding.**

Lau YS, Camoratto AM, White LM, Moriarty CM. Effect of lead on TRH and GRF binding in rat anterior pituitary membranes. *Toxicology*. 1991;68(2):169-79

# Effect of Cadmium on T4

**The effect of cadmium on thyroxine (T4) outer ring monodeiodination was studied *in vivo* and *in vitro* in the rat liver. One microgram of T4 was incubated with rat liver homogenates in 50 mM Tris--HCl buffer, pH 7.4, with or without 0.5, 5, and 50 mM dithiothreitol (DTT) for 60 min in the presence of  $10^{-8}$  to  $10^{-3}$  M  $\text{CdCl}_2$ , and the amount of 3,5,3'-triiodothyronine (T3) produced was determined by a specific radioimmunoassay.**

**Subcutaneous injection of  $\text{CdCl}_2$ , 1 mg/kg BW/day, 5 days a week for 10 weeks, to the rats resulted in a significant reduction in serum T3 concentration (by 37%) and hepatic T3 production from T4 (by 78 to 92%).**

# Effect of Cadmium on T4

*In vitro* addition of 1 microM to 1 mM CdCl<sub>2</sub> to liver homogenates caused a concentration-dependent reduction in T<sub>3</sub> generation. Without DTT a 50% reduction in the T<sub>4</sub> to T<sub>3</sub> converting activity was caused by  $4 \times 10^{-6}$  M CdCl<sub>2</sub>. DTT (0.5 to 50 mM) partially restored T<sub>3</sub> generation roughly in a concentration-dependent manner.

**These results indicate that cadmium has some effects on the metabolism of thyroid hormone.**

Yoshida K, Sugihira N, Suzuki M, Sakurada T, Saito S, Yoshinaga K, Saito H.  
Effect of cadmium on T<sub>4</sub> outer ring monodeiodination by rat liver. Environ  
Res. 1987;42(2):400-5.

# Mercury Toxicity

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Ellingsen et al. (2000) reported finding impaired thyroid function in a group of 47 chloralkali workers exposed to Hg, whom they compared with 47 controls.

The exposed workers showed a statistically significant rise in reverse T3 (rT3), a rise that was dose-related.



# Mercury

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Mercury and other dental metals may be playing a role in some cases of thyroid nodules.

In 1995 the journal *Analyst* reported on a recent study showing that heavy metals, including mercury, were found to be high in malignant and benign thyroid nodular tissue. The researchers examined concentrations of antimony, iron, iodine, rubidium, scandium, selenium, mercury, silver, cobalt, chromium and zinc in malignant and benign thyroid nodules (the latter 5 elements are metals commonly used in dentistry).

Zaichick VYe, Tsyb AF, Vtyurin BM. Trace Elements and Thyroid Cancer.  
*Analyst* 1995;120(3):817-21

# Impact of Lead Exposure on Pituitary-Thyroid Axis in Humans

Interestingly, T3 was significantly lower with the longer (210 months) exposure time in comparison with the group having shorter (29 months) exposure duration.

The mean TSH levels were significantly higher in workers exposed in comparison with the control group. This rise in TSH was independent of exposure time, but it was definitely associated with the Pb-B levels. The increase being more pronounced with mean Pb-B levels of 2.66 +/- 0.2 micromole/l (55.4 +/- 4.25 microg/dl) when compared with the group having mean levels of 1.51 +/- 0.30 micromole/l (31.5 +/- 6.20 microg/dl). The rise in TSH associated with Pb-B levels was only statistically valid, however, the levels fall within the normal laboratory range.

**We thus conclude that the Pb-B levels of > or = 2.4 micromole/l (50 microg/dl) enhance the pituitary release of TSH without having any significant alterations in the circulating levels of T3 and T4.**

Singh B, Chandran V, Bandhu HK, Mittal BR, Bhattacharya A, Jindal SK, Varma S. Impact of lead exposure on pituitary-thyroid axis in humans. Biometals. 2000 Jun;13(2):187-

# Cortisol Can Induce Hypothyroidism

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Elevated cortisol leads to

- Decreased fT3
- Increase rT3
- Decreased peripheral hormone metabolism by inhibition of the enzyme 5-deiodinase
- Increased risk of auto-antibody production and subsequent increased risks of AITD

# Hyperinsulinaemia

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## Hyperinsulinaemia

- Elevated insulin levels trigger increased production and release of Thyroxine Binding Globulin (TBG) from the liver
- This results in elevated levels of bound T4 and T3 and a deficiency of free thyroid hormones available to have metabolic cellular activity
- This will result in symptoms of hypothyroidism but often goes undetected

# Obesity Related to Thyroid Hormone Conversion Issues

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In high fat diet induced obesity, instead of increased serum T(3) and T(4) secondary to higher circulating leptin and thyrotropin levels, elevated serum rT3

Araujo RL, Carvalho DP. Bioenergetic impact of tissue-specific regulation of iodothyronine deiodinases during nutritional imbalance. J Bioenerg Biomemb 2011 Feb;43(1):59-65.

# T3/rT3-Ratio is Associated With Insulin Resistance Independent of TSH

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T3/rT3-ratio, which is supposed to reflect the tissue thyroid hormone metabolism, is significantly increased in insulin resistant subjects.

This supports a link between thyroid function and IR.

Ruhla S, et. al. T3/rT3-ratio is associated with insulin resistance independent of TSH. *Horm Metab Res.* 2011 Feb;43(2):130-4.

# Diagnostic Evaluation

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- ◉ Barnes Basal temperature test
- ◉ Iodine patch test
- ◉ The 24 hour urinary iodine excretion test
  - FFP or Doctors Data
- ◉ Thyroid function test (blood work)
- ◉ Palpation of thyroid (goitre or nodules)

# Hypothyroidism Blood Labs

| <b>T4</b>      | <b>TSH</b> | <b>T3</b>      | <b>Interpretation</b>                     |
|----------------|------------|----------------|---|
| Normal         | High       | Normal         | Mild (subclinical) hypothyroidism         |
| Low            | High       | Low or normal  | Hypothyroidism                            |
| Normal         | Low        | Normal         | Mild (subclinical) hyperthyroidism        |
| High or normal | Low        | High or normal | Hyperthyroidism                           |
| Low or normal  | Low        | Low or normal  | Rare pituitary (secondary) hypothyroidism |



# TFT Panel

- TRH
- TSH: if >2, then include:
  - fT4
  - fT3
  - rT3
- Thyroid antibodies
  - thyroid peroxidase antibody (TPOAb)
  - thyroglobulin antibody (TgAb) and
  - thyroid stimulating hormone receptor antibody (TRAb)
- 25-OH -D (D3)
- Iron studies
- Selenium RBC
- Zinc RBC
- Copper RBC
- Spot urinary Iodine (?)
- Fasting insulin
- Blood Lipid Panel
- AM fasting cortisol (start) or 24 hour urinary cortisol excretion test or ASI
- If Female: Oestradiol (test of day 2-3 of menses)

# Interpretation of TFT

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## Adults

- TSH (0.1 - 4 mU/L)
  - optimal 1-2
  - subclinical hypothyroidism 2-4 mU/L
  - clinical hypothyroidism >4 2-4 mU/L
- fT3 (3.5 - 6.3 pmol/L)
  - optimal 5-6 pmol/L
- fT4 (11 - 19 pmol/L)
  - optimal 16+ pmol/L

Owen PJ, Lazarus JH. Subclinical hypothyroidism: the case for treatment. Trends Endocrinol Metab 2003;14:257-261.

# Interpretation of TFT

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- **rT3: the ratio of T3/rT3 multiplied by 100 should be between 1.06 to 1.13**
  - if this ratio is  $<1$ , reverse T3 dominance is present
- **Reverse T3 is virtually inactive having only 1% the activity of T3 and being a T3 antagonist binds to T3 receptors blocking the action of T3**
- **Normal physiological production ratio of T4 to T3 is 3.3 : 1**

# Reverse T3 Dominance

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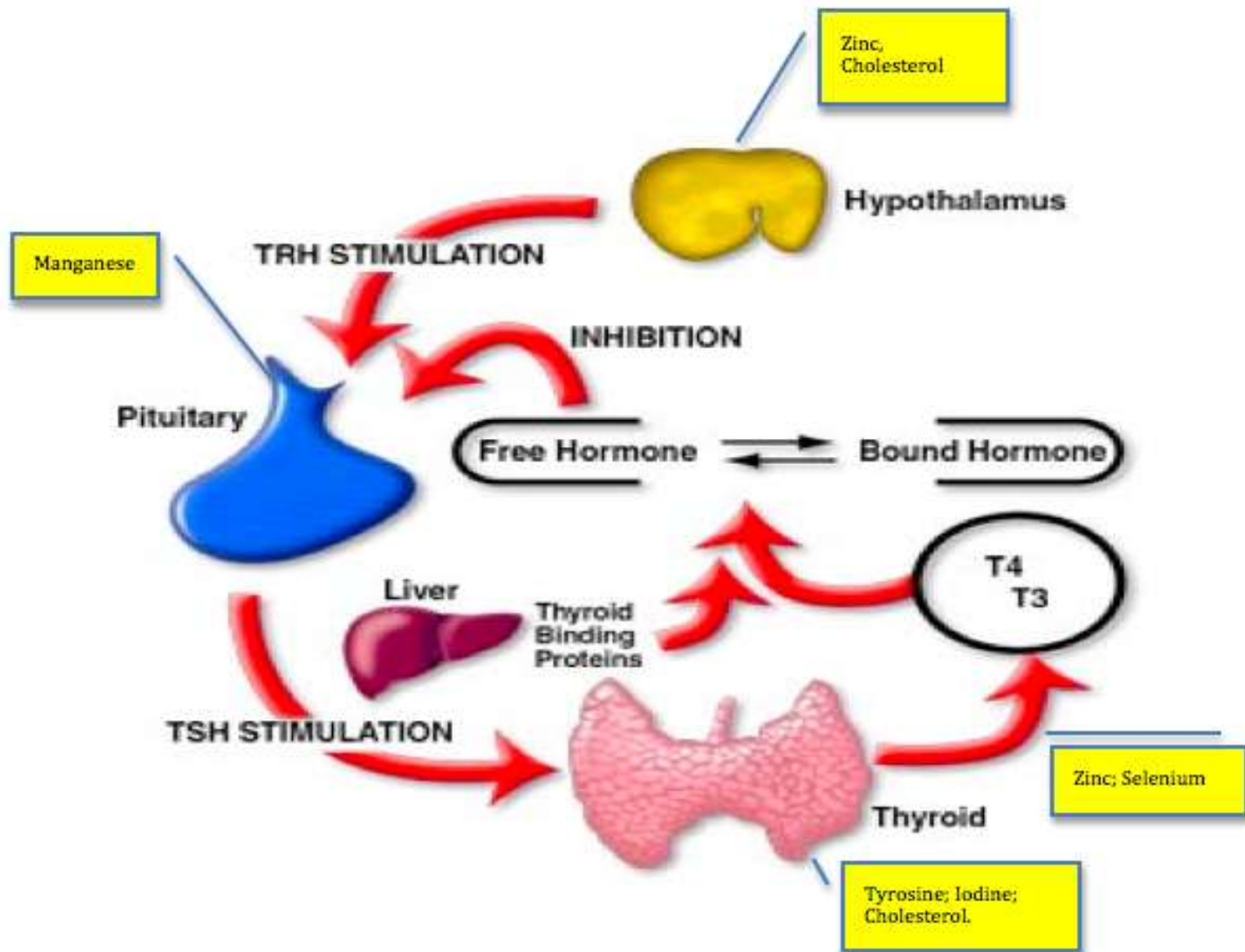
- If reverse T3 dominance is present, then slow release T3 therapy may need to be initiated once adrenal issues, hyperinsulinaemia, nutritional deficiencies, environmental toxicity have been ruled out and/or treated
- Slow release T3 therapy (S4) – GP Rx only
- Reverse T3 dominance is very often overlooked

Galton VA, Schneider MJ, Clark AS, St Germain DL. Life without thyroxine to 3,5,3'-triiodothyronine conversion: studies in mice devoid of the 5'-deiodinases. *Endocrinology*. 2009 Jun;150(6):2957-63

# Hypothyroidism: Signs and Symptoms

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- Slow Pulse
- Lethargy
- Puffy face
- Muscle fatigue
- Loss of eyebrows in outer third
- Carpel tunnel
- Depression
- Headaches
- Menstrual disturbance
- Hyperlipidemia
- Growth retardation in children, delayed teething and slow mental development
- Dull facial expression
- Hoarse voice with slow speech
- Intolerance to cold
- Dry, course skin, hair and nails
- Weight gain
- Drooping eyelid
- TSH levels are high, decreased T3 and T4 count



# Vitamin D3

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1,25-Dihydroxyvitamin D3 inhibits thyroid hormone-induced osteocalcin expression in mouse osteoblast-like cells via a thyroid hormone response element

Varga F, Spitzer S, Rumpler M, Klaushofer K. 1,25-Dihydroxyvitamin D3 inhibits thyroid hormone-induced osteocalcin expression in mouse osteoblast-like cells via a thyroid hormone response element. *J Mol Endocrinol.* 2003 Feb;30(1):49-57

# Vitamin D3 Linked to Autoimmune Thyroid Disease

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Significantly low levels of vitamin D were documented in patients with AITDs that were related to the presence of anti thyroid antibodies and abnormal thyroid function tests, suggesting the involvement of vitamin D in the pathogenesis of AITDs and the advisability of supplementation.

Kivity S, Agmon-Levin N, Zisappl M, Shapira Y, Nagy EV, Dankó K, Szekanecz Z, Langevitz P, Shoenfeld Y. Vitamin D and autoimmune thyroid diseases. *Cell Mol Immunol.* 2011 May;8(3):243-7



# Vitamin D is Necessary for DNA Transcription

The nuclear receptors for 1,25-dihydroxyvitamin D<sub>3</sub> (VD) and 3,5,3'-triiodothyronine (T<sub>3</sub>), that is, VDRs and T<sub>3</sub>R<sub>s</sub> respectively, control aspects of homeostasis, cell growth and differentiation. They activate transcription from response elements consisting of direct repeats, palindromes and inverted palindromes of a variety of hexameric core-binding motifs. VDRs bind preferentially to direct repeats spaced by three nucleotides, whereas T<sub>3</sub>R<sub>s</sub> bind to direct repeats spaced by four nucleotides. VDRs and T<sub>3</sub>R<sub>s</sub> can function as homodimers but heterodimerization with retinoid X or retinoic acid receptors increases their affinity for DNA in vitro and resulting transcriptional activity in vivo. We recently observed the formation of VDR-T<sub>3</sub>R heterodimers. Here we show that the polarity of the binding of such heterodimers to the VD response element of the rat 9K (relative molecular mass 9,000) calbindin gene promoter was 5'-T<sub>3</sub>R-VDR-3', whereas on the mouse 28K calbindin VD response element this polarity was reversed to 5'-VDR-T<sub>3</sub>R-3'. We also show that the ligand for the downstream receptor controls the transcriptional activity of the heterodimeric complex. Thus, polarity seems to be an important regulatory property of heterodimeric nuclear receptor complexes.

Nature. 1994 Aug 4;370(6488):382-6. Vitamin D<sub>3</sub>-thyroid hormone receptor heterodimer polarity directs ligand sensitivity of transactivation. Schröder M, Müller KM, Nayeri S, Kahlen JP, Carlberg C. Clinique de Dermatologie, Hôpital Cantonal Universitaire, Genève, Switzerland.

# Intracrine Importance of Sufficient Iron

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Ferritin is considered the true indicator of stored iron status

- Reference range of 120-200 ug/L
- Target level > 150 ug/L
- Retest at regular intervals

# A Note on Copper

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- Copper toxicity displaces zinc and competes for absorption
- Copper toxicity related to oestrogen dominance
- Oestrogen dominance partially suppresses thyroid function

# How Much Iodine is Enough?

WHO daily intake: optimal iodine nutrition

| Population sub-group    | Amount     |
|-------------------------|------------|
| Adults                  | 150 µg/day |
| Pregnancy and Lactation | 200 µg/day |
| Children (6-12 years)   | 120 µg/day |
| Infants (0-5 years)     | 90 µg/day  |

(µg =micrograms)

# Meet the Halides

**Periodic Table of the Elements**

|          |          |          |            |            |            |            |            |            |            |          |          |          |          |          |          |          |          |
|----------|----------|----------|------------|------------|------------|------------|------------|------------|------------|----------|----------|----------|----------|----------|----------|----------|----------|
| 1<br>H   |          |          |            |            |            |            |            |            |            |          |          |          |          |          |          |          | 2<br>He  |
| 3<br>Li  | 4<br>Be  |          |            |            |            |            |            |            |            |          |          | 5<br>B   | 6<br>C   | 7<br>N   | 8<br>O   | 9<br>F   | 10<br>Ne |
| 11<br>Na | 12<br>Mg |          |            |            |            |            |            |            |            |          |          | 13<br>Al | 14<br>Si | 15<br>P  | 16<br>S  | 17<br>Cl | 18<br>Ar |
| 19<br>K  | 20<br>Ca | 21<br>Sc | 22<br>Ti   | 23<br>V    | 24<br>Cr   | 25<br>Mn   | 26<br>Fe   | 27<br>Co   | 28<br>Ni   | 29<br>Cu | 30<br>Zn | 31<br>Ga | 32<br>Ge | 33<br>As | 34<br>Se | 35<br>Br | 36<br>Kr |
| 37<br>Rb | 38<br>Sr | 39<br>Y  | 40<br>Zr   | 41<br>Nb   | 42<br>Mo   | 43<br>Tc   | 44<br>Ru   | 45<br>Rh   | 46<br>Pd   | 47<br>Ag | 48<br>Cd | 49<br>In | 50<br>Sn | 51<br>Sb | 52<br>Te | 53<br>I  | 54<br>Xe |
| 55<br>Cs | 56<br>Ba | 57<br>La | 72<br>Hf   | 73<br>Ta   | 74<br>W    | 75<br>Re   | 76<br>Os   | 77<br>Ir   | 78<br>Pt   | 79<br>Au | 80<br>Hg | 81<br>Tl | 82<br>Pb | 83<br>Bi | 84<br>Po | 85<br>At | 86<br>Rn |
| 87<br>Fr | 88<br>Ra | 89<br>Ac | 104<br>Unq | 105<br>Unp | 106<br>Unh | 107<br>Uns | 108<br>Uno | 109<br>Une | 110<br>Unn |          |          |          |          |          |          |          |          |

|          |          |          |          |          |          |          |          |          |          |           |           |           |           |
|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|-----------|-----------|-----------|-----------|
| 58<br>Ce | 59<br>Pr | 60<br>Nd | 61<br>Pm | 62<br>Sm | 63<br>Eu | 64<br>Gd | 65<br>Tb | 66<br>Dy | 67<br>Ho | 68<br>Er  | 69<br>Tm  | 70<br>Yb  | 71<br>Lu  |
| 90<br>Th | 91<br>Pa | 92<br>U  | 93<br>Np | 94<br>Pu | 95<br>Am | 96<br>Cm | 97<br>Bk | 98<br>Cf | 99<br>Es | 100<br>Fm | 101<br>Md | 102<br>No | 103<br>Lr |

# The Halides

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A study published in May this year suggests that some halogenated phenolics, including current use compounds such as plastic monomers, flame retardants and their metabolites, may disrupt thyroid hormone homeostasis through the inhibition of DI activity in vivo.

Butt CM, Wang D, Stapleton HM. Halogenated phenolic contaminants inhibit the in vitro activity of the thyroid regulating deiodinases in human liver. *Toxicol Sci.* 2011 May 11.

# Testing for Halides

## Urinary Halides Test

- Doctors Data

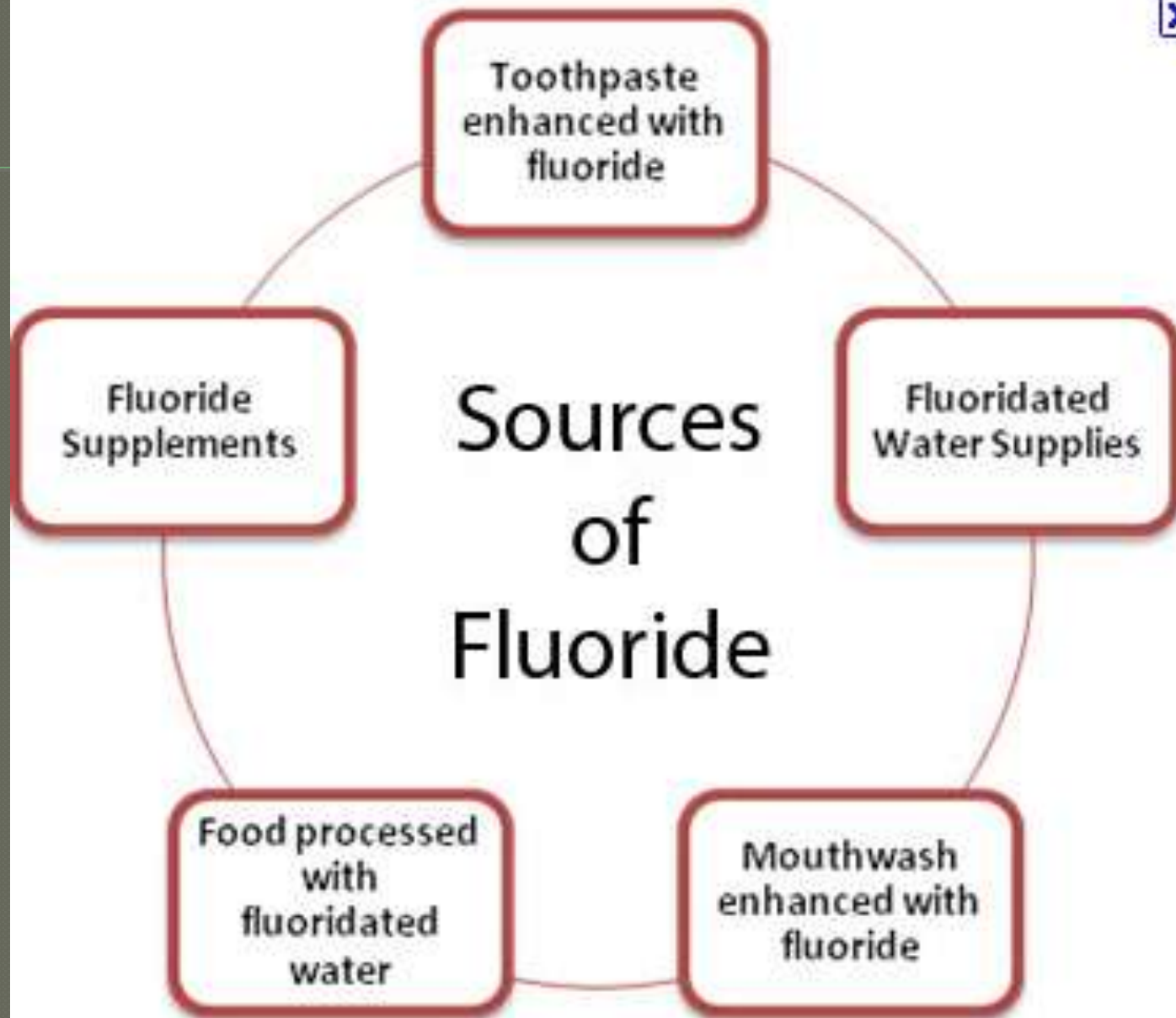
### Urine Halides; 24-hour collection

|                   | $\mu\text{g}/\text{mg cr}$ | $\text{mg}/24 \text{ hr}$ | Reference Range                     |   |
|-------------------|----------------------------|---------------------------|-------------------------------------|---|
| <b>Iodine</b>     | 32                         | 42                        | 0.1- 0.45 $\text{mg}/24 \text{ hr}$ | <b>Iodine</b> levels include iodine and iodide oxidized to iodine. <b>Excretion percentage</b> is calculated by dividing the patient's $\text{mg}/24\text{hour}$ iodine result by the iodine/iodide dosage (in mg) recorded on the requisition form, then multiplying by 100. |
| % Excretion/24 hr |                            | 84%                       |                                     |   |

|                | $\mu\text{g}/\text{mg cr}$ | $\text{mg}/24 \text{ hr}$ | Reference Range               |   |
|----------------|----------------------------|---------------------------|-------------------------------|---|
| <b>Bromine</b> | 2.5                        | 3.2                       | < 7 $\text{mg}/24 \text{ hr}$ | <b>Bromine</b> levels represent total bromine plus bromide, as measured by ICP-MS. Bromide is antagonistic to iodide, and is abundant in commercially produced baked goods, soft drinks, pesticides, brominated chemicals and some medications. |

|                 | $\mu\text{g}/\text{mL}$ | $\text{mg}/24 \text{ hr}$ | Reference Range                 |  |
|-----------------|-------------------------|---------------------------|---------------------------------|--|
| <b>Fluoride</b> | 0.81                    | 2                         | < 1.3 $\text{mg}/24 \text{ hr}$ | <b>Fluoride</b> in urine is measured using an ion specific electrode. Fluoride is neurotoxic, compromises integrity of bone, and interferes with iodide metabolism. Primary sources of fluoride include fluoridated water, beverages, toothpaste/mouth washes, dental treatments and some medications. |

|                   | Result | Reference Range                   |   |
|-------------------|--------|-----------------------------------|---|
| <b>Creatinine</b> | 1300   | 600- 1900 $\text{mg}/24\text{hr}$ | <b>Urine Creatinine</b> is used to assess the collection completeness in 24-hour collections. For estimation of glomerular filtration rate (GFR), a Creatinine Clearance test is recommended. |



# Sources of Fluoride

Toothpaste  
enhanced with  
fluoride

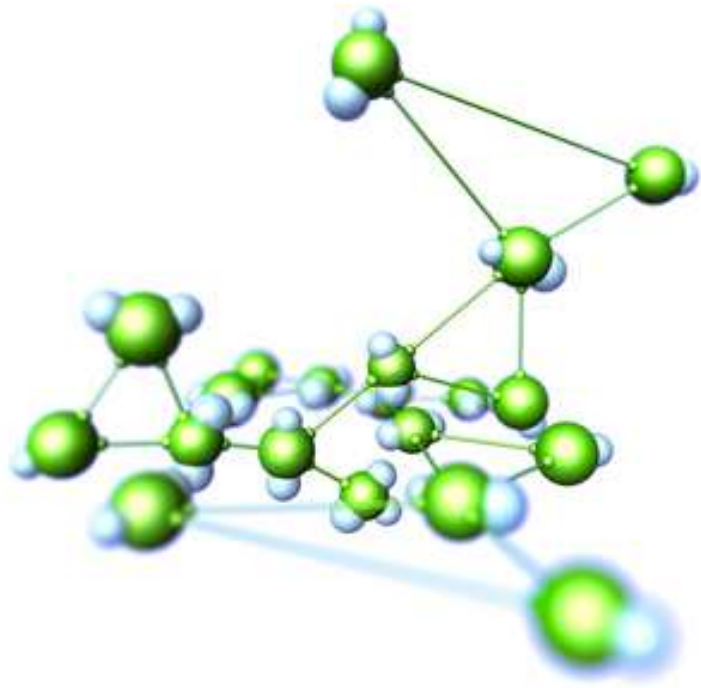
Fluoride  
Supplements

Fluoridated  
Water Supplies

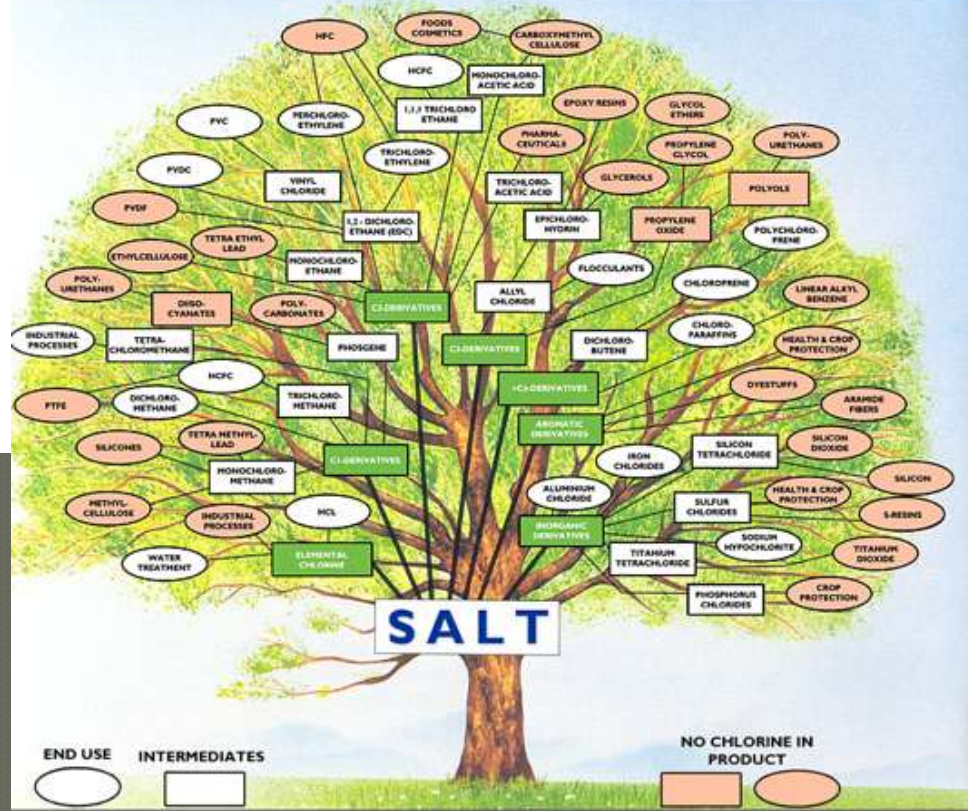
Mouthwash  
enhanced with  
fluoride

Food processed  
with  
fluoridated  
water





# The chlorine tree





79.904  
BROMINE

# Acknowledgments

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Associate Professor Kerry Bone

# New Insights in Integrative Medicine To Support Healthy Thyroid Function

Angela Hywood ND (Australia)  
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