

Fluoride and the Endocrine System

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Definitions

- **Endocrine system**
 - Cellular communication carried out by the classical endocrine glands and their hormones
- **Endocrine glands**
 - Communicate with other cells via internal (“endocrine”) secretion of a chemical signal into the bloodstream
- **Hormone**
 - A chemical signal secreted into the bloodstream by an endocrine gland
 - Elicits a typical physiological response in other cells (target cells)

“The ultimate mission of a hormone is to change the behavior of its target cells.”

- **Cellular behavior is determined by biochemical and molecular events that transpire within the cell**
- **These events are determined in turn by**
 - the genes that are expressed
 - the biochemical reactions that carry out cellular functions
 - the conformation and associations of the molecules that comprise the cell’s physical structure
- **Hormonal messages must be converted to biochemical events that influence**
 - Gene expression
 - Biochemical reaction rates
 - Structural changes

(Definitions and diagrams from H.M. Goodman, *Basic Medical Endocrinology*, Academic Press, 2003)

Effects of fluoride exposure on hormonal function

- **Selected parts of the endocrine system**
- **Basic biology**
- **Type(s) of effect(s)**
- **Summary of evidence to date**
- **Difficulties in interpretation**
- **Possible mechanism(s) of action**
- **Potential implications for human health**

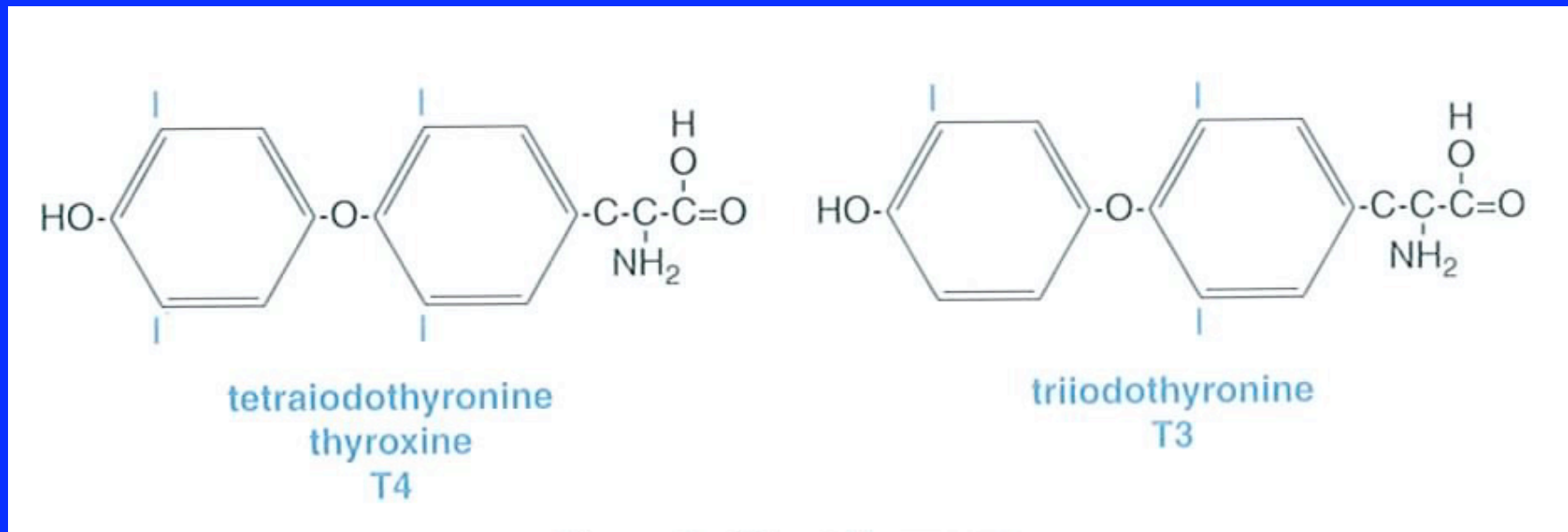
Major areas of focus in the NRC report

- **Thyroid gland**
 - Thyroid follicular cells
- **Calcium metabolism**
 - Parathyroid gland
 - Thyroid parafollicular cells (C cells)
- **Pineal gland**
- **Glucose metabolism**
 - Pancreas (Islets of Langerhans)

Normal thyroid function

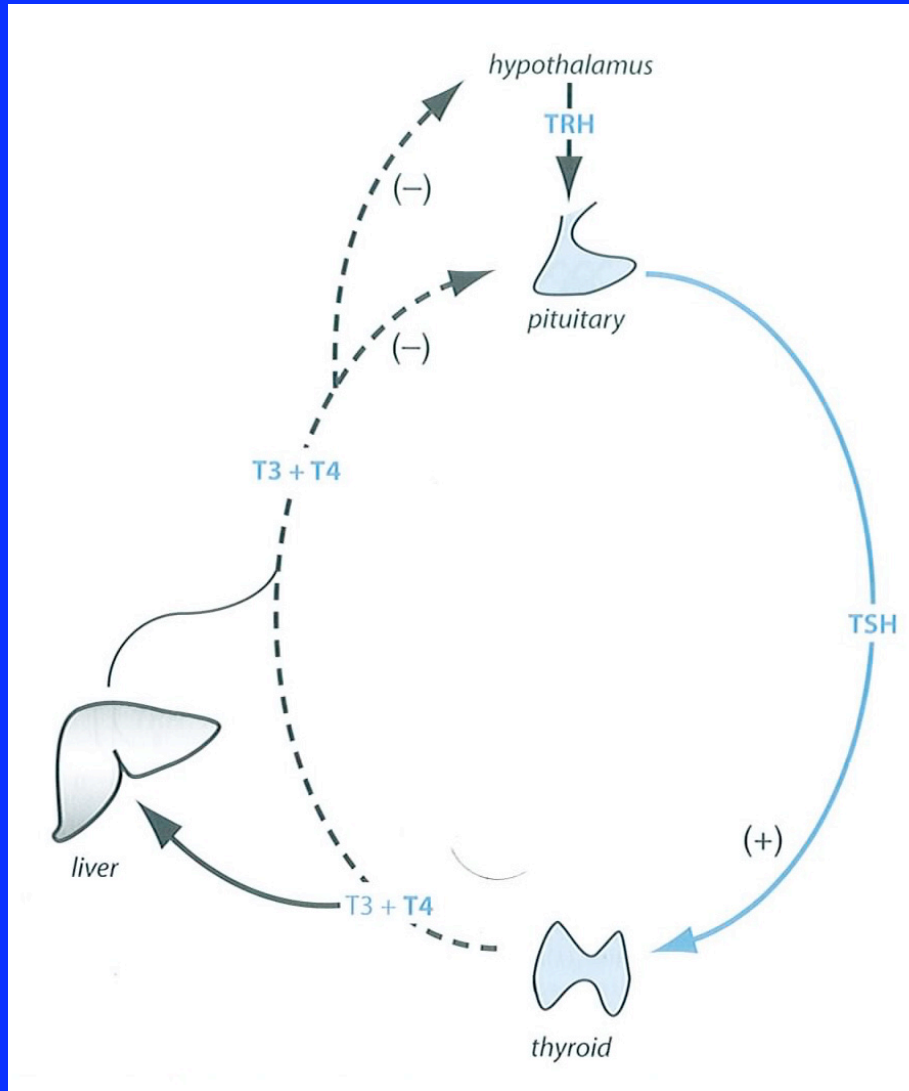
- **Thyroid hormones**
 - T4 (thyroxine)
 - T3 (triiodothyronine)
- **Modulates a variety of physiological processes**
 - Including normal growth and development
 - Essential for normal development of nervous system
 - Dependent on adequate iodine intake

Thyroid hormones



- T4 is the major secretory product of the thyroid
- T3 is the active form of thyroid hormone
 - Binds to the thyroid hormone receptor
- T3 is produced from T4 by the deiodinases
 - Type I (liver, kidney, thyroid)
 - Type II (nonhepatic tissues, including brain and pituitary)

Feedback regulation of thyroid hormone secretion



- Positive stimulation of thyroid hormone secretion by CNS (TRH) and anterior pituitary (TSH)
- Negative feedback inhibition of TSH secretion by T3 and T4
- TSH level usually indicative of the status of thyroid function

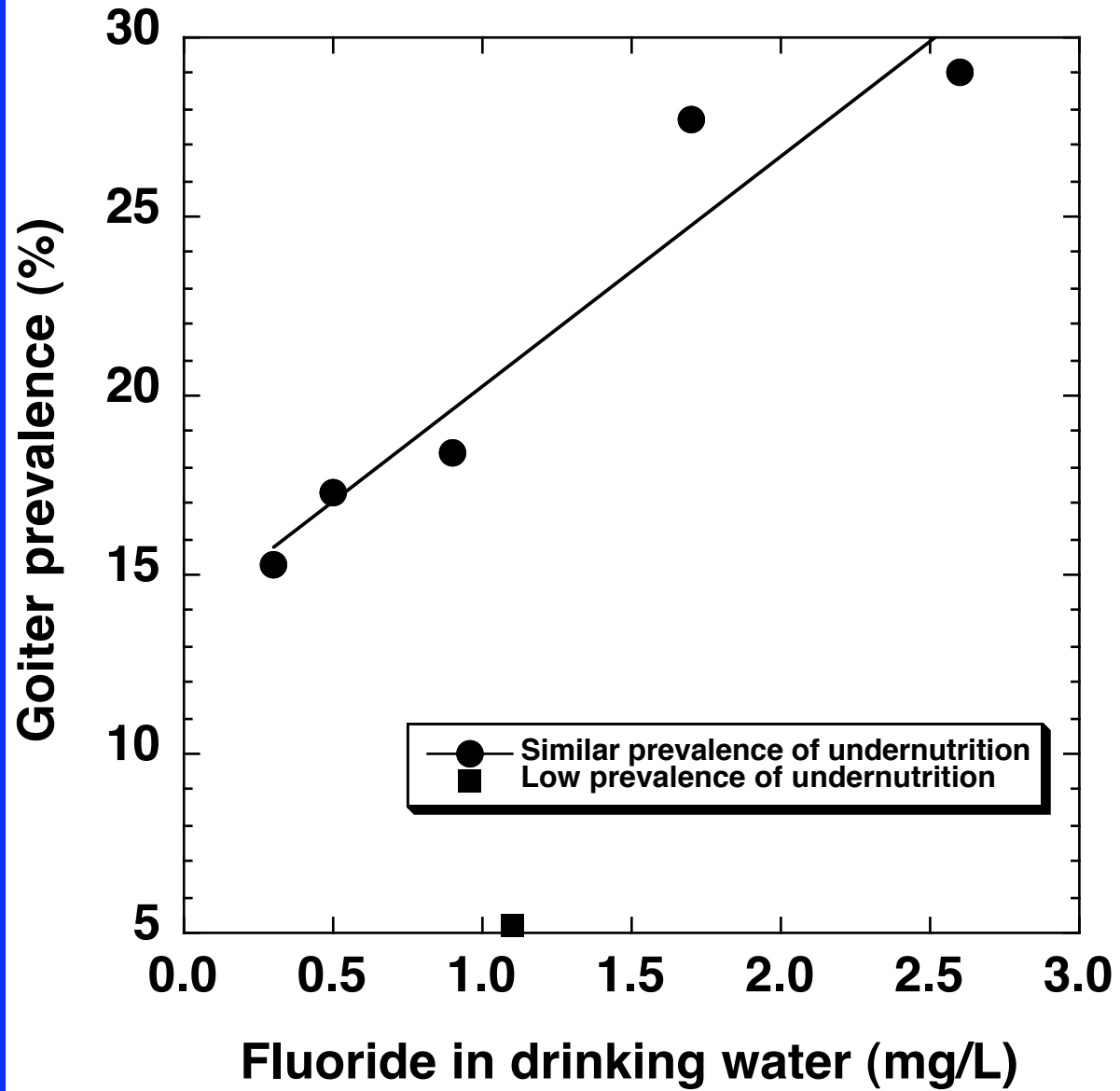
Fluoride effects on thyroid function: Animal studies

- **Decreased thyroid function (esp. decreased T4 and T3 concentrations)**
 - **Seen with fluoride doses of 3-6 mg/kg/d with sufficient dietary iodine (0.4-0.6 mg/kg/d in one study)**
 - **More severe effects seen at similar fluoride doses when dietary iodine was not sufficient**
 - **Effects seen at lower fluoride doses (0.06-1 mg/kg/d) when dietary iodine was not sufficient**
- **TSH not measured in most animal studies**

Fluoride effects on thyroid function: Human studies

- **Relieved hyperthyroidism in some patients**
 - 0.03-0.14 mg/kg/d
- **Goiter prevalence of at least 20%**
 - 0.07-0.13 mg/kg/d (adequate iodine)
 - ≥ 0.01 mg/kg/d (iodine deficiency)
- **Altered concentrations of T4 and T3**
 - 0.05-0.1 mg/kg/d (adequate iodine)
 - 0.03 mg/kg/d (iodine deficiency)
- **Elevated concentrations of TSH**
 - 0.05-0.1 mg/kg/d (adequate iodine)
 - 0.03 mg/kg/d (iodine deficiency)

Goiter prevalence in South African towns



Jooste et
al.
1999

Measurements of thyroid hormones for groups with different fluoride exposures

| Study | Water fluoride (mg/L) | Urine fluoride (mg/L) | Iodine status | T4 ($\mu\text{g/dL}$) | T3 (ng/dL) | TSH (mU/L) |
|------------------------|-----------------------|-----------------------|---------------|-------------------------|--------------|---------------|
| Baum et al. 1981 | 0.1-0.2 | NA | NA | 8.2 ± 0.4 | 220 ± 10 | 1.9 ± 0.2 |
| | 3 | NA | NA | 8.2 ± 0.3 | 230 ± 10 | 2.1 ± 0.2 |
| Bachinskii et al. 1985 | 1.0 ± 0.1 | 1.5 ± 0.2 | NA | 7.5 ± 0.62 | 180 ± 20 | 2.4 ± 0.2 |
| | 2.3 ± 0.1 | 2.5 ± 0.2 | NA | 7.3 ± 0.47 | 130 ± 13 | 4.3 ± 0.6 |
| Lin et al. 1991 | 0.34 | 1.34-1.61 | low | 10-11 | 186-200 | 11-16 |
| | 0.88 | 2.56 | low | 9 | 169 | 21 |
| | NA | NA | adequate | 12 | 199 | 6 |

Thyroid effects of fluoride: Possible mechanisms

- **Decreased production of thyroid hormone**
- **Effects on thyroid transport in blood**
- **Effects on peripheral conversion of T4 to T3 and on normal deiodination**
 - **inhibition of deiodinases**

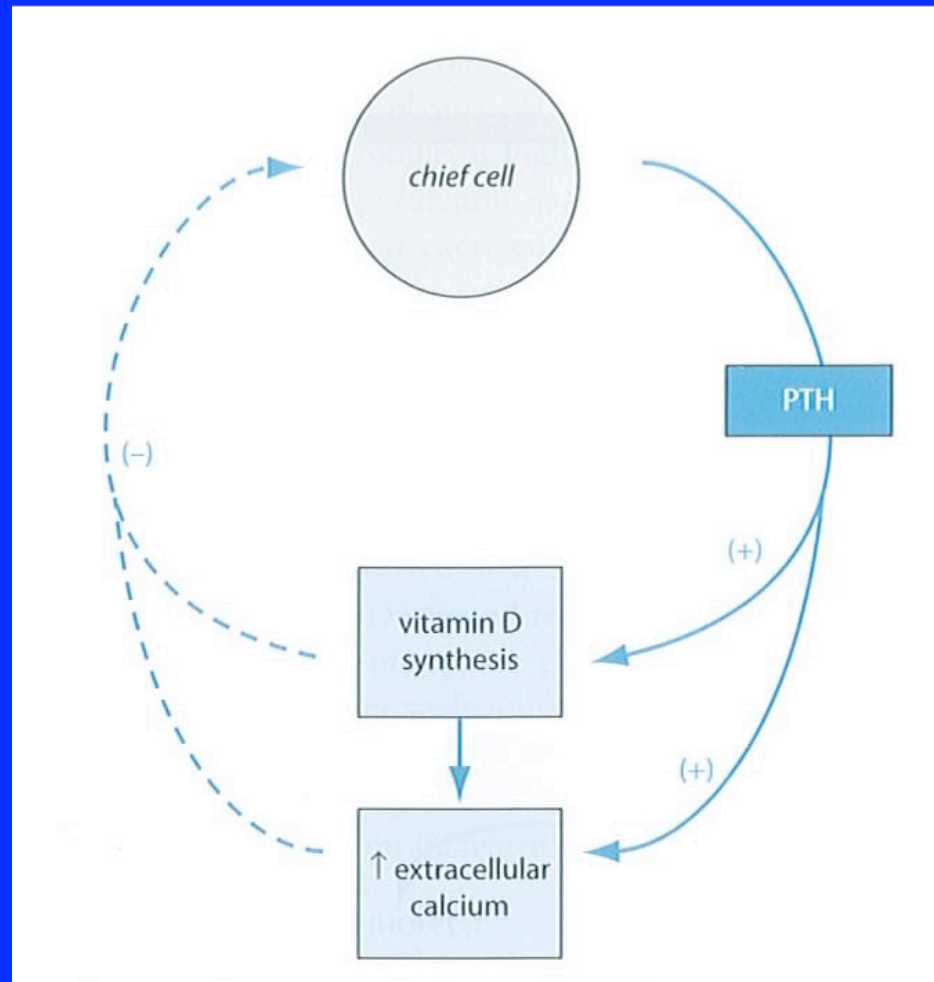
Thyroid effects of fluoride: Possible implications

- **Possible increase in symptomatic individuals?**
- **Increased risks associated with subclinical (asymptomatic) thyroid disease**
 - **Cardiac disease**
 - **Increased cholesterol concentrations**
 - **Increased incidence of depression**
 - **Diminished response to standard psychiatric treatment**
 - **Cognitive dysfunction**
 - **For pregnant women, decreased IQ of offspring**

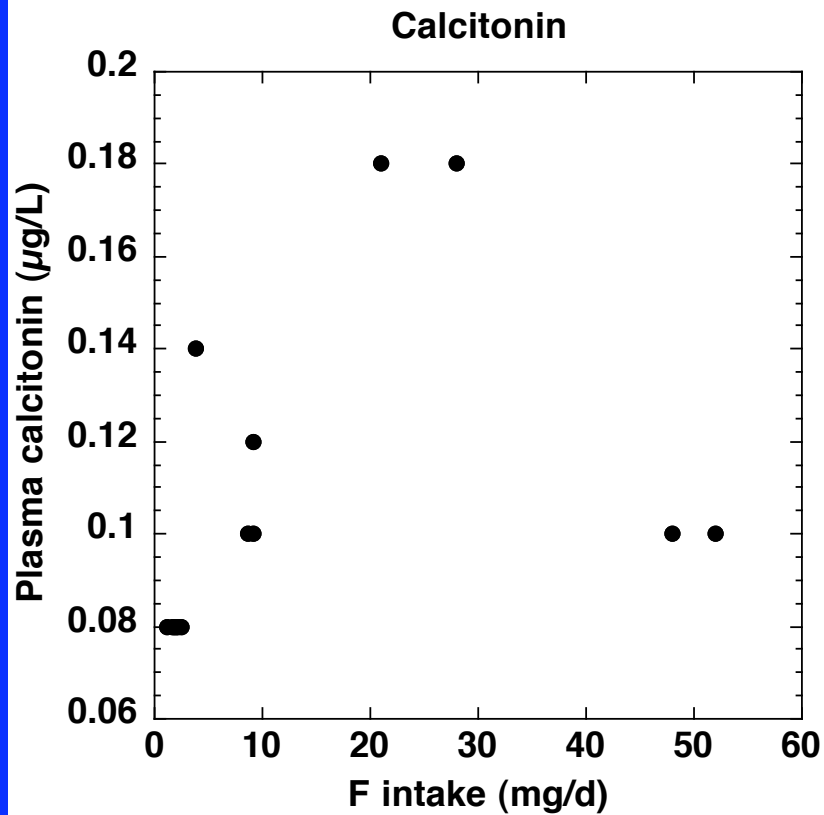
Calcium Metabolism

- **Parathyroid gland**
 - **Parathyroid hormone**
 - **Increases calcium concentrations in the blood**
 - **Stimulates bone resorption**
- **Thyroid parafollicular cells (C cells)**
 - **Calcitonin**
 - **Lowers calcium concentrations in the blood**
 - **Inhibits bone resorption**

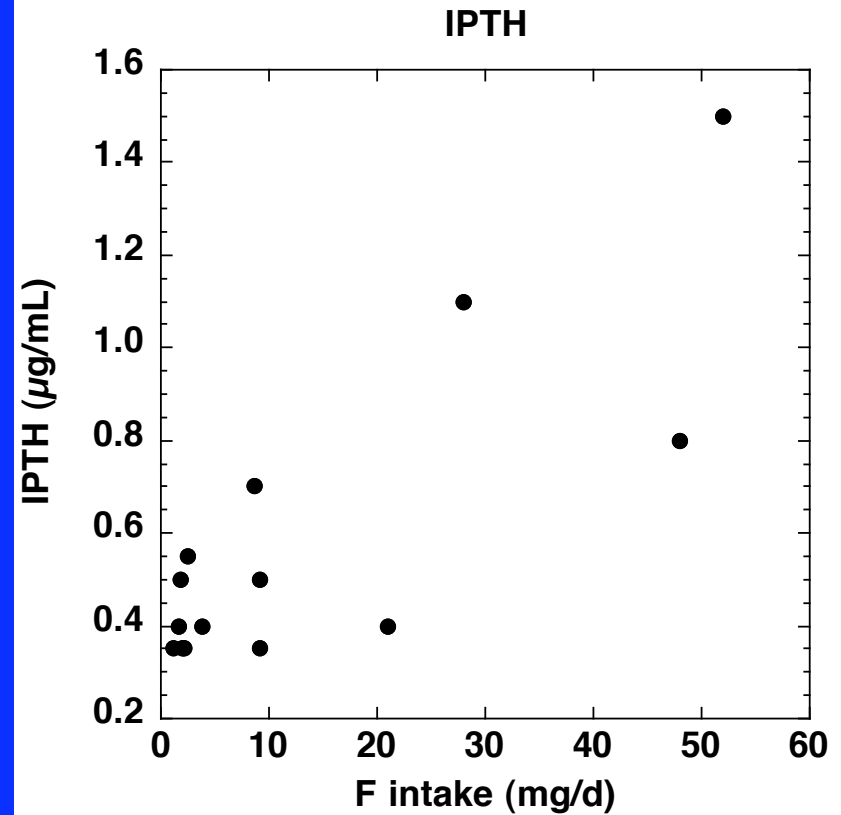
Parathyroid function



Elevated calcitonin in 8 of 9 skeletal fluorosis patients



Elevated PTH in 4 of 9 skeletal fluorosis patients



Teotia et al. 1978

Fluoride effects on thyroid parafollicular cell function

- **Animal studies**
 - Almost no information
- **Human studies**
 - Elevated calcitonin concentrations found in some but not all skeletal fluorosis patients
- **Significance of elevated calcitonin concentrations is not clear**

Fluoride effects on parathyroid function: Animal studies

- **Normal PTH response to dietary calcium deficiency was inhibited in one study**
 - 5.4 mg/kg/d
- **Some studies reported hypocalcemia but did not measure PTH**
 - 5-10 mg/kg/d
- **Several studies showed increased PTH activity**
 - 0.5-10 mg/kg/d

Fluoride effects on parathyroid function: Animal studies (continued)

- **Probable hypocalcemic response to fluoride, followed by increased PTH secretion in response to the hypocalcemia**
- **Changes in expression of genes associated with calcium uptake**
- **Effects dependent on calcium status**

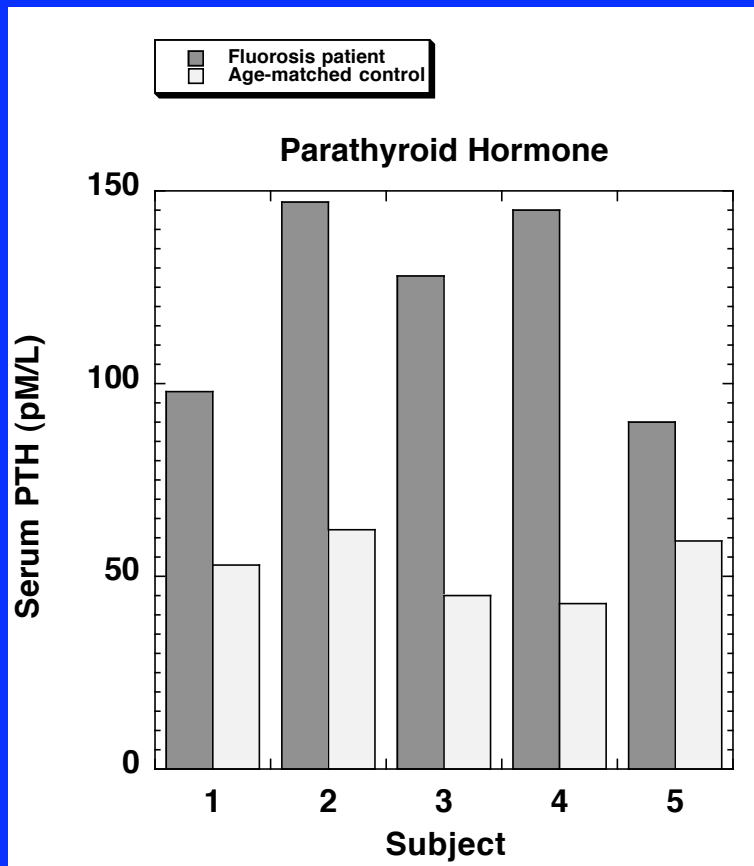
Fluoride effects on parathyroid function: Human studies

- **Elevated PTH concentrations in at least some individuals**
 - 0.4-0.6 mg/kg/d, occasionally as low as 0.15-0.34 mg/kg/d
- **Elevated PTH or clinical secondary hyperparathyroidism in skeletal fluorosis patients, usually with adequate dietary calcium**
 - Teotia and Teotia 1973; Teotia et al. 1978; Srivastava et al. 1989; Gupta et al. 2001
- **Hypocalcemia in 23% of children with high fluoride intake vs. 2-13% in comparable populations with low fluoride intake**
 - Pettifor et al. 1989

Fluoride effects on parathyroid function: Human studies (continued)

- **Hypocalcemia or decreased serum calcium in some individuals treated with fluoride for osteoporosis**
- **Elevated PTH in some individuals**
- **Variable response--at least two distinct sets of responses**
- **Inhibition of intestinal calcium absorption**
 - **Not explainable in terms of calcium fluoride complexes (reduced solubility)**
 - **Fluoride exposure appears to increase the calcium requirement**

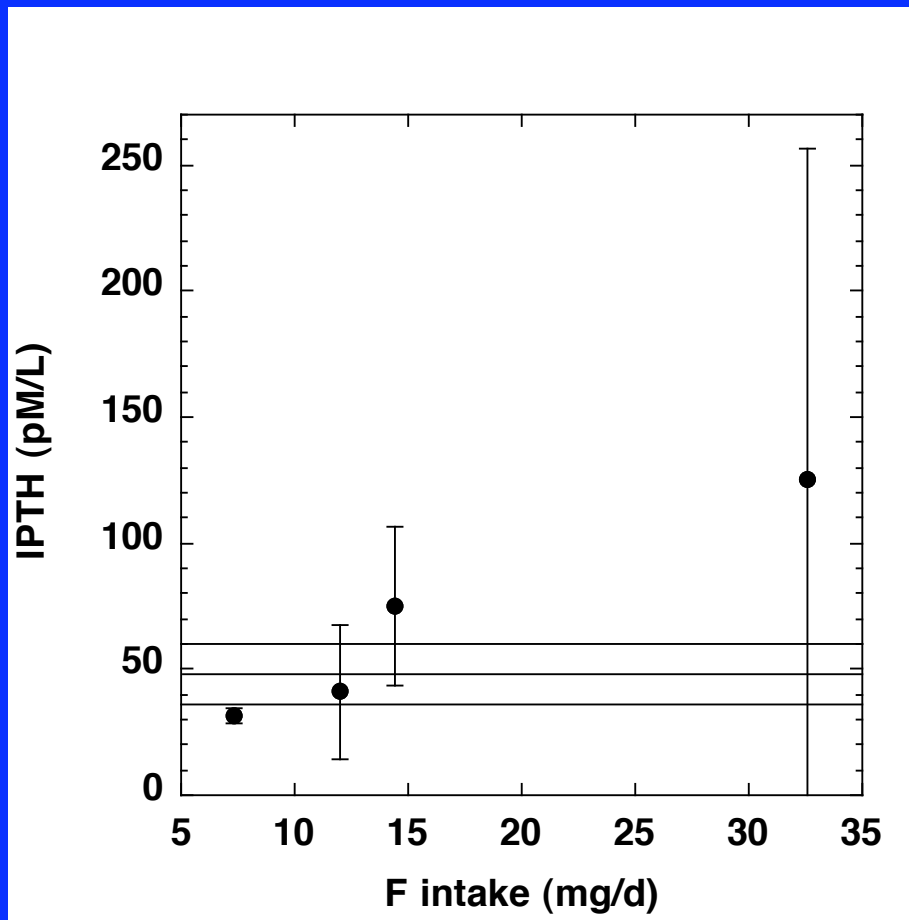
PTH concentrations in a family with skeletal fluorosis



- Fluoride intake between 16 and 49 mg/d
- Calcium concentrations low or normal
- Likely secondary hyperparathyroidism

Srivastava et al. 1989

PTH vs. fluoride intake



- Mean serum calcium concentrations within normal range for all groups
- Serum PTH correlated with fluoride intake and with severity of fluorosis

Gupta et al. 2001

Effects of fluoride on calcium metabolism: Possible mechanisms

- **Indirect action**
 - Net increase in bone formation
 - Net decrease in calcium absorption from GI tract
 - Overall increase in body's calcium requirement
 - If dietary calcium is inadequate, the response is an increase in PTH
- **Possible direct effects**
 - Stimulation or inhibition of the parathyroid gland
- **Specific changes in gene transcription**
 - For proteins associated with calcium uptake (Tiwari et al. 2004)

Fluoride effects on calcium metabolism: Possible implications

- **Secondary hyperparathyroidism (elevated PTH)**
 - **General response to any cause of hypocalcemia or vitamin D deficiency**
 - **The body's attempt to maintain calcium homeostasis**
 - **Clinical significance not clear for secondary hyperparathyroidism due to fluoride exposure**
 - **In general, secondary hyperparathyroidism may contribute to a number of degenerative diseases**

Fluoride effects on calcium metabolism: Possible implications (continued)

- **Calcium deficiency**
 - **May be induced or exacerbated by fluoride exposure**
 - **Calcium deficiency may contribute to other adverse health effects**
 - **Increased heavy metal toxicity**
 - **Development of nutritional (calcium-deficiency) rickets in children**

Normal pineal function

- **Melatonin production**
- **Pineal peptides**
- **Calcifying tissue**
 - Can accumulate fluoride
- **Associations with**
 - Status of the reproductive system
 - Regulation of circadian rhythms and sleep
 - Calcium and phosphorus metabolism, parathyroid activity, bone growth, development of postmenopausal osteoporosis
 - Oncostatic or anticarcinogenic effects
 - Antioxidant actions
 - Effects on central nervous system, psychiatric disease, sudden infant death syndrome

Fluoride effects on pineal function: Animal study (Luke 1997)

- **Decreased melatonin production in prepubescent gerbils**
 - Normal higher rate of melatonin production (relative to body weight) in sexually immature gerbils did not occur
- **Earlier sexual maturation in females**
- **Altered circadian rhythm of melatonin production**

Fluoride effects on pineal function: Human studies

- No direct studies
- Two studies of average age at menarche in girls
 - Lower average age at menarche
 - 12 years vs. 12 years, 5 months
 - Fluoride exposure had not been lifelong
 - Schlesinger et al. 1956
 - Postmenarcheal girls present at younger ages
 - No difference in median menarcheal age
 - Farkas et al. 1983

Fluoride effects on pineal function: Possible mechanisms and implications

- **Could cause decreased melatonin production**
- **Could contribute to a variety of effects in humans**
 - **Depending on age, sex, etc.**
- **Not enough information so far**

Glucose metabolism

- **Normal situation**
 - Insulin promotes uptake of glucose from the bloodstream
 - Glucagon acts to increase glucose in the bloodstream
 - **Pancreatic islets**
 - Alpha cells produce glucagon
 - Beta cells produce insulin

Effects of fluoride on glucose metabolism: Diabetic animals

- **Fluoride intake higher than in normal animals, due to increased water consumption**
- **Plasma and bone fluoride concentrations higher in diabetic animals due to increased fluoride intake**
- **Probable greater retention of fluoride in diabetic animals (reduced renal clearance)**
- **General severity of diabetes worse in fluoride-treated animals**

Effects of fluoride on glucose metabolism: Normal animals

- **Some studies report increased blood glucose, decreased insulin, impaired glucose tolerance**
- **Other studies report no differences in blood glucose concentrations, but other endpoints not reported**
- **Effects seen at plasma fluoride concentrations ≥ 0.1 mg/L**

Effects of fluoride on glucose metabolism: Human studies

- Impaired glucose tolerance in 40% of young adults with endemic fluorosis (Trivedi et al. 1993)
 - Fasting serum glucose concentrations related to serum fluoride concentrations
 - Impaired glucose tolerance reversed after 6 months with reduced fluoride intake
- Osteoporosis patients treated with fluoride (Jackson et al. 1994)
 - 3 of 25 individuals had fasting blood glucose values outside the normal range
 - vs. 1 of 38 untreated individuals
- Studies of “healthy” adults showed no differences between groups

Effects of fluoride on glucose metabolism: Possible mechanisms

- **Impaired glucose metabolism at plasma or serum fluoride concentrations ≥ 0.1 mg/L in animals and humans**
- **Inhibition of insulin secretion**
 - **Possible inhibition of prohormone convertases (enzyme that converts proinsulin to insulin prior to secretion of the insulin)**

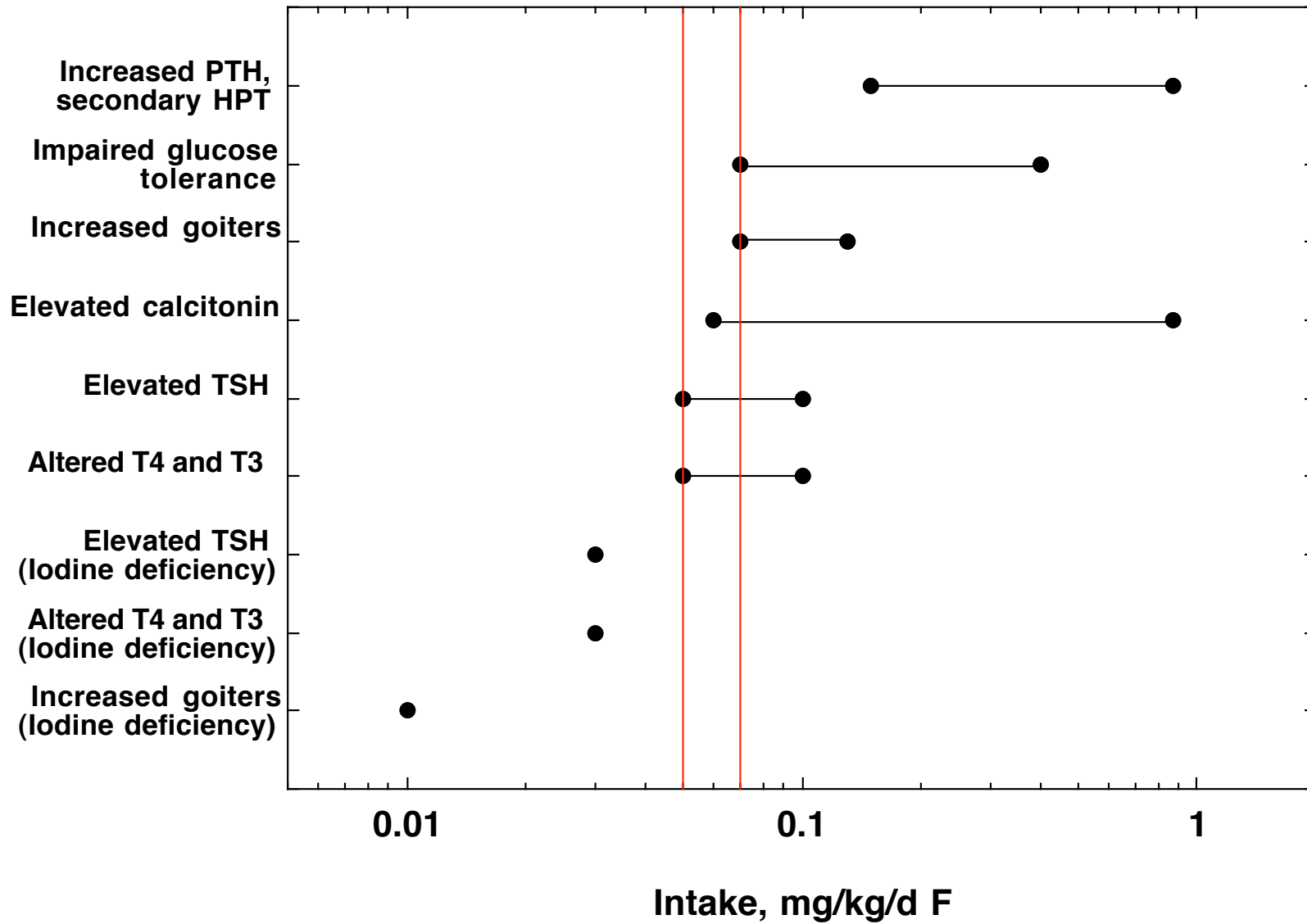
Effects of fluoride on glucose metabolism: Possible implications

- **Diabetic individuals may have higher fluoride intake and retention than normal individuals**
 - Increased water intake
 - Decreased renal clearance
- **Fluoride exposure may contribute to impaired glucose tolerance or increased blood glucose in some individuals**

Endocrine effects of fluoride exposure: Summary of effects

- **Elevated TSH with altered concentrations of T3 and T4**
- **Increased calcitonin activity**
- **Increased PTH activity**
- **Secondary hyperparathyroidism**
- **Impaired glucose tolerance**
- **Possible effects on timing of sexual maturity**

Summary of endocrine effects in humans



Endocrine effects of fluoride exposure: Difficulties in interpretation

- **Incomplete or inadequate exposure information**
 - Graph shows estimates of mean exposure for groups
 - Individual responses could occur at different exposures
 - Exposure groups often overlap
 - Measurements of serum and urine fluoride would be useful
- **Lack of nutritional information**
 - Iodine (“adequate” can vary)
 - Selenium (essential for deiodinase function)
 - Calcium (requirement appears to be increased)
 - General nutrition, especially protein
- **Other goitrogens not ruled out (thyroid effects)**

Endocrine effects of fluoride exposure: Difficulties in interpretation (continued)

- **Clinical status of study subjects not given**
 - Presence of clinical or subclinical disease
 - Percentage of individuals outside normal range for a given parameter
- **Measurement of hormone status**
 - Actual hormone concentrations not measured in some studies
 - Some studies report only the mean hormone concentration for the group
 - Additional information would be useful, e.g., number or percentage of individuals with values outside the normal range
- **Individual differences in susceptibility or response?**

Endocrine effects of fluoride exposure: Difficulties in interpretation (continued)

- **Most studies have not discussed the clinical significance for individuals**
- **Some studies have been limited to “healthy” individuals**
- **Adverse health effects or increased risk of adverse health effects may be associated with “borderline” hormonal imbalances**

Endocrine effects of fluoride exposure: Potential significance

- **4-5% of the US population may be affected by disorders of thyroid function**
- **6% of the US population has diabetes mellitus**
- **Iodine deficiency and calcium deficiency are increasing in the US**
- **Fluoride exposure ranges necessary for endocrine effects are reached by people in the US**