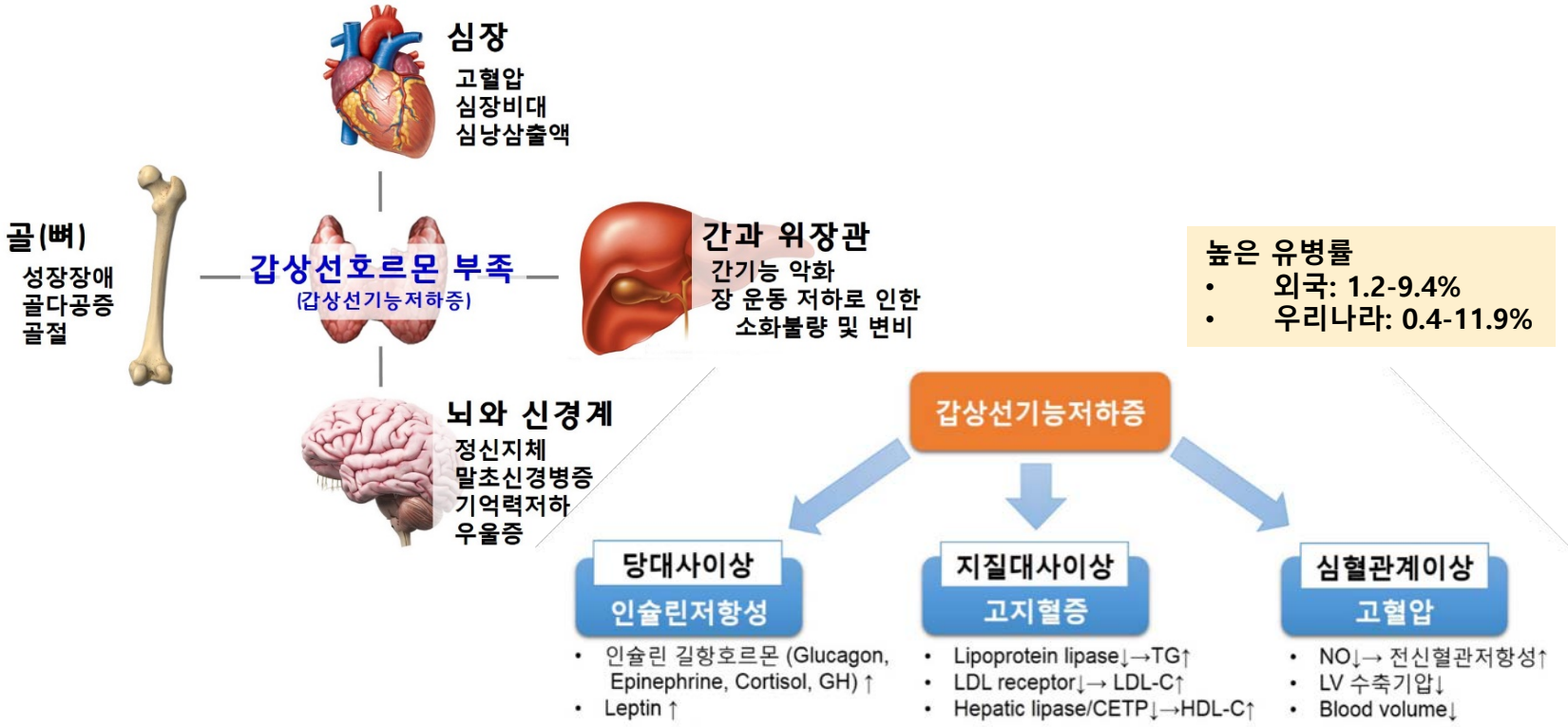
AOP기반의 IATA 개발과 규제적용 -갑상선 교란 물질 사례 연구

AOP-informed IATA Development for Regulatory Purposes: A Case Study on Thyroid Hormone Disruption

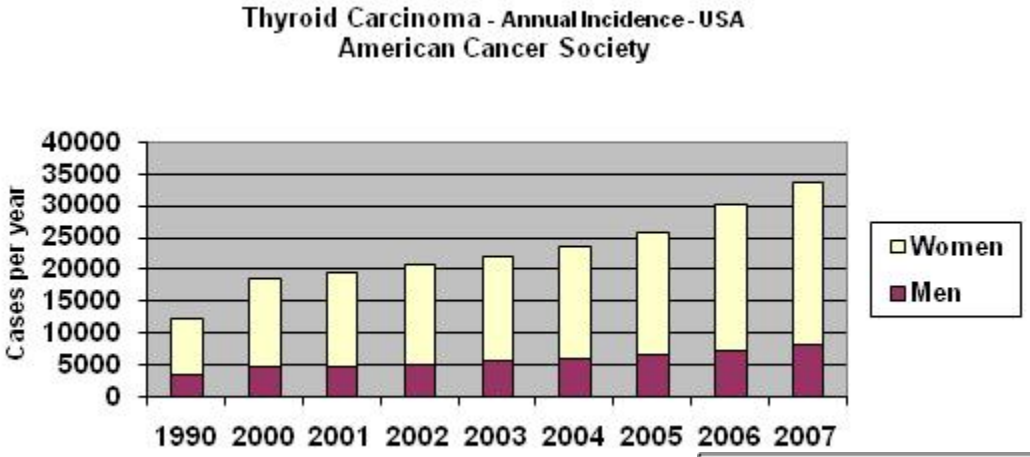
서울대학교 보건대학원 환경보건학과

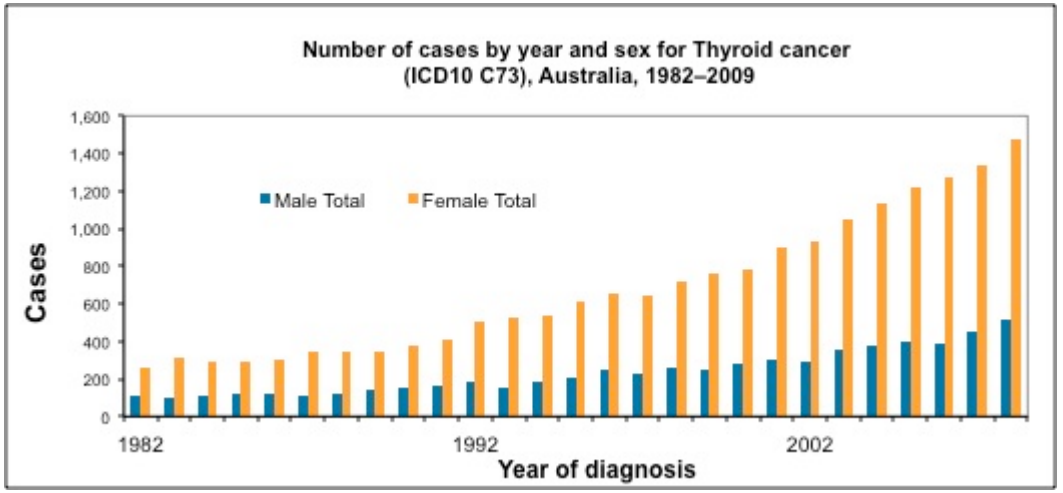
최경호

갑상선 호르몬의 중요성

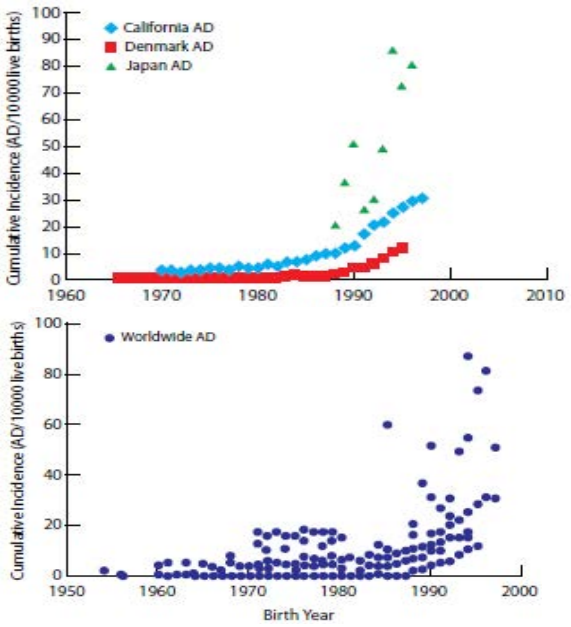

심장
고혈압
심장비대
심낭삼출액
골(뼈)
성장장애
골다공증
골절
갑상선호르몬 부족
(갑상선기능저하증)
간과 위장관
간기능 악화
장 운동 저하로 인한
소화불량 및 변비
뇌와 신경계
정신지체
말초신경병증
기억력저하
우울증
높은 유병률
• 외국: 1.2-9.4%
• 우리나라: 0.4-11.9%
갑상선기능저하증
당대사이상
인슐린저항성
• 인슐린 길항호르몬 (Glucagon, Epinephrine, Cortisol, GH) ↑
• Leptin ↑
지질대사이상
고지혈증
• Lipoprotein lipase↓→TG↑
• LDL receptor↓→ LDL-C↑
• Hepatic lipase/CETP↓→HDL-C↑
심혈관계이상
고혈압
• NO↓→ 전신혈관저항성↑
• LV 수축기압↓
• Blood volume↓

Thyroid disease

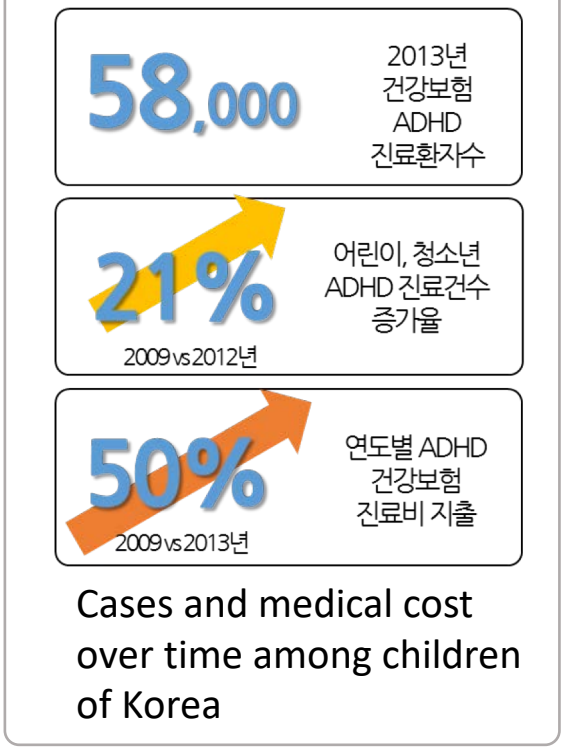




Neurodevelopmental diseases



Autism incidence by birth year

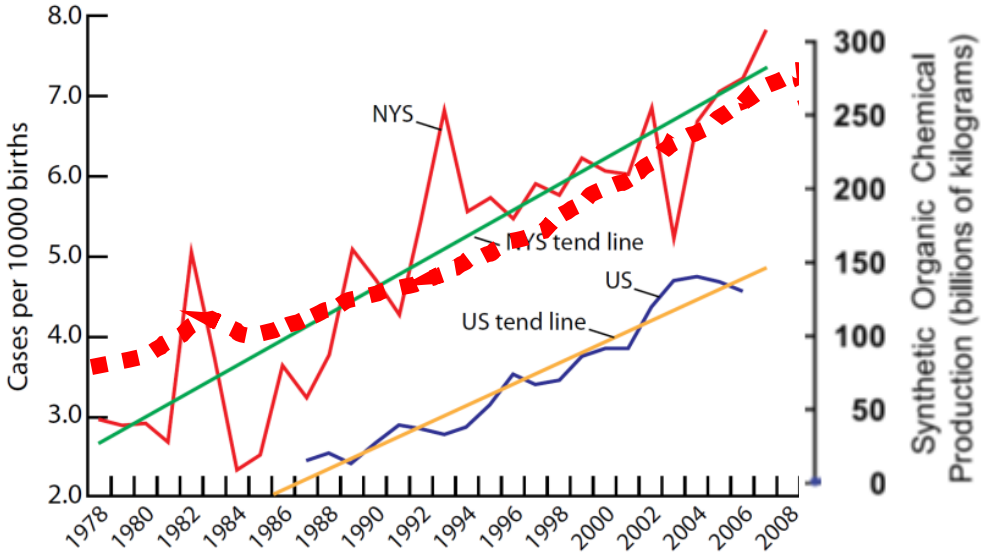


Cases and medical cost over time among children of Korea

Trend in childhood neuroendocrine diseases

Chemicals and thyroid disease

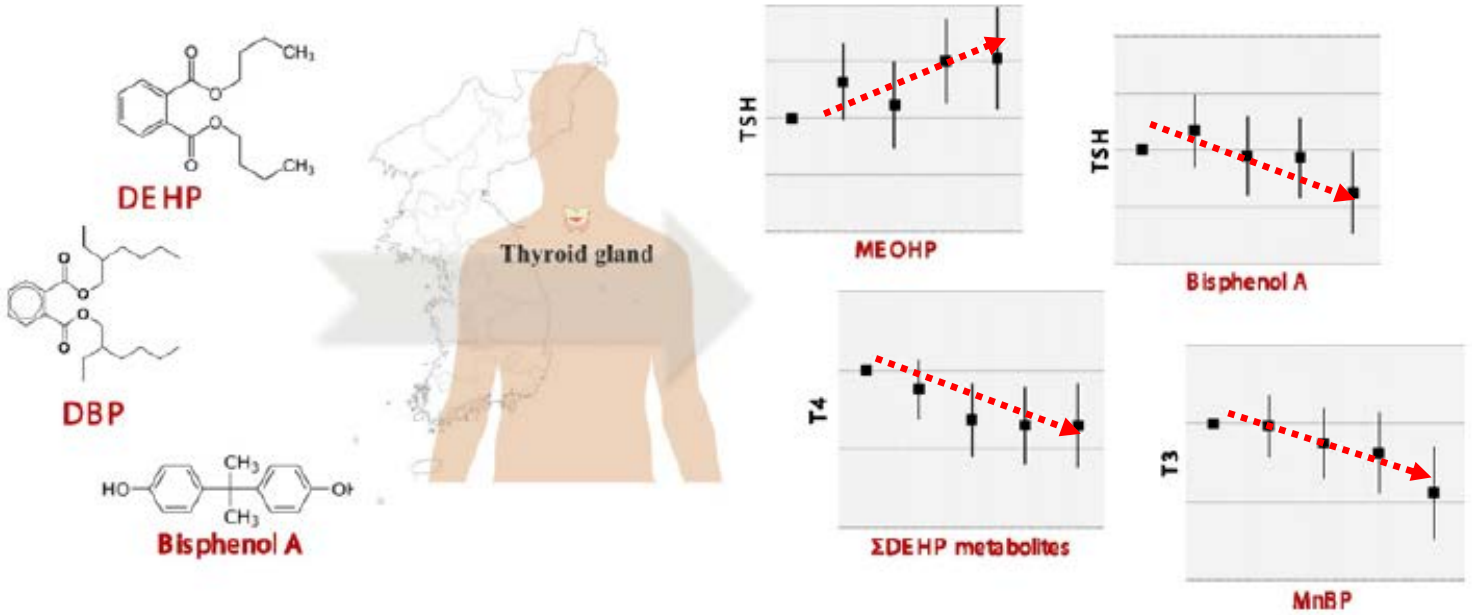
Congenital hypothyroidism in US



(Source on disease- WHO 2013; Source on chemical- Neel and Sargis, Diabetes 2011)

Bisphenol A and thyroid hormone

General adult population of Korea (n = 6003)

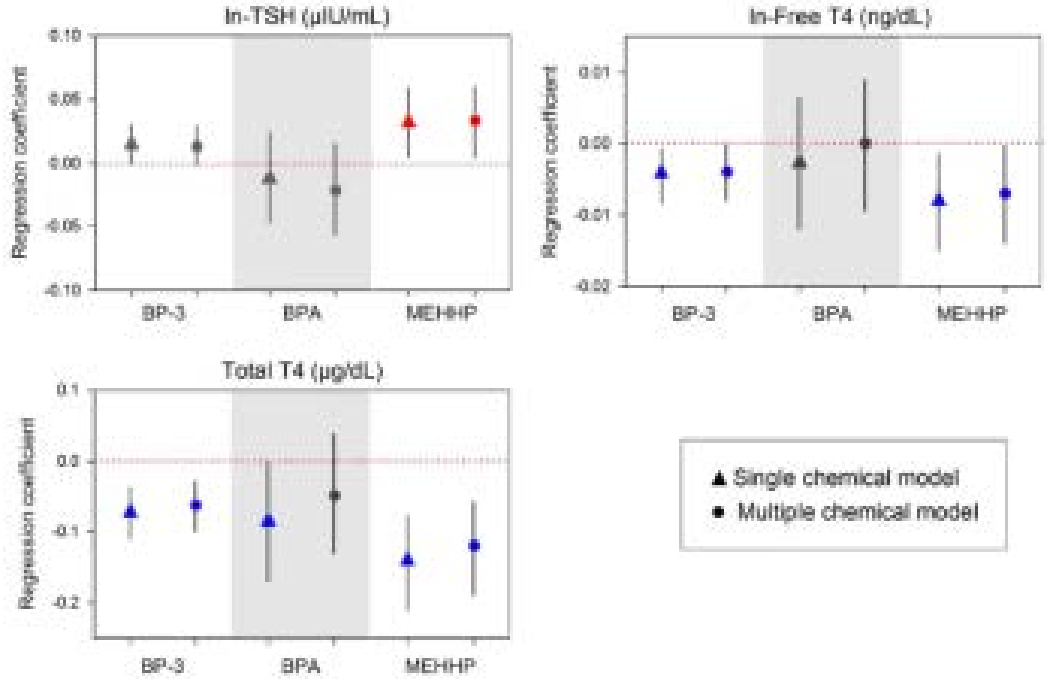


BPA, DEHP, and DBP are important determinants of THs of Korean adults

(Park CH et al., 2017, Sci Total Environ)

Benzophenone 3 and thyroid hormone

General population of US (age 12 year and older n = 1829)



DEHP, and BP-3 are important determinants of THs of US adults

(Kim SJ et al., 2017, Environ Int)

Major endocrine disrupting chemicals

- **식품 및 음료 포장**
  - 비스페놀류; 프탈레이트류; 벤조페논류
- **화장품, 개인위생용품**
  - 파라벤류; 트리클로산; 벤조페논류
- **소비자제품, 생활화학제품**
  - Brominated and phosphorylated flame retardants; 프탈레이트류; Perfluoroalkyl substances (PFASs)
- **살생물제**
  - Organophosphate pesticides; Triazoles and other fungicides; Pyrethroids ; Neonicotinoids

Major EDCs are thyroid disruptors

Molecular and Cellular Endocrinology 355 (2012) 240–248

Contents lists available at SciVerse ScienceDirect

Molecular and Cellular Endocrinology

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

Review

Thyroid effects of endocrine disrupting chemicals

Malene Boas [a,*], Ulla Feldt-Rasmussen [b], Katharina M. Main [a]

[a] Department of Growth and Reproduction GR, Rigshospitalet, University of Copenhagen, Denmark
[b] Department of Medical Endocrinology PE, Rigshospitalet, University of Copenhagen, Denmark

ARTICLE INFO

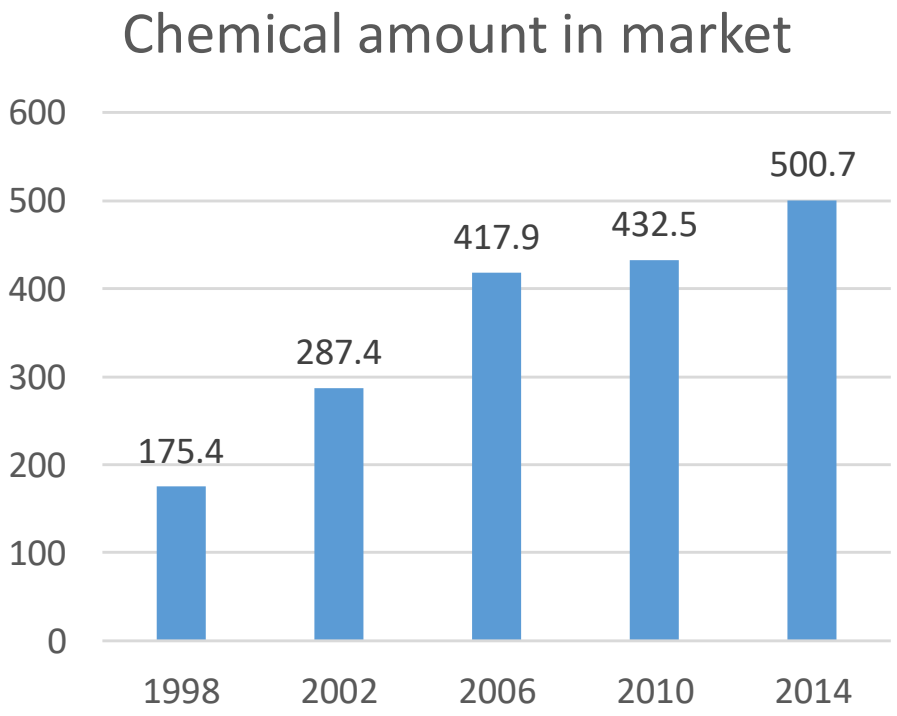
Article history:
Available online 10 September 2011

Keywords:
Thyroid
Thyroxine
Endocrine disrupters
EDC
Chemicals

ABSTRACT

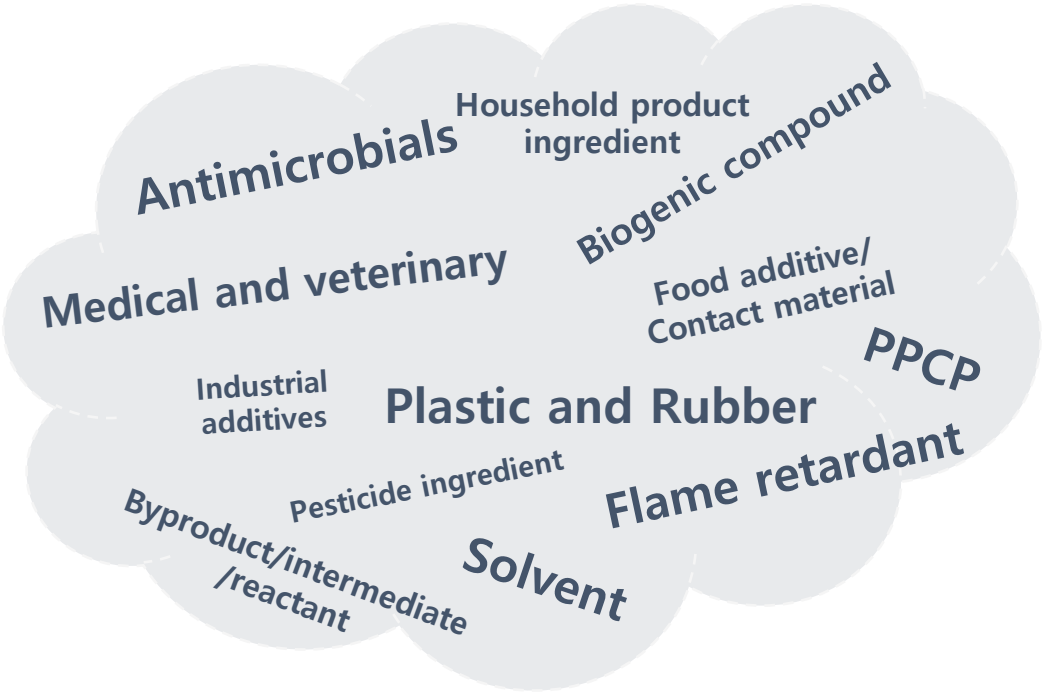
In recent years, many studies of thyroid-disrupting effects of environmental chemicals have been published. Of special concern is the exposure of pregnant women and infants, as thyroid disruption of the developing organism may have deleterious effects on neurological outcome. Chemicals may exert thyroid effects through a variety of mechanisms of action, and some animal experiments and in vitro studies have focused on elucidating the mode of action of specific chemical compounds. Long-term human studies on effects of environmental chemicals on thyroid related outcomes such as growth and development are still lacking. The human exposure scenario with life long exposure to a vast mixture of chemicals in low doses and the large physiological variation in thyroid hormone levels between individuals render human studies very difficult. However, there is now reasonably firm evidence that PCBs have thyroid-disrupting

Chemicals are increasing (Korea)



(Source: National Health Insurance Service DB; Ministry of Environment)

Potential EDCs are growing



INSIGHTS

Immune therapies for sepsis *p. 1201*

Meeting demand for rare earth minerals *p. 1209*

PERSPECTIVES

CHEMISTRY

Toward substitution with no regrets

Advances in chemical design are needed to create safe alternatives to harmful chemicals

By **Julie B. Zimmerman** *and* **Paul T. Anastas**

Vast numbers of synthetic chemicals are used in everyday consumer products. Many are safe, but some can have unintended biological or environmental effects. For example, phthalates are widely used to increase the flexibility of plastics but also disrupt hormonal balance (*1*). Organophosphates are highly effective insect repellents but cause severe neurotoxicity to mammals (*2*). In many cases, chemicals of concern have been replaced by other chemicals that are functionally equivalent and believed to be of less concern (see the photo). However, the need for expedient substitution can lead to the use of chemicals that are no less harmful than those they replace. How can such "regrettable substitutions" be avoided?

There have been many examples of regrettable substitution over the years. The example gaining most attention recently is the substitution of bisphenol S (BPS) for bisphenol A (BPA) (see the figure, panel A). BPA is widely used to make clear and rough plastics, used in water bottles, sports equipment, and CDs and DVDs; it is also used in food and beverage can coatings (where it helps to protect food from contamination and spoilage)

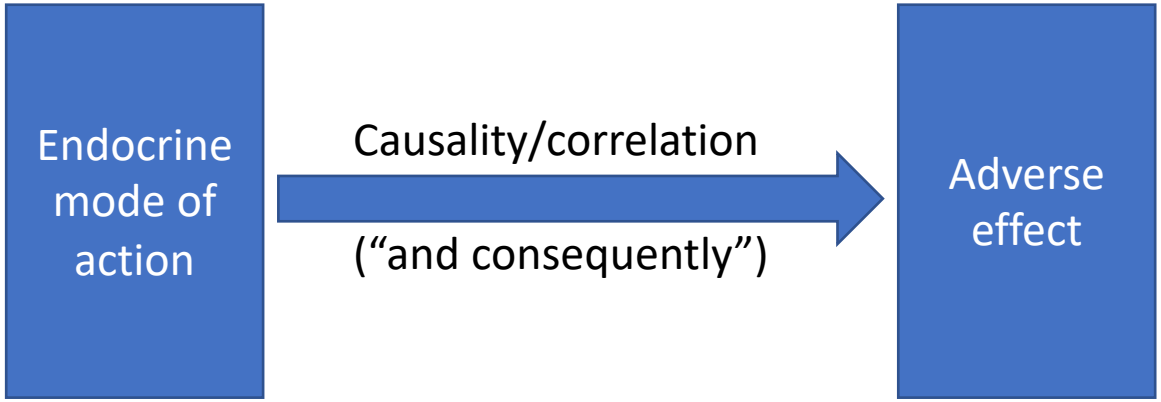
Replacement troubles. In many plastic baby bottles, bisphenol A (BPA) has been replaced with bisphenol S (BPS), but the latter compound may also have adverse health effects.

Published by AAAS

Science 2015

Lack of test methods

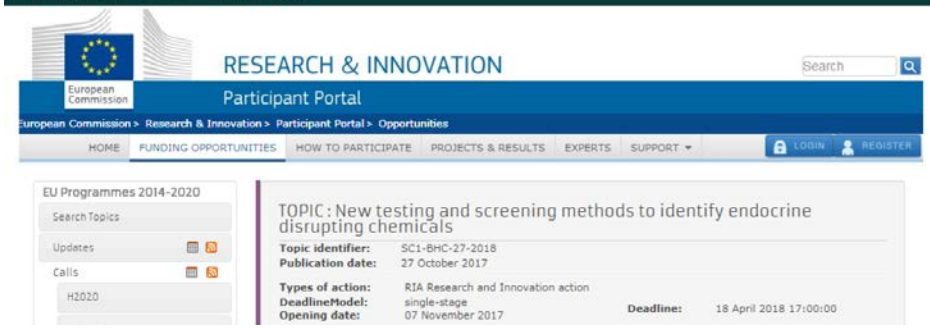
- Thyroid axis
- Developmental neurotoxicity
- Metabolic disorders
- Female reproduction
- Non-genotoxic carcinogenicity



Regulation of the Plant Protection Products (EC1107/2009)
Regulation of Biocidal Products (EU 528/2012)

European development

Horizon 2020 Call 4-6 million € per project/52 million € total



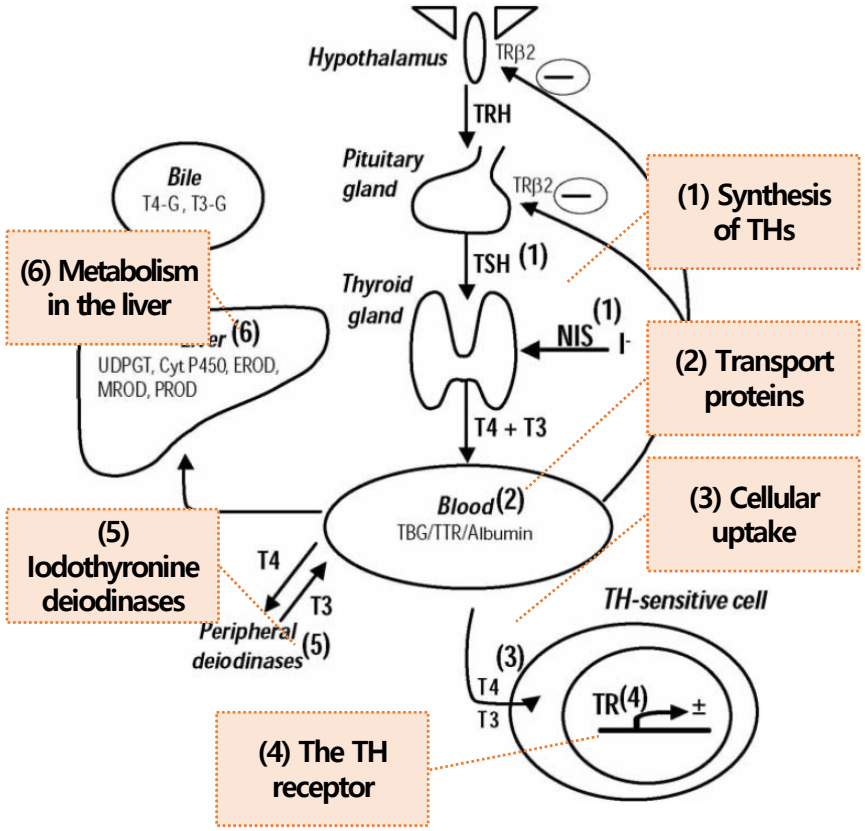
Focus of RFP

- Thyroid axis
- Developmental neurotoxicity
- Metabolic disorders
- Female reproduction
- Non-genotoxic carcinogenicity

Acronym, title	Focus
ATHENA Assays for the identification of thyroid hormone axis-disrupting chemicals: elaborating novel assessment strategies Andreas Kortenkamp, UK (10 partners)	Thyroid hormone disruption athena
ERGO Breaking down the wall between human health and environmental testing of endocrine disrupters: endocrine guideline optimisation Henrik Holbech, DK (15 partners)	Thyroid hormone disruption ERGO
SCREENED A multistage model of thyroid gland function for screening endocrine-disrupting chemicals in a biologically sex-specific manner Lorenzo Moroni, NL (9 partners)	*In vitro* assays, thyroid disruption SCREENED

Thyroid hormone regulation is complex

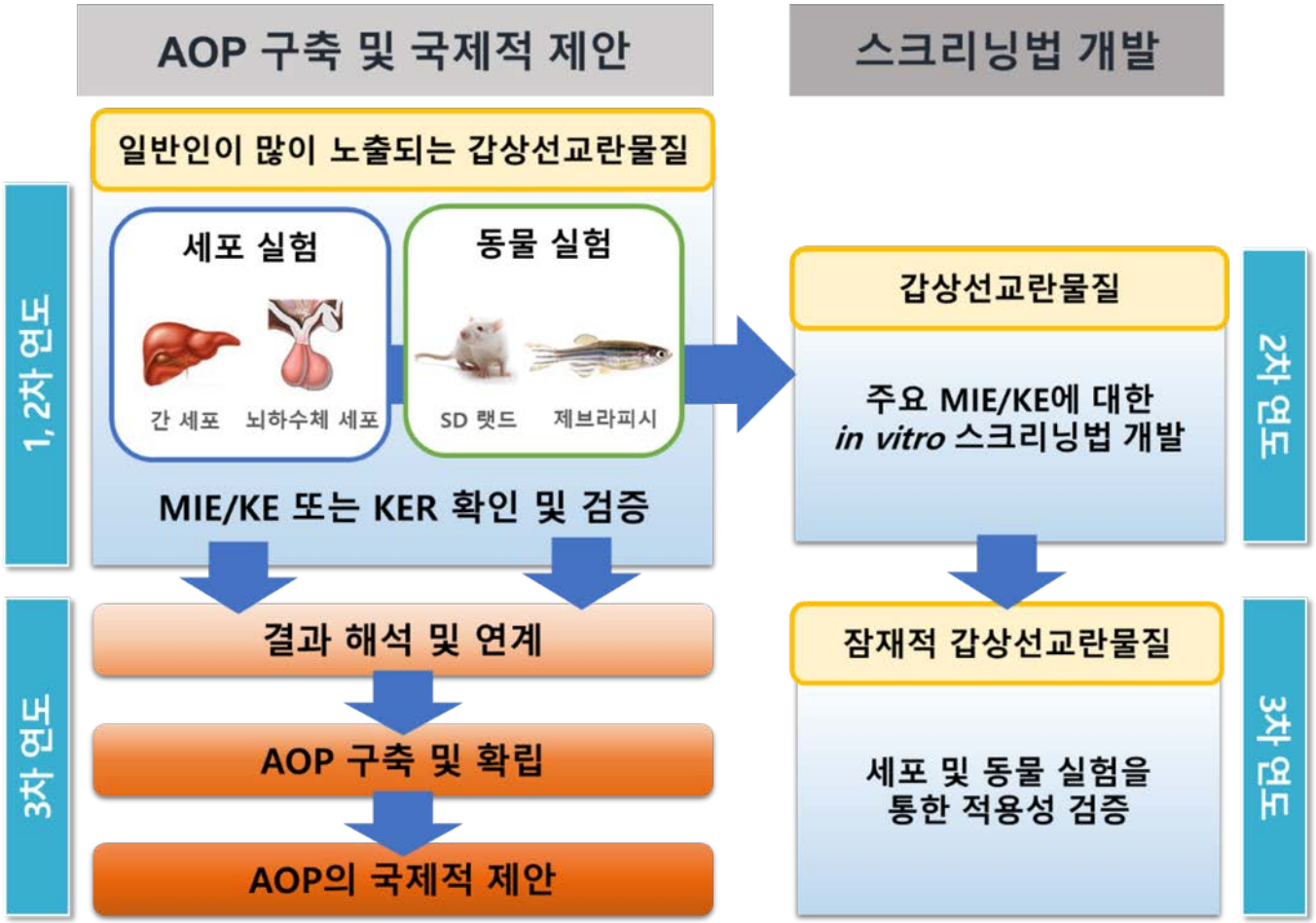
- **Persistent organic pollutant의 예**



(Lyn et al., 2009; Boas et al., 2012)

화학물질	기전	교란 영향	
DDT, PCBs	Inhibiting TSH receptor	Decreased production of T3 and T4	(1)
PCBs, Flame retardants	Competitive binding to thyroid transport protein (TTR)	Possible effect on fetal brain T4 production	(2)
PBDEs, Chlordane	Altering transport across cell membrane	Increased billiary elimination of T3 and T4	(3)
PCBs, HCB, Flame retardants	Altering binding to thyroid receptor	Altered thyroid hormone directed gene transcription	(4)
PCBs	Inhibition of sulfation	Decreased sulfation of thyroid hormones leading to possible decrease of peripheral T3 synthesis	(5)
PCBs	Inhibition of deiodinase activity	Decreased peripheral T3 synthesis	(5)
PCBs	Enhanced hepatic metabolism	Increased billiary metabolism of T3 and T4	(6)

Developing thyroid disruption AOP



식약처 2018-2020

Combined *in vitro* and *in vivo* methods

in vitro cell lines

Pituitary gland
GH3 cell (Rat)
Central regulation

TSH

Thyroid gland
FRTL-5 cell (Rat)
Thyroid hormone
Synthesis/Regulation

T3, T4

- Gene analysis

in vivo organism

Zebrafish embryo/larva

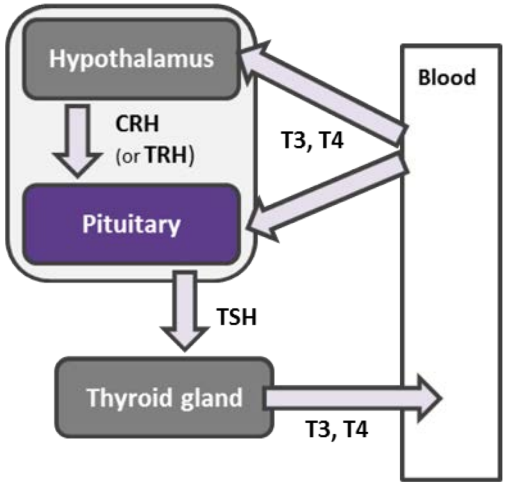
0 hpf embryo → **48-72 hpf** → **120 hpf larva**

(hpf, hours post-fertilization)

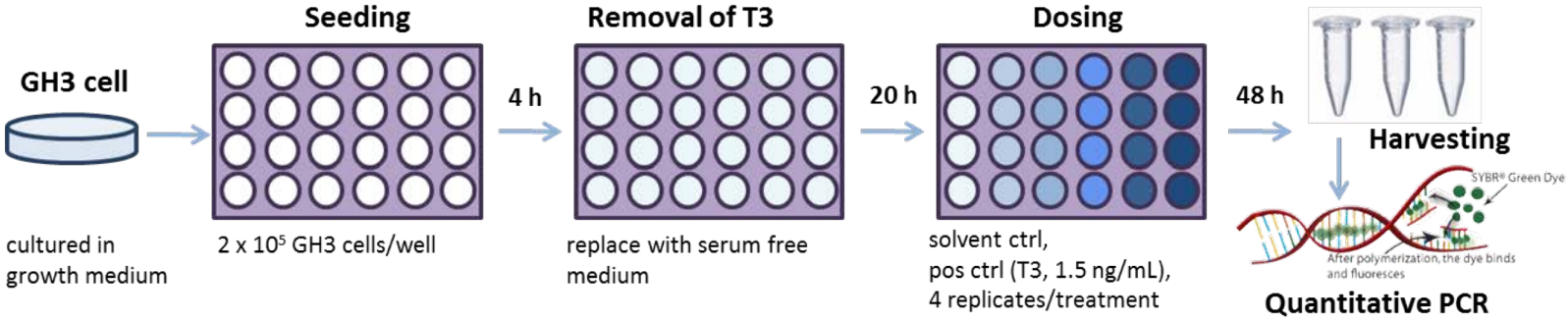
- Phenotypic changes eg, developmental toxicity
- Hormone and gene analysis

GH3 cell

- **GH3 cell (rat pituitary tumor cell)**
  - T-screen : commonly used screening assay for thyroid disrupting compounds (proliferation)



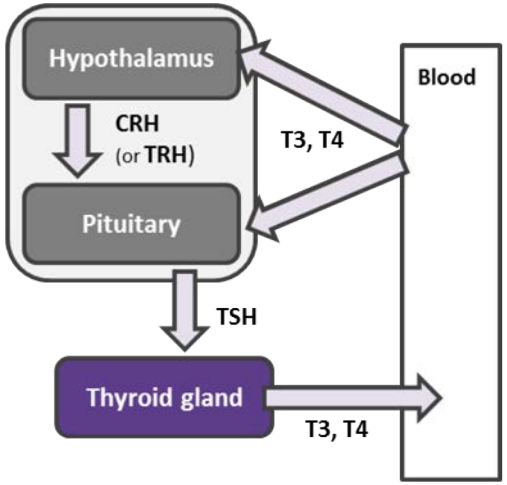
- **Chemical exposure (48 h)**



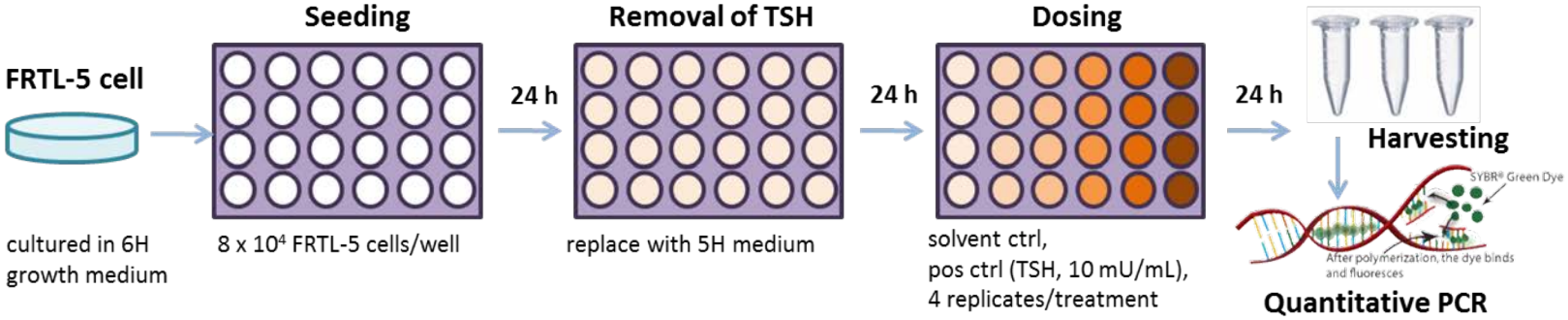
- **Central regulation**
  - *tshβ, trα , trβ, dio1 , dio2* gene expression

FRTL-5 cell

- **FRTL-5 cell (rat thyroid follicular cell)**



- **Chemical exposure (24 h)**



- **Thyroid hormone synthesis/regulation**
  - *nis, tg, tpo, tshr, pax8, nkx2.1* gene expression

Fish

- **Thyroid hormone disruption to measure**

1) 배아

OECD TG 236: Fish embryo acute toxicity (FET) test

- 갑상선 호르몬(T3, T4)
- 유전자 발현(RT-qPCR)
  - 갑상선 기전과 관련된 유전자

2) 성어

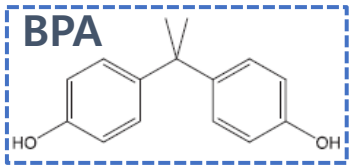
OECD TG 229: Fish short term reproduction assay

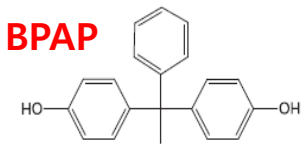
- 갑상선 호르몬(T3, T4)
- 유전자 발현(RT-qPCR)
  - 갑상선 기전과 관련된 유전자

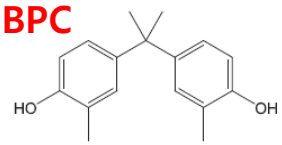
(필요시 성체 21 d 노출)

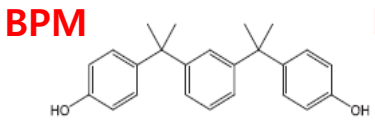
BPA and its analogues

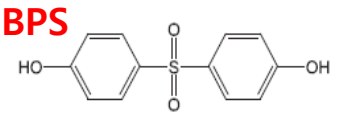
Chemicals substituting BPA

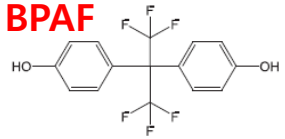


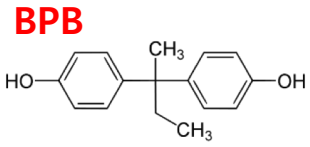


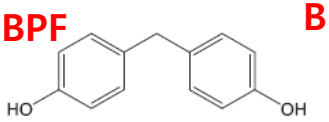


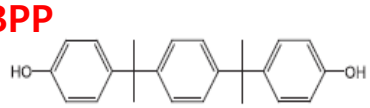


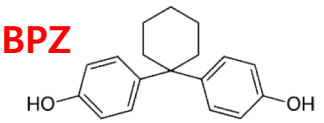




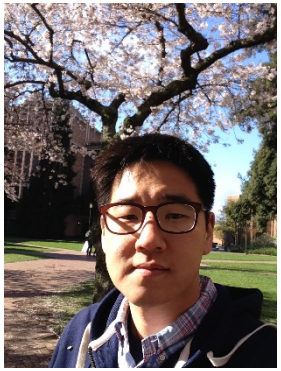




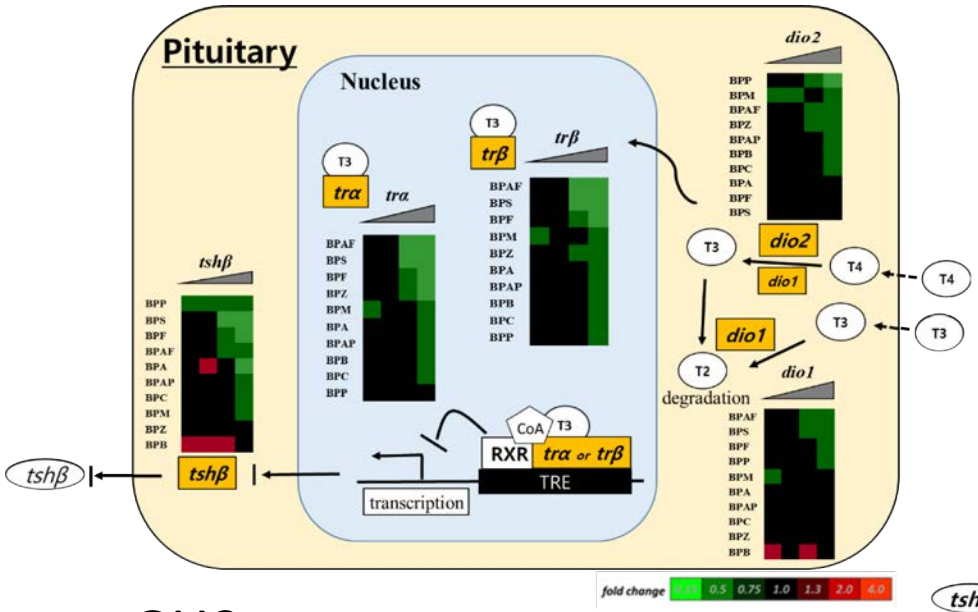




Bisphenols alter brain and thyroid

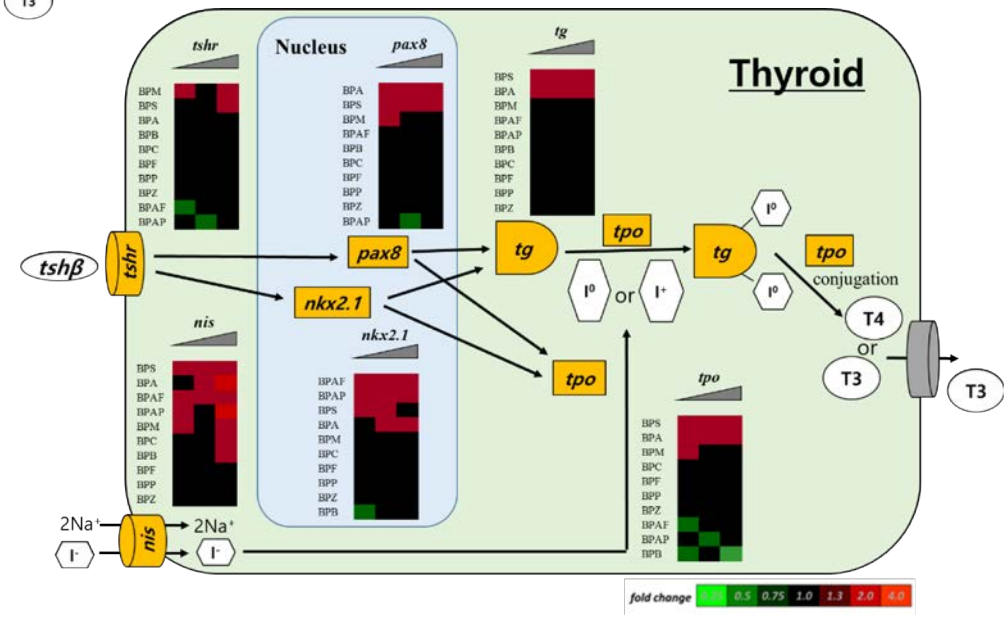


이상우



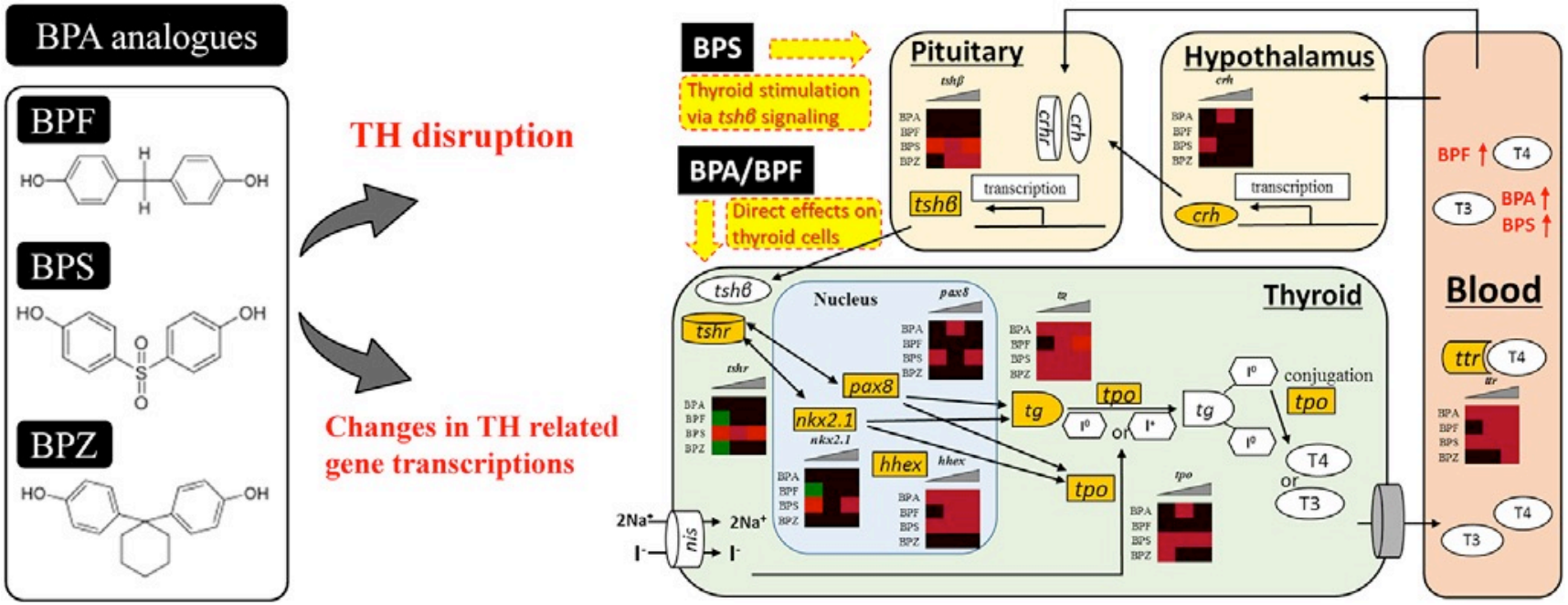
GH3

FRTL-5



(Lee SW et al., 2017. Toxicol In Vitro)

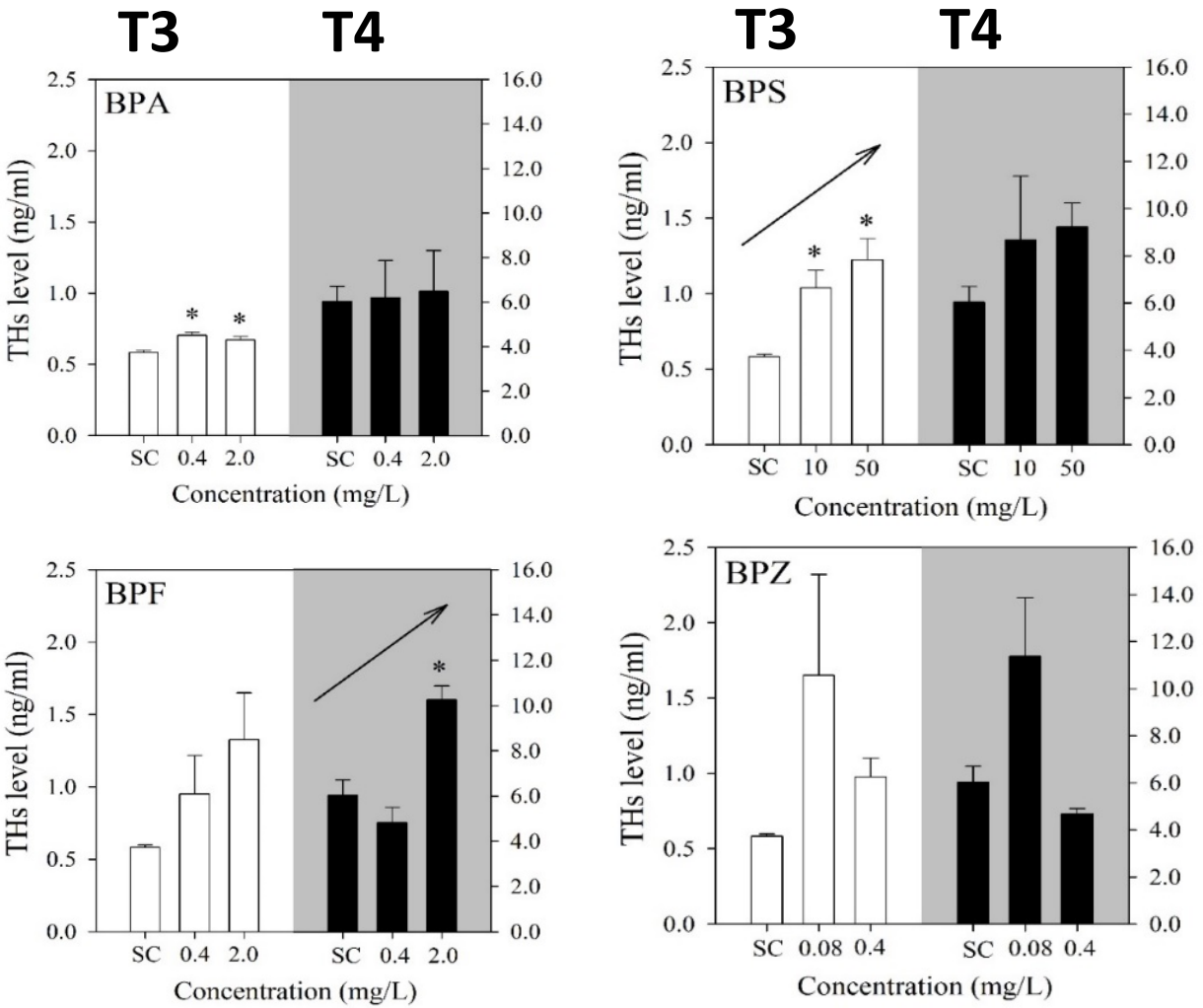
Bisphenols alter central regulation and synthesis of thyroid hormone (Fish)



Zebrafish larva

(Lee SW et al., 2019. Chemosphere)

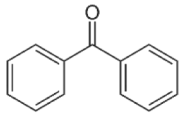
Bisphenols increase thyroid hormones



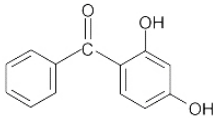
(Lee SW et al., 2017. Toxicol In Vitro)

Benzophenone-3 and its analogues

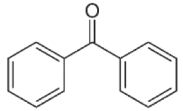
Plastic packaging



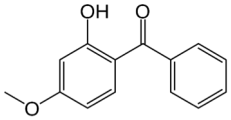
Benzophenone



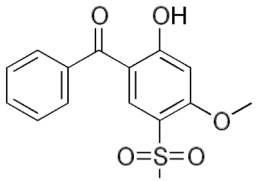
Benzophenone-1



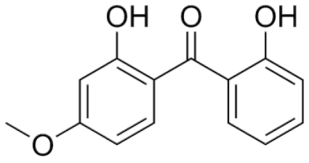
Benzophenone-2



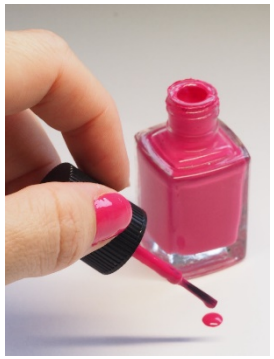
Benzophenone-3



Benzophenone-4



Benzophenone-8



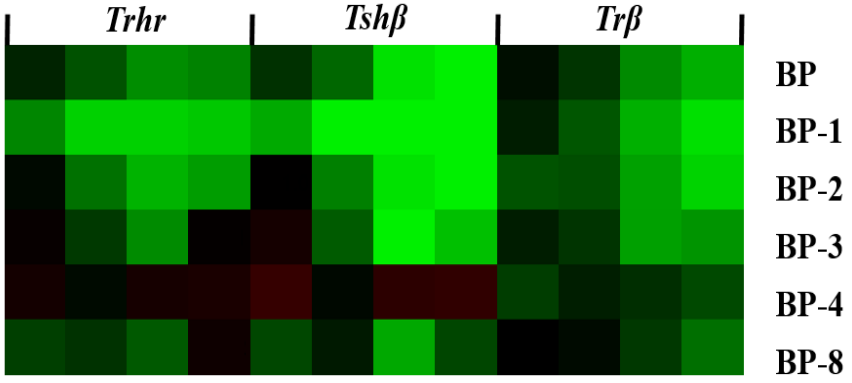
Nail polish

lotions

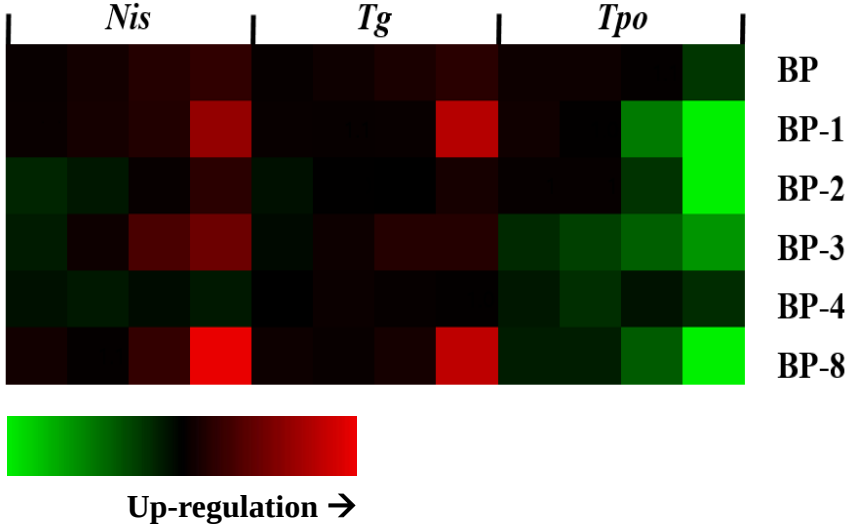
Benzophenones alter brain and thyroid

이정은

Rat Pituitary GH3 cells

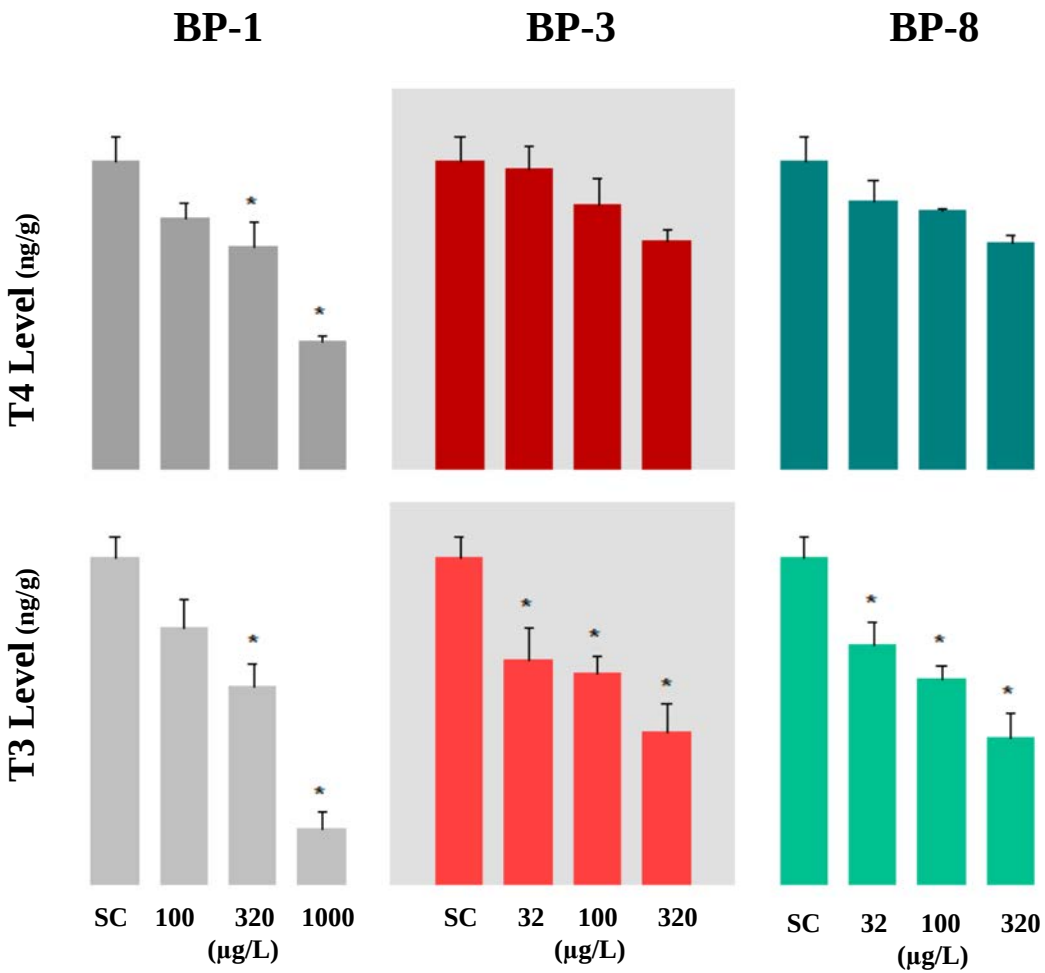


Rat Thyroid Follicular FRTL-5 cells



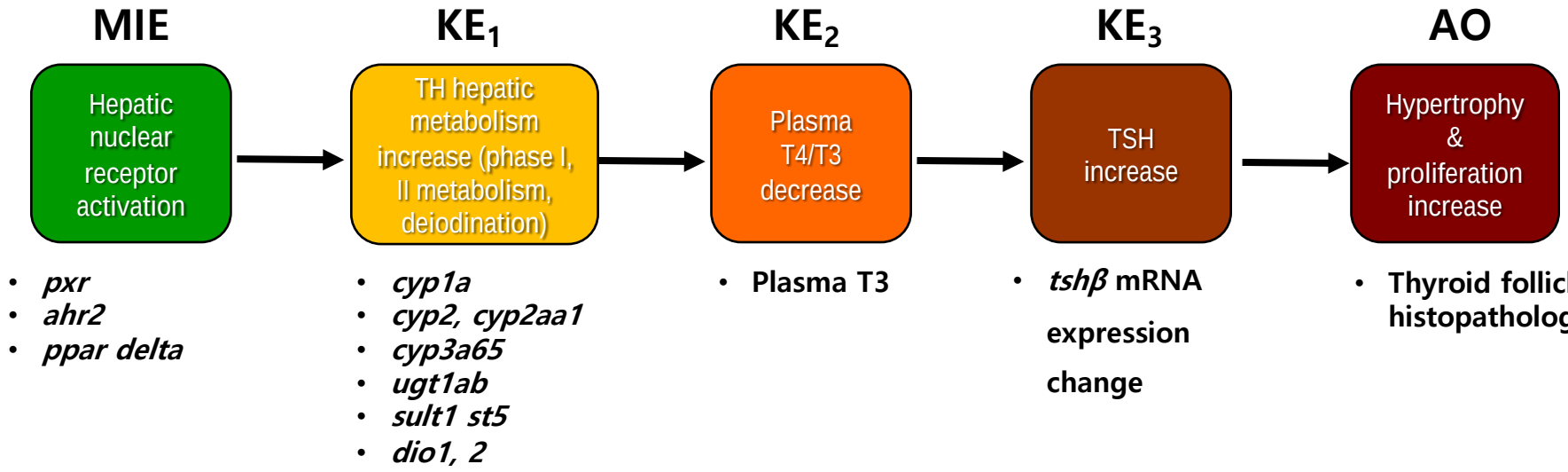
(Lee JE et al., 2018 Environ Sci Technol)

Benzophenones disrupt thyroid hormone (Fish)



(Lee JE et al., 2018 Environ Sci Technol)

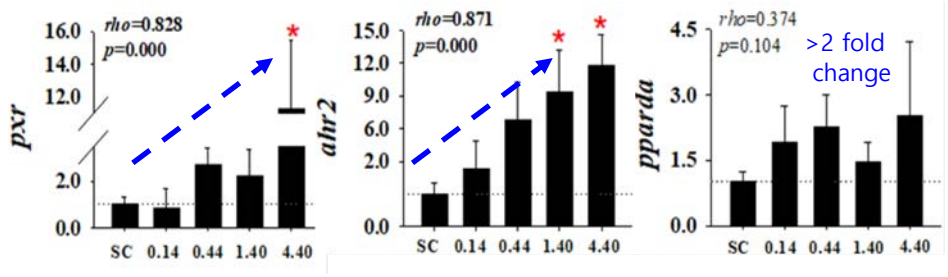
One AOP for thyroid disruption



BP-3 caused hepatic nuclear receptor activation leading to thyroid status change

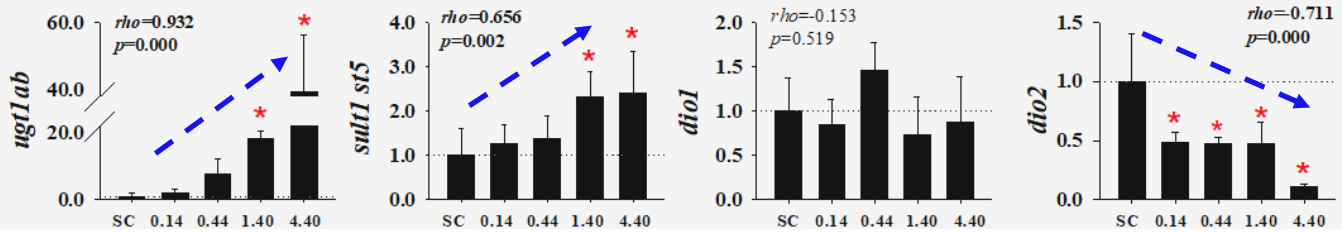
Hepatic nuclear receptor activation

MIE



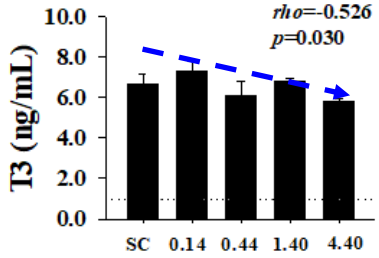
TH hepatic metabolism increase (phase I, II metabolism, deiodination)

KE_1



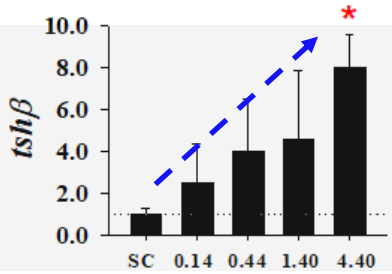
Plasma T4/T3 decrease

KE_2



TSH increase

KE_3

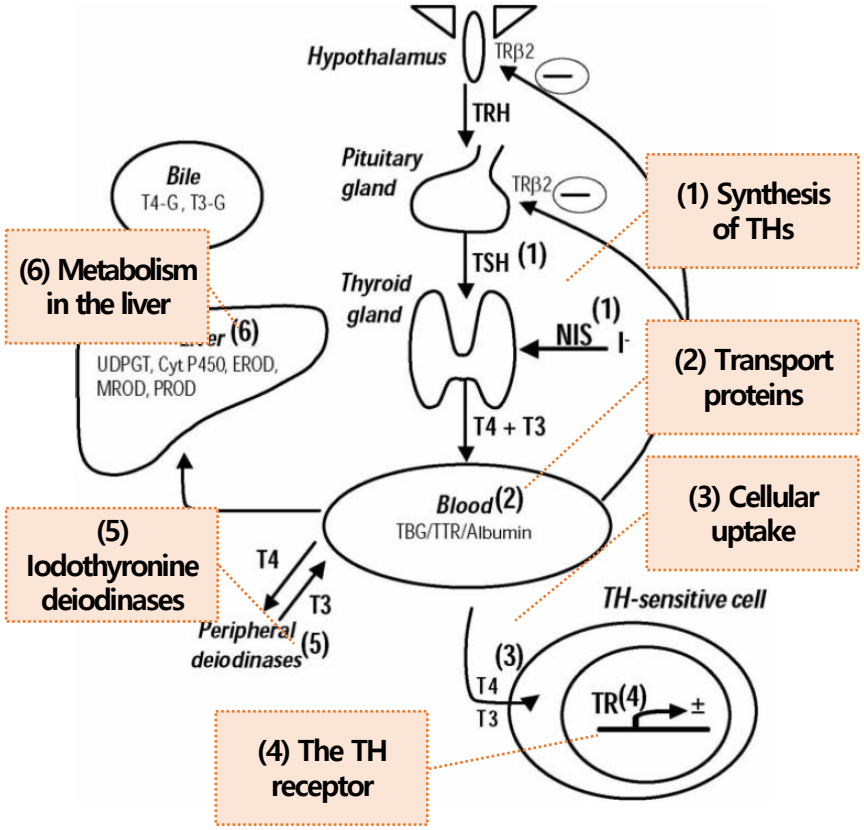


Hypertrophy & proliferation increase

AO

Thyroid hormone regulation is complex

- **Combination of multiple KEs is useful**



(Lyn et al., 2009; Boas et al., 2012)

Summary

- 갑상선호르몬 교란물질 규제의 필요성이 크다
- 적절한 시험방법은 정립되어 있지 않다
- In vitro 방법을 이용하여 잠재적 갑상선호르몬 교란물질을 탐색할 수 있다
- 항상성 조절기전의 복잡성 때문에 여러 핵심적 KE의 조합을 이용한 탐색법 마련이 필요하다
- In vivo와 in vivo 실험 결과를 통합하여 갑상선 교란물질의 유해성 특성을 파악할 수 있다

고맙습니다

AOP기반의 IATA 개발과 규제적용-갑상선교란물질 사례 연구

2020. 10. 26.