

Kanno J, Ward JM, Maronpot RR,  
Mechanisms of chemically induced  
thyroid follicular carcinogenesis, in Prog  
Clin Biol Res, 394,: Cellular and Molecular

Mechanisms of hormonal carcinogenesis  
/Environmental Influences, (editors:  
James Huff, Jeff Boyd, J Carl Barrett),  
Wiley-Liss, Inc. press, 353-398, 1996

ana	adipose tissue
ana	adrenal glands.
ana	anterior lobe
ana	areolas.
ana	birth defects
ana	brain
ana	bulbocavernosus muscle
ana	Cloacal gland
ana	Fat
ana	foam gland
ana	glands
ana	gonad
ana	hypothalamus
ana	levator ani
ana	Leydig cells
ana	nervous system
ana	nipples.
ana	nurse cells
ana	ovary
ana	oviduct.
ana	oxidation
ana	pancreas);
ana	pituitary
ana	pronephros
ana	prostate
ana	reproductive tract of males
ana	Sertoli cells
ana	sex accessory glands
ana	testis
ana	thyroid gland);
ana	uterine glands
ana	uterine histology
ana	vaginal histology
bio	20-carbon fatty acid
bio	adrenalin
bio	agonists
bio	Ah-receptor
bio	allosteric effect
bio	amines
bio	amino acids
bio	Amphibian/
bio	androgen
bio	Androgen Receptor
bio	antagonists
bio	antiestrogens
bio	apoptosis
bio	arachidonic acid
bio	ARE
bio	autoimmune thyroid diseases
bio	avian cell lines.
bio	birth control.
bio	blood sugar
bio	breast cancer.
bio	C3
bio	cancer.
bio	cell receptors (at cell surface allow entry into cell);
bio	cell wall
bio	Chemically-Induced Alterations
bio	cholesterol
bio	cortisol
bio	development.
bio	developmental processes
bio	DNA
bio	DNA response elements
bio	dose-response assessment
bio	drug resistant
bio	eicosanoids

bio	endocrine
bio	endocrine system
bio	ERE
bio	ERE DNA sequence,
bio	estradiol 17 $\beta$ ,
bio	estradiol,
bio	estriol,
bio	estrogen
bio	estrogen receptor alpha
bio	estrogen receptor beta
bio	estrone,
bio	estrous cyclicity
bio	feedback systems
bio	fertilization,
bio	First Estrus
bio	follicle stimulating hormone (FSH)
bio	FSH,
bio	functional equivalency
bio	gene
bio	gene transcription
bio	genomic DNA
bio	germ cells
bio	gestation
bio	GH
bio	gland genesis
bio	glucocorticoid receptors
bio	GnRH,
bio	gonadotropin-releasing hormone (GnRH)
bio	gonadotropins
bio	Graves disease
bio	growth factor,
bio	growth hormone
bio	growth,
bio	hAR
bio	Hashimotos thyroiditis,
bio	heart disease,
bio	heterodimers,
bio	homeostasis
bio	homodimers
bio	hormone fluctuations
bio	hormone receptor,
bio	hormone response element (HRE)
bio	hormones
bio	HSV TK promoter
bio	Hydrolysis
bio	hypothalamic pituitary development
bio	hypothalamic-pituitary axis
bio	hypothyroidism,
bio	implantation,
bio	insemination
bio	insulin
bio	lactation,
bio	LH,
bio	lutinizing hormone (LH),
bio	male secondary sex characteristics
bio	male-determining genes
bio	Mammal Development
bio	mammals,
bio	messenger ribonucleic acid (mRNA)
bio	mineralocorticoid receptors
bio	mitochondrial respiration
bio	neurotoxicity,
bio	NGF,
bio	nonaldrenalin);
bio	nuclear receptor
bio	Onset of Cyclicity
bio	oocyte maturation,

bio	organogenesis
bio	parturition,
bio	peptide hormone,
bio	peptides proteins
bio	phosphorylation pathways.
bio	Photolysis
bio	plasma steroids,
bio	plasma vitellogenin.
bio	polyadenylation sequences
bio	polylinker sequence
bio	pregnancy,
bio	prenatal
bio	progesterone
bio	progesterone receptor,
bio	prohormone metabolism
bio	prolactin
bio	Promoter sequences
bio	prostaglandins
bio	Puberty
bio	RARs
bio	Receptor/ligand equilibrium
bio	receptors
bio	receptors found cytoplasm cells (to which steroid hormones bind);
bio	receptors found nuclei cells (to which thyroid hormones bind).
bio	receptors found on surface cells (to which peptide hormones bind);
bio	recombinant serum albumin
bio	reporter (luc or CAT) construct.
bio	reporter gene expression
bio	restriction endonuclease
bio	retinoic acid
bio	retinoid receptors
bio	ribosomes
bio	RXRs
bio	selectable marker
bio	serum batch
bio	sex hormones
bio	sexual differentiation
bio	Sexual Functional Development
bio	SHBG
bio	signal transduction (which causes activation gene);
bio	sperm production
bio	splicing
bio	stereospecific
bio	steroid hormone binding globulin
bio	Steroid Production
bio	Steroid response element
bio	steroidogenesis.
bio	steroids
bio	SV-puro
bio	T3
bio	target organs tissues
bio	taxa
bio	testosterone.
bio	thyroid hormone receptor.
bio	thyroid peroxidase
bio	thyroid receptor.
bio	thyroid responsive elements
bio	thyronines
bio	thyroxin
bio	TR alpha
bio	TR beta
bio	TR/RXR interaction.
bio	transcription (to generate messenger RNA);
bio	transcription factor (TF).
bio	translation (to generate proteins, e.g., enzymes, regulatory proteins, structural proteins, other receptors, etc.); and/or metabolism
bio	translational machinery.

bio	transport protein
bio	transport serum binding:
bio	TRE
bio	TSH.
bio	tyrosine
bio	urinary excretion,
bio	Uterine peroxidase
bio	vaginal cornification
bio	vitamin D receptor
bio	vitellogenin
bio	VITpromoter
bio	weaning,
che	alcohols,
che	aldehydes,
che	alkylphenol-monoethoxylates,
che	alkylphenols
che	antibiotic
che	antithyroidal toxicants
che	aquatic organisms
che	atrazine
che	bisphenol A,
che	catecholamines
che	chlordane,
che	chlorinated pesticides
che	clomiphene,
che	coumesterol,
che	cyproterone acetate
che	DDT,
che	Degradation in water.
che	DES
che	dexamethasone
che	DHT
che	dibenzofurans
che	dihydrotestosterone (DHT),
che	dimethacrylate,
che	Dioxins
che	dithiocarbamate
che	EE2
che	endocrine disrupting chemicals,
che	environmental estrogens,
che	environmental hormones,
che	estrogenic PCBs
che	ethoxylates,
che	ethylenethiourea,
che	flavones
che	fungicides,
che	furans,
che	histidine),
che	ICI 182,780
che	inorganics polymers
che	inorganics,
che	isoflavones
che	isoforms,
che	kepone
che	ketones,
che	lead
che	leukotrienes
che	lipophilic toxicants
che	Mercury
che	metals†
che	Methoxychlor,
che	Mixtures
che	monomers
che	multi-functional compounds,
che	naturally occurring substances,
che	non-hydroxylated PCBs
che	non-petroleum fractions,

che	non-polymeric chemicals
che	nonlyphenol
che	nonsteroidal chemicals
che	o,p' DDT
che	octylphenol,
che	oligomers
che	organics,
che	organochlorines,
che	oxygenates contaminants
che	p,p' ODE,
che	PCBs,
che	pesticides,
che	petroleum hydrocarbons,
che	phenolic *A* ring
che	phenolic chemicals
che	phenols
che	phthalates
che	phytoestrogens
che	Polychlorinated dibenzodioxins
che	polyethoxylates
che	polymers,
che	Potential (Anti-) Androgenic
che	Potential (Anti-) Estrogenic
che	PTU
che	semivolatile organics
che	soy
che	soy formula
che	tamoxifen,
che	TCDD
che	toremifine,
che	triphenylethylene
che	xenoantiandrogen
che	xenoestrogens
edu	EDSTAC describes endocrine disruptor exogenous substance mixture alters structure function(s) endocrine system causes adverse effects at level organism, its progeny, populations, subpopulations organisms, based on scientific principles, data, weight-of-evidence, precautionary principle.
env	Aerobic soil metabolism
env	anaerobic soil metabolism
env	Bioaccumulation
env	bioconcentration
env	birds
env	Fathead Minnow
env	Fish Monitoring
env	fish,
env	insects,
env	invertebrates
env	Japanese quail,
env	lobsters,
env	Metamorphosis
env	microorganisms,
env	mysids
env	Nest Attentiveness/Incubation Behavior
env	non-mammalian vertebrates
env	Rana
env	Red-eared slider
env	reptiles,
env	Scaphiopus
env	Sheepshead Minnow
env	snails,
env	soil degradation
env	soil metabolite(s)
env	Trachemys scripta
env	turtles
env	wildlife
env	Xenopus
enz	5-alpha-reductase,

enz	aromatase activity.
enz	Aromatase Inhibition
enz	CYP3A4.
enz	cytochrome P 450
enz	enzyme.
enz	isozyme.
enz	liver enzymes
enz	Malic Enzyme
enz	Metabolism
enz	ODC
enz	SIS
met	Alexander Method
met	Allen-Doisy Assay
met	Amphibian Metamorphosis Assay (Conceptual)
met	Anogenital distance
met	automation
met	Avian Cell Culture
met	Avian Egg-Injection Assay
met	Avian xPlaque Assayf
met	behavior.
met	brain weight.
met	Cartilage Growth in Chick
met	castrate
met	charcoal-dextran stripped serum
met	Chicken Early Life Stage
met	Cold Stress Test
met	colorimetric assay
met	CoMFA software
met	conception.
met	conjugation.
met	COS Cells
met	Cotransfected Reporter Gene Assay in Mammalian Cells
met	crowing behavior
met	CV-1
met	cyp3A4 metabolism
met	Daphnia
met	Daphnia magna.
met	Daphnia Reproduction (Life Cycle) Test
met	database development
met	Developmental Uterotrophic Assay
met	diet
met	E-SCREEN
met	EC2X (agonist activity).
met	EC50
met	ECOSAR
met	efficiency of DSP 13
met	egg-injection
met	Electroporation
met	Endocrine Change Test (Fail et al., 1995)
met	Endocrine modulator assays
met	epididymal sperm number.
met	ER Binding Assay
met	ESCREEN
met	Estrogen Competitor (Binding) Screening Assay (A Receptor/Ligand Assay, PanVera)
met	eucaryotic selectable markers
met	FETAX
met	Fish Early Life Stage Test
met	Fish Embryo and Sac Fry Test
met	Fish Full Life Cycle Test
met	Fish In Vitro Vitellogenin Assay
met	fish life cycle test
met	Fish Partial Life Cycle Test
met	Fish Vitellogenin Assay
met	Flounder Metamorphosis
met	fluorescence polarimeter
met	fluorescence polarization
met	fluorescent estrogen

met	Frog Embryo Teratogenesis Assay Xenopus (FETAX)
met	Frog In Vivo Screening Assay (Conceptual)
met	FRTL-5 cells
met	Germinal Vesicle Breakdown (GVBD) Bioassay
met	GH3 cells
met	gonado-somatic index,
met	hAR Transactivation Assays Using Stable Cell Lines
met	hAR Transcriptional Activation Assay in Mammalian Cell
met	hAR Whole Cell Binding Assay .
met	HeLa cervical carcinoma cell line
met	hER Binding From MCF-7 Cell Lysate
met	Hershberger Assay
met	high throughput pre-screening. $\bar{t}$
met	High-Throughput
met	hold screening testing:
met	human breast carcinoma
met	IC50
met	in utero exposure
met	Induction of Female Sex Behavior
met	informatics/quantitative structure-activity relationship (QSAR) package.
met	Japanese Quail Androgenicity Screen
met	Japanese Quail Early Life Stage
met	juvenile female mice
met	juvenile female rats
met	Ki values
met	Larval-Juvenile Exposure (
met	Leydig Cell Culture
met	log Kow
met	Long-Term Serum T4
met	Luc activity
met	Luciferase
met	luciferase reporter gene
met	luciferase)
met	luciferin
met	luminometer.
met	MCF-7
met	MCF-7 Proliferation Assay
met	MDA-MB-453
met	microplates
met	minced ovary
met	MMTV-luciferase reporter
met	monkey kidney cell line (COS).
met	MTT
met	multigenerational tests
met	MVLN Assay
met	Mysid Life Cycle Test
met	ovariectomized female
met	Ovariectomy
met	passage number
met	PC12 cells
met	Peripubertal male rat.
met	permanent anomaly of VO
met	Permanently transformed
met	pheochromocytoma cell line
met	photo-regressed adult males
met	photoperiod
met	prioritize Tier 1 Screening (T1S);
met	Priority setting
met	proliferation assay.
met	pUV120
met	QSAR for Androgen
met	QSAR for Estrogen
met	QSAR for Thyroid
met	Rat AR Equilibrium Binding Assay
met	Receptor Binding
met	robotics systems.
met	SAR equations



met	Second Generation Embryo Exposure
met	Second Generation Larval-juvenile Exposure
met	serum DHT
met	serum T
met	Sex Determination in Turtles
met	Short-Term Serum T4
met	Southern blot hybridization analysis
met	spermatid head counts (SHC).
met	stably transfected human cell lines
met	Stably Transfected Reporter Gene Assay in Mammalian Cells
met	Steroid Receptor Competition Assay
met	structure activity relationships (SARs).
met	subclone
met	subsequent generations
met	Substructure-based Computerized Chemical Selection Expert System (SuCCSES)
met	sulforhodamine-B assay
met	Super Apical Developmental Toxicity Test
met	testicular homogenization-resistant
met	Testing
met	Testis/Ovary Culture
met	Thyroid Hormone-Responsive Cells.
met	Thyroid Stably Transfected Cell Lines
met	Thyroid Whole Cell Binding Assays.
met	Tier 2 (T2T);
met	TR Binding Assay
met	transfection.
met	transient transfections
met	trout hepatocytes.
met	TRPM2
met	two-generation reproductive toxicity study
met	uterine biochemical measures
met	Uterine Peroxidase Assay
met	Uterine Weight Bioassay in Adult Ovariectomized Female
met	Uterine Weight Bioassay in Juvenile Female Rats
met	vaginal cornification via nonestrogenic mechanisms
met	Vaginal lavages
met	vaginal mucification.
met	Vaginal Opening
met	Vaginal patency
met	Vaginal Smears (Mucification and Cornification)
met	vaginal sperm/copulation plug
met	Visual Cliff Test
met	Vitellogenin Assay
met	Vitellogenin Production in Adult Male Birds: Japanese Quail, Chickens
met	Vitellogenin Production In Adult Male Turtles
met	Vitellogenin Production in Female Japanese Quail
met	whole embryo teratogenesis screening assay.
met	xenobiotic challenge
met	Xenometrix's molecular toxicology database
met	XLT-15 cell line
met	YAS
met	Yeast Androgen Screen
met	yeast cells
met	Yeast Estrogen Screen
met	YES
sta	coefficients of variation
tox	ADME
tox	adverse at population level
tox	adverse effects
tox	agenesis of epididymis
tox	agenesis of prostate
tox	alteration during key developmental stages
tox	anovulation
tox	beneficial effects
tox	biological plausibility.
tox	CNS defeminization
tox	criteria setting priorities

tox	daily sperm production (DSP).
tox	delayed VO
tox	endocrine disrupters.
tox	Endocrine Disruptor Screening Advisory Committee (EDSTAC).
tox	endocrine disruptors
tox	endocrine modulators.
tox	Environmental Protection Agency (EPA)
tox	estrogenicity
tox	exogenous agent which interferes synthesis, secretion, transport, binding, action, elimination natural hormones body which are responsible maintenance homeostasis, reproduction, development behavior.
tox	exogenous substance changes endocrine function causes adverse effects at level organism, its progeny, and/or (sub)populations organisms.
tox	FALSE NEGATIVES
tox	false positives
tox	Feeding Behavior.
tox	Food Consumption and Growth Rate
tox	GLP requirements
tox	goiter.
tox	hazard assessment:
tox	hazard identification.
tox	hind-limb growth rate
tox	hold box
tox	hypospadias
tox	infertility.
tox	international harmonization
tox	later life
tox	lordosis
tox	luminal epithelial height
tox	malformations
tox	mating behavior.
tox	Mucification of smears
tox	neonatal survival.
tox	non-hormone- mediated cancer
tox	normal physiological adaptation
tox	not adverse to individual
tox	nutritional status.
tox	postmenopausal osteoporosis
tox	Preputial Separation
tox	prevention
tox	Proceptive and Receptive Behaviors
tox	proestrus
tox	Pubertal Development in Male Rodent
tox	reproduction.
tox	reproductive developmental toxicity
tox	reversal hair loss
tox	secondary sex characteristics.
tox	soy infant formula.
tox	sperm morphology:
tox	sperm motility.
tox	spermatogenesis
tox	standard cytotoxicity
tox	strain variability
tox	teratogenesis.
tox	undescended testis
tox	weight-of-evidence

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分担研究報告書

人の健康影響に関する検査法等に関する調査研究（実験系の開発とデータベース）

分担研究者 菅野 純 国立医薬品食品衛生研究所・毒性部

研究要旨：

内分泌かく乱物質問題には、対象化学物質の数が膨大であるという点と、核内受容体を介する遺伝子転写活性制御の基礎生物額であり、その影響のエンドポイントの問題である等の広い分野の知識を結集した上で、対処しなければならないという問題点がある。そのため、内分泌かく乱化学物質の影響に関する試験法の開発に関する研究結果を広く一般に報告するために関連の「内分泌かく乱化学物質試験法提要（仮称）」の編集を計画したものである。

A. 研究目的

内分泌かく乱物質問題には、その生体影響の有無を判定すべき対象化学物質の数が膨大であるという問題点の他に、核内受容体を介する遺伝子転写活性制御の基礎生物学的問題から、その影響がヒトや動物の生殖・後世代影響に如何に現れるかを検討するエンドポイントの問題まで、広い分野の知識を結集した上で、対象物質あるいは物質群に対処しなければならないという問題点がある。

本研究班の目的は、広い科学的知識を基礎にした内分泌かく乱化学物質の影響に関する試験法の開発である。この研究結果を広く研究者のみならず一般に報告するために、関連の研究成果を結集した、「内分泌かく乱化学物質試験法提要（仮称）」の編集を計画した。

B. 研究方法

内分泌かく乱化学物質の影響に関する試験法の開発であるが、この研究結果を広く研究者のみならず一般に報告するために、今井班班員等の研究成果を結集した、「内分泌かく乱化学物質試験法提要（仮称）」の編集を計画

した。

C. 研究結果

今年度は、下記、各班員の研究課題についてまとめた。

内分泌かく乱化学物質研究の概要と今井班の位置づけ 井上 達

【スクリーニング試験】

永井 賢司 *in vitro* スクリーニング手法のバリデーション研究

武吉 正博 新規 *in vivo* スクリーニング法開発のための研究

－  $\alpha_2\mu$ -globulin の生体内動態と内分泌攪乱物質の Screening 法への応用－

塚田 俊彦 培養細胞を用いた内分泌攪乱物質検出系の検討

【薬理・代謝生化学】

大野 泰雄 内分泌攪乱作用を修飾するヒト代謝活性化系及び不活性化系導入・発現細胞の開発

小島 幸一 薬理学的影響に関するスクリーニング法の開発研究

鈴木恵真子 内分泌かく乱化学物質のエストロゲン代謝に及ぼす影響とそのスクリーニング法の開発

【生殖・発生】

長尾 哲二 内分泌攪乱化学物質の胎生期および新生児期曝露による視床下部神経核の構造変化と生殖異常

渡辺 敏明 哺乳動物胎児における中枢神経および生殖細胞に及ぼす影響

川島 邦夫 フタル酸エステルによる生殖障害に関する研究

【がん原性】

白井 智之 内分泌かく乱物質の発がんプロモーション作用の検討

広瀬 雅雄 甲状腺腫瘍に対する内分泌攪乱物質の影響に関する研究

【情報・3D-QSAR】

長谷川隆一 内分泌かく乱物質等の文献情報に関する調査研究

神沼 二真 データベースの構築と3次元構造活性相関に関する研究

関沢 純 健康影響に関する情報収集と評価 -日本人における植物由来ホルモン作用物質の役割-

thyroid follicular carcinogenesis, in Prog Clin Biol Res, 394,: Cellular and Molecular Mechanisms of hormonal carcinogenesis /Environmental Influences, (editors: James Huff, Jeff Boyd, J Carl Barrett), Wiley-Liss, Inc. press, 353-398, 1996

## F. 研究発表

### 1. 論文発表

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Kanno J, Ward JM, Maronpot RR, Mechanisms of chemically induced