Appendix C:

Mammalian Studies Describing the Effects of Chemicals That Disrupt the Thyroid Signaling Pathways

Table of Contents

Literature Search and Analysis

A literature search was conducted to identify published literature with evidence of NMDR for thyroid endpoints. This search was based on an ongoing (10+ year) literature review by one of the authors (KC). Starting from the list of references in Brucker-Davis (1998), other references were identified from additional review papers (Table C.1). PubMed searches were also conducted using the list of key words provided in Table C.2. Finally, further additions to the chemical list and references provided by Dr. Pamela Hurley, Office of Pesticides Program, US EPA and Dr. Theo Colbourn, World WildLife Fund (personal communications). The end result was 1256 publications for evaluation as to their relevance for the present effort.

Table C.1. Sources of information for references on thyroid disrupting chemicals

Source	Description
Gaitan and Cooksey (1989)	Review of environmental goitrogens, with 40 chemicals and 45 references
Mcconnell (1992)	Review of 342 2 yr NCI/NTP Cancer Bioassay for thyroid effects
Atterwill et al. (1992)	Review of over 50 drugs and chemicals with 88 references
Brucker-Davis (1998)	Published review of 381 references for over 90 chemicals
Devito et al. (1999)	Review of screening methods to detect thyroid dysfunction, 108 references
Hurley et al. (1998)	Table of 29 pesticides found to alter the structure or function of thyroid
Howdeshell (2002)	Review of impact of thyroid disruption on brain development, 116 chemicals and 184 references.
Boas et al. (2006)	Review of environmental chemicals and thyroid function, 153 references
Köhrle (2008)	Review of environmental chemicals and thyroid, 79 references
Pickford (2010)	Comparison of rodent and amphibian assays for detection of thyroid disruption, 36 chemicals and 185 references
Colborn (personal communications)	Reference list of 1436 publications (contains original Brucker-Davis list)
Crofton (personal communications)	Personal reference library of ~1200 references for over 400 pharmaceuticals, pesticides, and industrial chemicals.

Table C.2. List of key words used for searching literature for thyroid disrupting chemicals.

Thyroid	Receptors, Thyroid Hormone	Transthyretin (TTR)
Hypothyroidism	Thyroid Hormone Receptors alpha	Thyroid binding globulin (TBG)
Hypothyroxinemia	Thyroid Hormone Receptors beta	
Hyperthyroidism	Thyrotropin-Releasing Hormone Receptor	Uridine diphosphoglucurono syltransferases (UGTs)
Hyperthyroxinemia	Pregnane X receptor (PXR; NR1I2)	Sultfotransferases (SULTs)
Thyroid dysgenesis		
Thyrotoxicosis		
Thyroid neoplasms	Constitutive androstane receptor (CAR; NR1I3)	Phase III Hepatic cellular transporters
Thyroid follicular tumors	Sodium iodine symporter (NIS)	Organic anion-transporting polypeptides (OATPs)
Thyroiditis	Iodine uptake	Monocarboxylate transporters (MCTs)
Follicular cell size/shape	Iodine uptake inhibition	Pendrin
Thyroid lumen size/area	Peroxidases	
Diiodothyronines	Thyroperoxidase (TPO)	Metamorphosis
Diiodotyrosine	Lactoperoxidase	frog tail length
Monoiodotyrosine	Iodine peroxidase	frog hind limb growth
Thyroid Hormones	Thyroglobulin	
Thyronines	Deiodinases (Type I, Ii, III)	Male pubertal assay
Thyrotropin	Iodothyronine deiodinases	Female pubertal assay
Thyroxine(T4)		OECD 407
Triiodothyronine (T3)		Extended F1 Study
Triiodothyronine, Reverse		
Thyroid stimulating hormone (TSH)		
Thyrotropin releasing hormone (TRH)		

Information on chemical names, doses, number of dose groups, species, lifestage and significant thyroid-related effects were extracted from the references and added to a thyroid knowledgebase. The knowledgebase was used to perform analyses of the available literature to determine whether a publication had a sufficient number of doses reported to search for nonmonotonicity in thyroid-related endpoints, and second whether any data in the publication suggested an NMDR. Of these 1153 references, 339 were eliminated because they were review papers, meeting reports, used undefined mixtures, or failed to contain thyroid-related endpoints. The remaining 814 papers evaluated were original reports containing data from 987 chemicals. Information was then extracted from each publication on the number of "chemical-studies" (Table C.3). Chemical-studies were defined as independent determinations of a dose or concentration-response for a chemical. Thus a publication could have more than one chemical-study for a single chemical (*e.g.*, an acute and a subchronic on one chemical) or could report on multiple chemicals (*e.g.*, acute studies for 5 chemicals). A total of 2060 chemical-studies were identified, and this information was further divided into mammalian and in vitro (1831 chemical studies) and non-mammalian chemical studies (229 chemical studies). Most of the non-mammalian studies were reported in the aquatic models section of the document (Section 4.2.2). Information on the number of relevant papers based on species used, life stages evaluated, and use of *in vivo* or *in vitro* techniques is shown in Table C.4. The number of dose groups in chemical-studies is summarized in Table C.5.

The publications containing the 1831 mammalian and in vitro chemical-studies were then evaluated for the presence of NMDR effects at low doses that would impact regulatory action (*e.g.*, lowest effective dose for a chemical). The evaluation was conducted according to criteria outlined in the 'Decision Tree' in Figure 1 of Appendix C. Briefly, the criteria for inclusion were:

Filter 1: Minimum of 3 dose levels plus a control evaluated

Filter 2: Evidence of a statistically significant NMDR on any thyroid endpoint

Filter 3: Absence of observations at lower dose levels in the study that would have been used to determine the LOEL/LOAEL

Filter 4: a) Absence of other published reports on this chemical where effects were observed at low levels.

b) Absence of other published reports for effects on other endpoints that would have been used to determine the LOEL/NOEL below the dose identified as an NMDR.

c) Absence of study quality concerns or statistical power issues that weakened confidence in the NMDR observation.

Table C.3. Reference filters used to compile the final list of published papers searched for any evidence of NMDRC for thyroid-related endpoints. All studies rated as relevant (*i.e.*, primary publication of chemical-specific information on thyroid endpoints) were further divided into chemical-studies (see text for definitions).

Total Number of References	1153
Numbers of reference that were reviews or otherwise not relevant	339
Total number of relevant references with data from chemical exposures	814
Total Number of Chemical-Studies from relevant references	2060
Number of Non-Mammalian Chemical-Studies	229
Number of Mammalian In Vivo & All In Vitro Chemical-Studies	1831

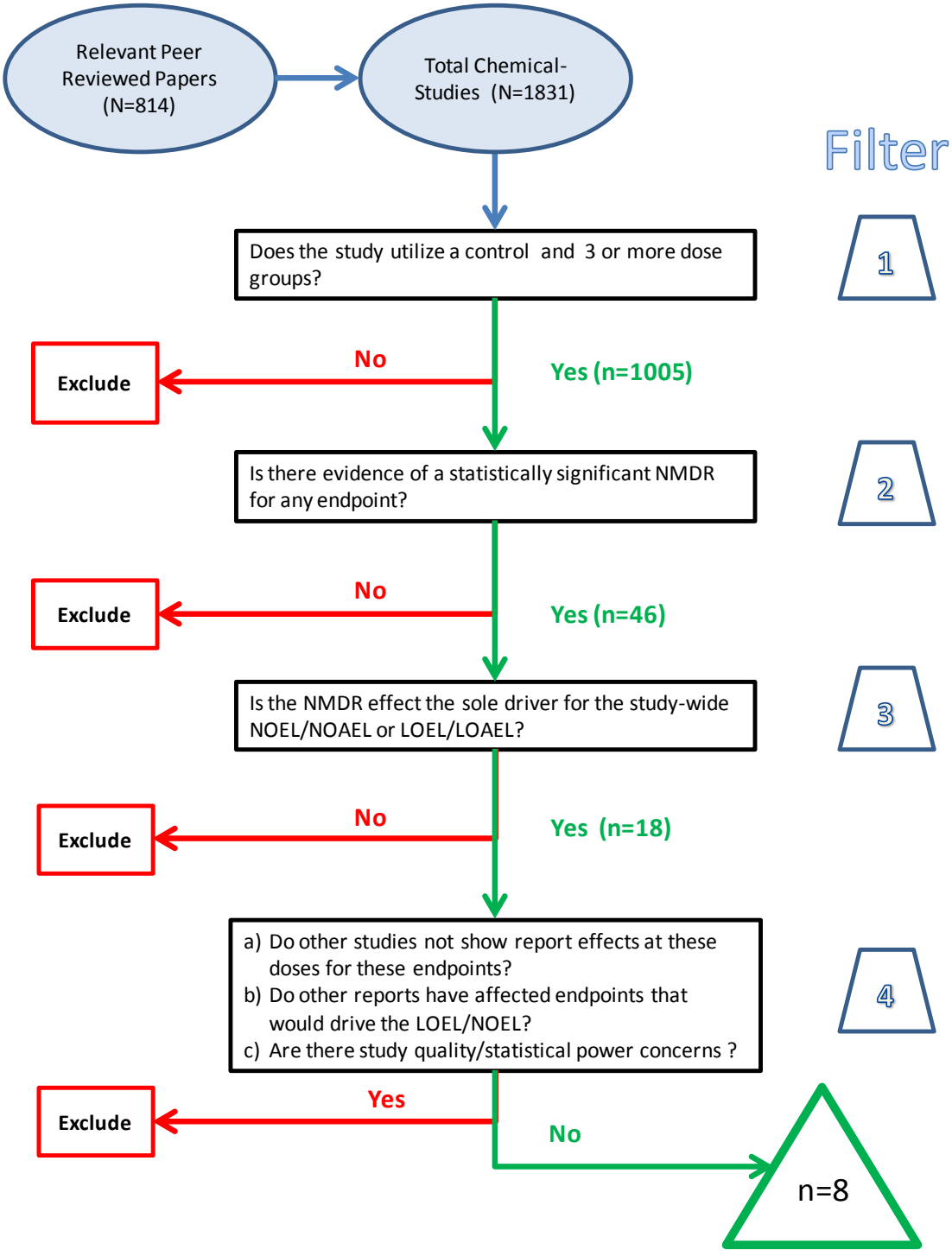
Table C.4. Breakdown of all chemical-studies by species, adult or developmental exposures and in vitro studies. Note that some papers contained data on more than one species or life-stage.

Summary of Non-mammalian chemical-studies species			
	Adult	**Developmental**	**Sums**
Bird	26	50	76
Fish	40	54	94
Frog	1	51	52
Lizard	3	0	3
Turtle	4	0	4
Total Non-Mammalian			**229**
Summary of mammalian chemical-studies by species			
	Adult	**Developmental**	**Sums**
Cattle	5	3	8
Dog	10	0	10
Gerbil	2	0	2
Goat	2	0	2
Guinea pig	3	0	3
Hamster	6	0	6
Horse	1	0	1
Human	26	2	28
Mice	87	13	100
Mink	3	0	3
Monkey	8	0	8
Pig	3	1	4
Rabbit	3	2	5
Rat	915	165	1080
Sheep	10	4	14
Squirrel	2	0	2
Vole	2	0	2
Total Mammalian *In vivo*			**1278**
All In Vitro studies			**553**
Total Mammalian In Vivo & All In Vitro Chemical-Studies			**1831**

Table C.5. Breakdown of the number of dose groups not including controls for all 814 relevant references that include 2060 mammalian, non-mammalian and in vitro chemical-studies.

# Dose Groups	*In vivo*	In Vitro
1 or 2	859	81
3	284	32
4	191	66
5	89	75
6	26	85
7	34	85
8	12	92
9 or more	10	39

Figure C.1. Flow Diagram for Mammalian Thyroid Inclusion Criteria



Study Evaluation Summaries

The following represents the summaries and evaluation decisions based on our filtering paradigm that passed Filter Level 2 – i.e., these papers evaluated control and at least 3 dose levels and reported data for a thyroid-related endpoint that displayed an NMDR curve. Further filters were applied as indicated in Figure D.1 and 8 papers were identified that exhibited NMDR of concern as described above. These were the 8 papers that were carried forward for discussion in the main document in Section 4.2.3.

17α-methyltestosterone

Reference: Okazaki et al. (2002)

Study Details: 17α-methyltestosterone (0, 5, 20, 80 mg/kg-day) was administered once daily via gavage to male and female SD rats. Male rats were dosed for 28 days with terminal sacrifice one day after the 28th administration. Female rats were dosed for 28-31days until it was determined that the female was in the diestrus stage of the estrous cycle. Females were dosed until the day before sacrifice.

Primary Mode of Action: Unknown

NMDR Observation: Statistically significant increase in thyroid weight in female rats at lowest dose. Changes in thyroid weight were not observed at any other dose level.

Decision/Comments: **Exclude Filter 3**. The NMDR for the increase in thyroid weight is not the determinant of the study-wide NOEL. Monotonic dose response effects were observed in organ weights of the adrenal and pituitary glands of the female rats, as well as the ovaries and were significant at the lowest dose tested.

Table 4 Body weight and relative organ weights (g/100 g body weight) for female rats treated with 17α-methyltestosterone for 28–31 days

Parameter	Dose (mg/kg per day)			
	0	5	20	80
No. of animals	10	10	9	10
Body weight (g)	259.2 ± 13.3	272.2 ± 16.4	284.3 ± 10.1**	285.4 ± 16.4**
Liver	3.73 ± 0.44	3.57 ± 0.24	3.67 ± 0.28	4.05 ± 0.40
Adrenal	0.026 ± 0.003	0.019 ± 0.003**	0.018 ± 0.003**	0.014 ± 0.003**
Kidney	0.68 ± 0.05	0.70 ± 0.05	0.67 ± 0.04	0.78 ± 0.11**
Pituitary	0.006 ± 0.001	0.005 ± 0.001*	0.005 ± 0.001**	0.004 ± 0.001**
Thyroid	0.006 ± 0.001	0.008 ± 0.001**	0.007 ± 0.001	0.006 ± 0.001
Ovaris	0.035 ± 0.003	0.026 ± 0.06**	0.024 ± 0.005**	0.17 ± 0.002**
Uterus	0.19 ± 0.03	0.16 ± 0.02	0.14 ± 0.03*	0.18 ± 0.03

*$P < 0.05$, significantly different from the 0 mg/kg group
**$P < 0.01$, significantly different from the 0 mg/kg group
Data represent mean values ± SD

17β-Estradiol (E2)

Reference: Tyl et al. (2008)

Study Details: E2 was administered in the diet (0, 0.001, 0.005, 0.05, 0.15, 0.5ppm; ~0, 0.2, 1, 10, 30, 100 µg E2/kg BW/day, n=16-25) to CD-1 mice for 8 weeks prior to breeding, 2 weeks during mating, throughout gestation (~3 weeks) and for 3 weeks during lactation. After weaning, selected F1 mice continued to be administered the same doses until the conclusion of the study at F2 weaning. Animals were sacrificed at various times and tissues collected.

Primary Mode of Action: Unknown

NMDR Observations: A statistically significant increase in thyroid weight in the F1 parental male generation was seen at the 0.05 and 0.5 ppm dietary E2 exposure concentrations, and no difference from control was seen at the 0.15 ppm exposure concentration or at the lower doses.

Decision/Comments: **Exclude Filter 3**. The NMDR for thyroid weight was not the determinant of the study-wide NOEL. Additionally, there is no statistical difference in thyroid weight between the 0.05, 0.15, and 0.5 ppm exposure groups.

Excerpt from Table 3 is below:

TABLE 3
Selected Organ Weights from F0 and F1 Parental and Retained F1 Adult Males

		E2 dietary concentration (ppm)					
Parameter	Generation[a]	0	0.001	0.005	0.05	0.15	0.5
No. males	F0	24	25	25	25	24	25
	F1	25	25	25	25	25	25
	F1 retained	18	17	19	21	21	16
Terminal body wt. (g)	F0	36.66 ± 0.77	38.34 ± 0.89	36.45 ± 0.57	37.29 ± 0.75	35.98 ± 0.53	35.68 ± 0.50
	F1	37.37 ± 0.71	37.67 ± 0.75	38.70 ± 0.78	38.45 ± 0.74	36.60 ± 0.65	38.01 ± 0.75
	F1 retained	38.89 ± 1.12	39.37 ± 1.16	39.70 ± 1.10	37.58 ± 0.72	38.66 ± 0.72	35.91 ± 0.75
Thyroid (g)	F0	0.0055 ± 0.0003	0.0053 ± 0.0003	0.0053 ± 0.0002	0.0054 ± 0.0002	0.0049 ± 0.0002	0.0053 ± 0.0002
	F1	0.0028 ± 0.0001	0.0027 ± 0.0001	0.0031 ± 0.0001	0.0032 ± 0.0001*	0.0031 ± 0.0001	0.0033 ± 0.0001**
	F1 retained	0.0038 ± 0.0001	0.0039 ± 0.0002	0.0038 ± 0.0001	0.0039 ± 0.0002	0.0042 ± 0.0002	0.0038 ± 0.0002

Note. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$, respectively; Dunnett's test for pairwise comparisons to the concurrent control group value.
[a]There were 24–25 F0 and F1 adult males per group and 16–21 retained F1 adult males per group.

1-chloro-4-(chloromethyl)benzene

Reference: Yamasaki et al. (2012)

Study Details: 1-chloro-4-(chloromethyl)benzene (0, 10, 50, 250 mg/kg-day in olive oil) was administered to male and female SD rats via oral gavage daily for 28 days, beginning at 8 weeks of age.

Primary Mode of Action: Unknown, possible effect on liver metabolism

NMDR Observation: Statistically significant increase in serum T4 found at the middle dose in female rats. No other changes were noted for serum T3, T4, or TSH in either sex.

Decision/Comments: **Filter 4 Include.** Changes in female serum T4 is not consistent with observations in male rats from the same study. No other changes in female serum thyroid hormones (T3 or TSH) were found. A very high standard deviation was reported for male serum TSH values, it is not clear if this is biological variability or assay variability. No histopathological changes were noted in the thyroid gland at any dose in either sex. Gender was not in the statistical model. The statistical increase in T4 noted for females at the mid dose would be selected as the LOEL for thyroid effects for this study. No other studies on the thyroid effects of this chemical were found in the literature for this compound.

Table 5
Hormonal values (mean ± SD) in 1-chloro-4-(chloromethyl)benzene.

Items	Male				Female			
	Control	10 mg/kg	50 mg/kg	250 mg/kg	Control	10 mg/kg	50 mg/kg	250 mg/kg
T3 (ng/ml)								
28-day administration	0.64 ± 0.11	0.59 ± 0.11	0.62 ± 0.13	0.61 ± 0.10	0.74 ± 0.07	0.71 ± 0.07	0.79 ± 0.10	0.76 ± 0.15
14-day recovery	0.79 ± 0.15	NE	NE	0.68 ± 0.21	0.76 ± 0.19	NE	NE	0.82 ± 0.13
T4 (ng/ml)								
28-day administration	44.1 ± 10.4	40.7 ± 1.6	45.6 ± 6.0	37.9 ± 5.1	46.0 ± 3.8	47.5 ± 5.9	55.3 ± 3.9*	50.1 ± 4.4
14-day recovery	59.0 ± 6.0	NE	NE	51.8 ± 7.9	38.2 ± 5.3	NE	NE	41.8 ± 4.7
TSH (ng/ml)								
28-day administration	2.54 ± 0.97	2.97 ± 0.95	2.53 ± 0.99	1.86 ± 1.58	0.93 ± 0.41	0.80 ± 0.29	0.91 ± 0.61	0.98 ± 0.31
14-day recovery	1.63 ± 0.90	NE	NE	1.98 ± 1.00	0.68 ± 0.29	NE	NE	0.61 ± 0.31

NE = not examined.
* Significantly different from control at $P < 0.05$.

1-methyl-3-propylimidazole-2-thione (PTI)

Reference: Biegel et al. (1995)

Study Details: 1-Methyl-3-propylimidazole-2-thione (PTI 0, 5, 10, 25, 75 mg/kg/day) was administered orally by gavage in canola oil to adult male and female CD BR rats. Tail blood was sampled for serum hormones 1 and 3 weeks and at the end of dosing. Animals were sacrificed and tissue collected after 5 or 90 days of dosing.

Primary Mode of Action: TPO inhibition; liver metabolism

NMDR Observation: Statistically significant decrease in serum T3 at 5, 25 and 75 mg/kg with no effect at the mid dose of 10 mg/kg/day at the 1-week time point in male rats only.

Decision/Comments: **Exclude Filter 3** The NMDR for serum T3 is not the sole determinant of the study-wide NOEL. Monotonic dose -response effects were observed for serum T3 and T4, and hepatic UDPGT activity which were significant at the lowest dose tested.

TABLE 3
Mean Serum Thyroid Hormone Concentration in Male Rats

Dose[a] (mg/kg/day)	0	5	10	25	75
			1-Week analysis		
T_4 μg/dl	4.351 ± 0.6597[b]	3.639 ± 0.7435*	2.999 ± 0.3637*	2.127 ± 0.6098*	0.695 ± 0.3151*
T_3 ng/dL	74.960 ± 8.5196	55.333 ± 10.2213*	66.438 ± 13.7647	61.817 ± 10.2596*	52.048 ± 17.2260*
TSH ng/ml	0.957 ± 0.2949	1.027 ± 0.2848	1.158 ± 0.2624	1.622 ± 0.6576	5.069 ± 3.8064*
			3-Week analysis		
T_4 μg/dl	4.695 ± 0.5905	3.697 ± 0.8394	2.786 ± 1.3641*	1.705 ± 0.5141*	0.383 ± 0.9243*
T_3 ng/dl	64.602 ± 16.3646	52.241 ± 5.6094*	52.397 ± 11.1925*	47.877 ± 8.1456*	22.429 ± 9.8503*
TSH ng/ml	1.768 ± 1.6360	1.250 ± 0.3386	1.856 ± 1.6741	4.372 ± 4.5468	38.149 ± 36.0498*
			3-Month analysis		
T_4 μg/dl	4.802 ± 0.6790	3.984 ± 0.9543*	2.753 ± 0.5042*	2.407 ± 0.6588*	0.942 ± 1.1847*
T_3 ng/dl	56.884 ± 10.5621	51.380 ± 13.5649	44.622 ± 12.8095	35.552 ± 9.6824	75.988 ± 47.1221
TSH ng/ml	1.004 ± 0.9468	0.771 ± 0.3870	0.680 ± 0.2404	0.753 ± 0.2908	1.766 ± 0.7397*

[a] $n = 15$.
[b] Mean ± standard deviation.
* Statistically significant ($p < 0.05$).

TABLE 4
Mean Serum Thyroid Hormone Concentration in Female Rats

Dose[a] (mg/kg/day)	0	5	10	25	75
			1-Week analysis		
T_4 μg/dl	3.424 ± 1.0074[b]	3.128 ± 0.8744	2.753 ± 0.6914	1.540 ± 0.6683*	0.478 ± 0.3521*
T_3 ng/dl	70.613 ± 10.0168	75.165 ± 11.5588	73.081 ± 14.4891	61.676 ± 7.7728	36.984 ± 8.2839*
TSH ng/ml	0.880 ± 0.2024	0.939 ± 0.1866	0.949 ± 0.1971	0.801 ± 0.3601	1.254 ± 0.4346*
			3-Week analysis		
T_4 μg/dl	4.106 ± 0.8581	3.113 ± 1.2869*	2.588 ± 0.6732*	2.118 ± 0.6833*	0.820 ± 0.6362*
T_3 ng/dl	78.298 ± 14.3467	73.483 ± 15.0866	70.379 ± 18.2218	58.372 ± 12.7213*	67.435 ± 18.8918
TSH ng/ml	0.851 ± 0.2024	0.951 ± 0.1311	0.953 ± 0.1507	1.026 ± 0.3166	2.783 ± 2.7419*
			3-Month analysis		
T_4 μg/dl	2.601 ± 0.8302	2.492 ± 0.7640	2.060 ± 0.5594	1.681 ± 0.5235*	1.976 ± 0.4795*
T_3 ng/dl	78.981 ± 10.5746	68.747 ± 12.7325	70.010 ± 14.5077	61.256 ± 11.8370*	88.560 ± 16.3990
TSH ng/ml	0.843 ± 0.0664	0.852 ± 0.0979	0.802 ± 0.1389	0.880 ± 0.1594	0.853 ± 0.1445

[a] $n = 15$.
[b] Mean ± standard deviation.
* Statistically significant ($p < 0.05$).

2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)

Reference: Potter et al. (1986)
Study Details: A single dose of TCDD (0, 6.25, 12.5, 25, 50, 100 µg/kg) was administered to adult male SD rats by gavage in acetone/corn oil vehicle. Measurements were obtained 7 days later. Data compare to vehicle, pair fed and ad lib controls.
Primary Mode of Action: Increase liver metabolism
NMDR Observation: Statistically significant increase in serum TSH at lowest doses that decline as doses increase.
Decision/Comments: **Exclude Filter 4a.** Increases in TSH are inconsistent with many reports of TCDD which also reported declines in serum T4. Peak in serum TSH at lowest dose followed by decline higher doses is secondary to hypophagia accompanying higher dose levels. Monotonic effects of dioxin on other serum hormone levels have been reported at much lower doses under repeated dosing regimens (e.g., Seo et al, Toxicol Lett 1995).

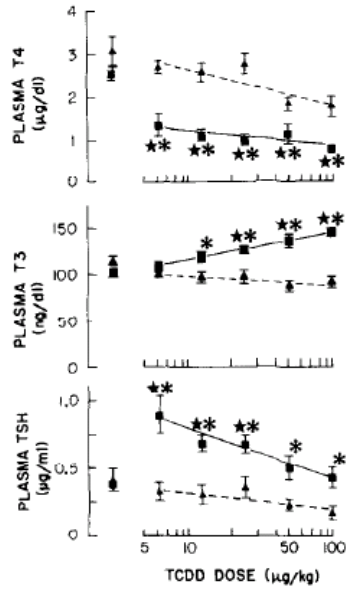


FIG. 2. Effects of TCDD treatment (■) or paired feed restriction (▲) on plasma T_4 (top), T_3 (middle), and TSH (bottom) concentrations. Plasma was taken late in the daily light cycle 7 days after dosing. Each point represents $\bar{x}$ ± SE, $N = 12$. Significant differences ($p < 0.05$) between TCDD and ALC (★) or TCDD and PFC (*) are as shown.

4,4'-butylidenebis(2-tert-butyl-5-methylphenol)

Reference: Yamasaki et al. (2008)

Study Details: 4,4'-butylidenebis(2-tert-butyl-5-methylphenol) (0, 5, 25, 125 mg/kg-day in olive oil) was administered via oral gavage for at least 28 days to male and female SD rats beginning at 8 weeks of age.

Primary Mode of Action: Unknown

NDMR Observation: A statistically significant increase in serum T4 was observed at the low dose in male rats; no change in T4 at the mid dose, and a statistically significant decrease in T4 at the high dose.

Decision/Comments: **Filter 4 Include.** Thyroid histopathology was not performed for the low and mid dosed male rat thyroids; however, no hypertrophy of the follicular epithelial cells was noted in the control or high dose male rats. No changes were found in serum T4 for female rats. An increase in serum TSH was found for both male and female rats at the high dose. It is logical that as the thyroid hormone decrease (e.g., T4-- males at the high dose), the serum TSH is elevated in an attempt to up-regulate the thyroid hormone. The reason for the increase in serum T4 is unknown and not supported by any other endpoint in this study. No additional studies on the thyroid effects of this compound were identified.

Table 2 Hormonal values (mean ± SD) in the enhanced TG 407 of 4,4′-butylidenebis(2-tert-butyl-5-methylphenol)

Items	Male				Female			
	Control (n = 10)	5 mg/kg/day (n = 10)	25 mg/kg/day (n = 10)	125 mg/kg/day (n = 10)	Control (n = 10)	5 mg/kg/day (n = 10)	25 mg/kg/day (n = 10)	125 mg/kg/day (n = 10)
T3 (ng/dl)	82 ± 7	87 ± 11	80 ± 7	67 ± 9*	87 ± 10	86 ± 6	87 ± 6	86 ± 9
T4 (μg/dl)	4.47 ± 0.53	5.25 ± 0.71*	4.86 ± 0.54	3.43 ± 0.56*	4.34 ± 0.57	4.88 ± 0.98	5.12 ± 0.54	4.85 ± 0.82
TSH (ng/ml)	2.61 ± 0.92	2.33 ± 1.01	2.69 ± 1.31	5.53 ± 3.77*	1.16 ± 0.45	1.13 ± 0.61	1.22 ± 0.70	2.18 ± 0.78*

* Significantly different from control at $P < 0.05$

5-ethylidene-2-norbornene

Reference: Ballantyne et al. (1997)

Study Details: 5-Ethylidene-2-norbornene (ENB; 0, 52, 148, 359 ppm) vapor was administered to male and female F344 rats. The rats were exposed 6 hr per day in inhalation chambers for 5 days, then given a 2 day rest period, then exposed for 4 more days.

Primary Mode of Action: Unknown

NDMR Observation: At the end of the 9 day exposure study, a significant decrease in serum T3 uptake compared to air-alone-exposed rats was reported for the low and high dose males, but not for the middle dose. A statistically significant increase in serum total T4 was seen in the middle male dose group, but not in any other male or female dose group. A statistically significant decrease in relative thyroid weight was found for the lowest dosed female rats, and no other changes in female thyroid weight were observed.

Decision/Comments: **Exclude Filter 3**. There appears to be a statistical issue surrounding the T3 uptake. The change in T3 uptake is -1.3, 0.76, and 2.3% for low-high dose with corresponding standard deviations of 1.3, 1.4, and 1%, respectively. The NMDRs for the T3 uptake or thyroid weight are not the determinants of the study-wide NOEL. A monotonic dose response effect was observed in colloid size for male rats and was significant at the lowest dose tested.

Table 5. Serum thyroid hormones for ENB- and air-alone-exposed rats in the 9-day study[a]

		Exposure group (ppm ENB)			
Serum measurement	Sex	0[b]	52	148	359
Free T_3 (pg ml^{-1})	M	2.08 ± 0.91	1.90 ± 0.46	1.94 ± 0.28	1.74 ± 0.61
	F	1.92 ± 0.26	1.44 ± 0.37	1.93 ± 0.61	1.74 ± 0.12
Total T_3 (ng dl^{-1})	M	103.22 ± 21.99	93.55 ± 12.71	105.05 ± 19.92	100.68 ± 8.76
	F	90.21 ± 9.25	80.88 ± 6.88	89.33 ± 14.81	101.56 ± 9.62
Free T_4 (ng dl^{-1})	M	1.87 ± 0.20	1.99 ± 0.26	2.06 ± 0.16	2.02 ± 0.26
	F	1.34 ± 0.45	1.31 ± 0.48	1.29 ± 0.34	1.61 ± 0.40
Total T_4 (μg dl^{-1})	M	5.65 ± 0.93	5.78 ± 0.50	6.76 ± 0.54**	6.66 ± 1.20
	F	3.54 ± 0.43	3.50 ± 0.50	3.72 ± 0.71	4.15 ± 0.67
T_3 uptake (%)	M	60.74 ± 1.05	59.46 ± 1.27*	59.98 ± 1.39	58.46 ± 1.02***
	F	53.58 ± 1.35	53.58 ± 1.17	53.04 ± 1.63	52.55 ± 1.26

[a]Results as mean ±SD; *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ compared to control.
[b]Air-alone control group.

Table 10. Thyroid gland weights of rats exposed to ENB vapor or air alone[a]

		Exposure groups			
Thyroid weight	Sex	Control	Low	Mid	High
9-Day study					
ENB (ppm)		0	52	148	359
Absolute (mg)	M	16 ± 1.9	16 ± 3.9	18 ± 1.5**	21 ± 5.2*
	F	16 ± 46	11 ± 2.5**	14 ± 3.0	15 ± 2.7
Relative to body weight (% × 10^{-3})	M	8 ± 1	8 ± 2.1	9 ± 0.8*	11 ± 2.6*
	F	12 ± 3.2	8 ± 1.6**	11 ± 2.4	12 ± 2
Subchronic study: 14-week sacrifice[b]					
ENB (ppm)		0	4.9	24.8	149.0
Absolute (mg)	M	18 ± 2.3	19 ± 2.7	19 ± 3.0	20 ± 2.0
	F	15 ± 2.6	14 ± 3.1	14 ± 1.9	13 ± 2.8
Relative to body weight (% × 10^{-3})	M	5 ± 0.6	6 ± 0.8	6 ± 0.6	6 ± 0.8
	F	8 ± 1.1	7 ± 1.6	7 ± 0.8	7 ± 1.4
Subchronic study: 18-week sacrifice[c]					
Absolute (mg)	M	20 ± 2.9	20 ± 4.8	18 ± 4.0	21 ± 2.1
	F	19 ± 3.6	20 ± 3.2	16 ± 6.0	18 ± 2.9
Relative to body weight (% × 10^{-3})	M	6 ± 0.5	6 ± 1.1	5 ± 1.5	6 ± 0.4
	F	9 ± 2.0	11 ± 1.9	8 ± 2.9	9 ± 1.5

[a]Results as mean ± SD; *$P < 0.05$ and **$P < 0.01$ compared to control.
[b]Sacrificed after the final exposure.
[c]Sacrificed 4 weeks after the final exposure.

Amiodarone

Reference: Freitas et al. (2011)

Study Details: Amiodarone (0, 0.5, 1, 5, 10, 15 uM) was added to cell culture of transfected rat pituitary tumor GH3 cells (GH3.TRE-Luc) for 24hrs.

Primary Mode of Action: Thyroid receptor mediated, deiodinase inhibitor

NDMR Observation: A statistically significant increase in cell proliferation as measured in luciferase reporter gene assay 24-hr after exposure to1 uM amiodaraone. No changes in luciferase induction were observed at 0.5 or 5 uM; with a decrease at the 2 highest concentrations.

Decision/Comments: **Exclude Filter 4c.** The reduction in luciferase induction at the higher dose levels (10 and 15 uM) is due to cytotoxicity, as indicated by the decreased resazurine. Visible evidence of cytotoxicity was reported by the authors at the 5uM concentration. The NMDR function for luciferase induction is due to cytotoxicity at concentrations exceeding 1uM.

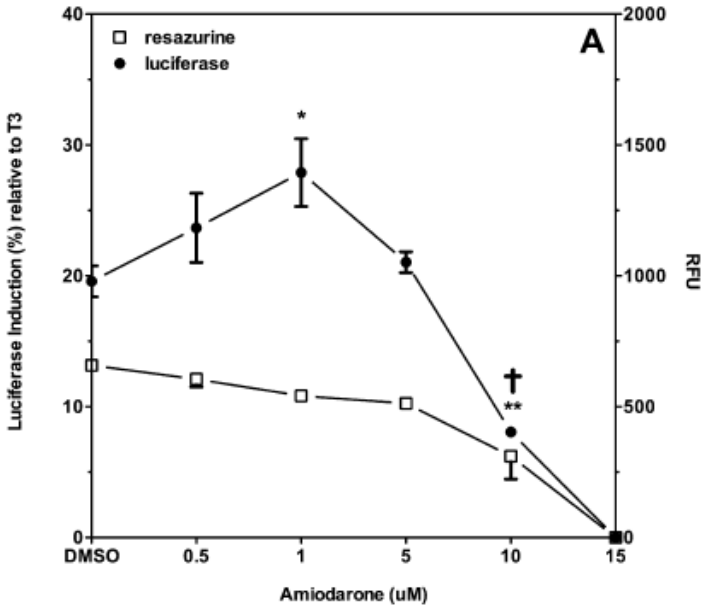


Fig. 6. GH3.TRE-Luc induction after 24 h exposure, in the presence of 0.25 nM of T_3, to (A) amiodarone and (B) sodium arsenite. Luciferase activity (●, left axis) relative to T_3 maximal induction (at 10 nM set at 100%, DMSO set at 0%) and the number of viable cells (□, right axis) expressed as relative fluorescence units (RFU). Error bars indicate SD of triplicate data points. *Significantly different from control (*$p < 0.05$, **$p < 0.01$). † = visible cytotoxicity.

Chlorpyrifos

Reference: Jeong et al. (2006)

Study Details: Chlorpyrifos-methyl (CPM; 0, 1, 10, or 100 mg/kg-bw in corn oil) was administered once daily via gavage to male and female SD rats for 14 days before breeding, throughout gestation, lactation, and for 13 weeks post weaning.

Primary Mode of Action: Unknown; possibly through cholinesterase inhibition.

NMDR Observation: Statistical significant increase in thyroid weight in PND 21 male rats at the lowest dose and in F1 females at lowest dose 13 weeks after weaning. Changes in thyroid weight were not observed at any other dose level.

Decision/Comments: **Exclude Filter 3**. The increase in male thyroid weight at PND21 was not seen in females. The increase in female thyroid weight at 13 weeks after weaning was not seen in males. The NMDR for the increase in thyroid weight is not the determinant of the study-wide NOEL. A monotonic dose response effect was observed in serum T4 and was significant at the lowest dose tested.

Table 4
Body weights and organ weights of F1 rats exposed to CPM at weanling time

Organs (g)	CPM dose (mg/kg)			
	0	1	10	100
F1 female body weight	53.3 ± 5.0	51.8 ± 4.9	57.0 ± 3.6	49.4 ± 3.9
Liver (%)	2.10 ± 0.31 (3.93 ± 0.26)	2.11 ± 0.34 (4.05 ± 0.41)	2.35 ± 0.15* (4.13 ± 0.18)	2.06 ± 0.25 (4.17 ± 0.26)
Spleen (%)	0.231 ± 0.040 (0.432 ± 0.055)	0.230 ± 0.042 (0.443 ± 0.060)	0.245 ± 0.019 (0.432 ± 0.042)	0.198 ± 0.019 (0.401 ± 0.024)
Kidney (%)	0.251 ± 0.024 (0.472 ± 0.028)	0.253 ± 0.044 (0.490 ± 0.088)	0.275 ± 0.031 (0.482 ± 0.035)	0.241 ± 0.033 (0.486 ± 0.033)
Adrenal gland (%)	0.0074 ± 0.0009 (0.0140 ± 0.0012)	0.0073 ± 0.0010 (0.0141 ± 0.0018)	0.0081 ± 0.0008 (0.0142 ± 0.0012)	0.0070 ± 0.0009 (0.0142 ± 0.0008)
Thyroid gland (%)	0.0070 ± 0.0012 (0.0132 ± 0.0022)	0.0058 ± 0.0010 (0.0112 ± 0.0019)	0.0068 ± 0.0014 (0.0120 ± 0.0024)	0.0064 ± 0.0012 (0.0130 ± 0.0027)
Ovary (%)	0.0070 ± 0.0012 (2.8257 ± 0.3937)	0.0066 ± 0.0012 (2.7771 ± 0.2809)	0.0069 ± 0.0013 (2.5599 ± 0.4648)	0.0056 ± 0.0008* (2.3944 ± 0.4867)
Uterus (%)	0.0276 ± 0.0041 (0.0520 ± 0.0079)	0.0264 ± 0.0073 (0.0510 ± 0.0122)	0.0257 ± 0.0059 (0.0454 ± 0.0111)	0.0244 ± 0.0037 (0.0497 ± 0.0082)
Brain (%)	1.342 ± 0.044 (2.537 ± 0.224)	1.310 ± 0.048 (2.542 ± 0.185)	1.324 ± 0.038 (2.332 ± 0.164)	1.286 ± 0.027* (2.615 ± 0.159)
Pituitary gland (%)	0.0024 ± 0.0006 (0.0045 ± 0.0010)	0.0021 ± 0.0006 (0.0042 ± 0.0012)	0.0025 ± 0.0005 (0.0044 ± 0.0008)	0.0022 ± 0.0005 (0.0044 ± 0.0007)
F1 male body weight	53.1 ± 3.8	54.6 ± 4.6	54.9 ± 4.5	48.0 ± 3.1*
Liver (%)	2.12 ± 0.22 (4.00 ± 0.22)	2.19 ± 0.23 (4.01 ± 0.14)	2.27 ± 0.23 (4.14 ± 0.16)	2.00 ± 0.18 (4.27 ± 0.52*)
Spleen (%)	0.213 ± 0.030 (0.403 ± 0.053)	0.222 ± 0.035 (0.406 ± 0.052)	0.242 ± 0.029 (0.442 ± 0.038)	0.225 ± 0.044 (0.489 ± 0.099*)
Kidney (%)	0.241 ± 0.019 (0.455 ± 0.032)	0.247 ± 0.022 (0.452 ± 0.017)	0.247 ± 0.026 (0.449 ± 0.021)	0.232 ± 0.022 (0.480 ± 0.017)
Adrenal gland (%)	0.0070 ± 0.0025 (0.0133 ± 0.0060)	0.0077 ± 0.0010 (0.0142 ± 0.0023)	0.0066 ± 0.0011 (0.0121 ± 0.0016)	0.0062 ± 0.0012 (0.0120 ± 0.0023)
Thyroid gland (%)	0.0054 ± 0.0017 (0.0103 ± 0.0031)	0.0076 ± 0.0040* (0.0141 ± 0.0072)	0.0060 ± 0.0012 (0.0108 ± 0.0021)	0.0051 ± 0.0019 (0.0096 ± 0.0045)
Testes (%)	0.147 ± 0.018 (0.276 ± 0.021)	0.147 ± 0.013 (0.269 ± 0.013)	0.155 ± 0.019 (0.283 ± 0.020)	0.136 ± 0.021 (0.296 ± 0.036)
Epididymis (%)	0.0142 ± 0.0035 (0.0265 ± 0.0054)	0.0155 ± 0.0020 (0.0287 ± 0.0046)	0.0147 ± 0.0033 (0.0267 ± 0.0055)	0.0158 ± 0.0030 (0.0335 ± 0.0068*)
Ventral prostate (%)	0.0233 ± 0.0045 (0.0439 ± 0.0082)	0.0255 ± 0.0060 (0.0470 ± 0.0116)	0.0244 ± 0.0042 (0.0443 ± 0.0056)	0.0231 ± 0.0052 (0.0472 ± 0.0126)
Seminal vesicle (%)	0.0197 ± 0.0024 (0.0372 ± 0.0037)	0.0233 ± 0.0050 (0.0430 ± 0.0093)	0.0218 ± 0.0057 (0.0401 ± 0.0110)	0.0184 ± 0.0033 (0.3901 ± 0.0071)
Brain (%)	1.344 ± 0.024 (2.545 ± 0.202)	1.378 ± 0.035* (2.539 ± 0.209)	1.369 ± 0.054 (2.505 ± 0.161)	1.307 ± 0.036* (2.732 ± 0.112)
Pituitary gland (%)	0.0024 ± 0.0008 (0.0045 ± 0.0014)	0.0023 ± 0.0002 (0.0042 ± 0.0054)	0.0021 ± 0.0005 (0.0038 ± 0.0009)	0.0020 ± 0.0005 (0.0043 ± 0.0010)

Organ weights were measured on PND 21. Values are mean ± S.D. of 12 weaned pups from CPM treated F0 female rats. (%) Relative weight represented the percentage of organ weight per body weight.

* Significantly different from control at $p < 0.05$.

Table 5
Body and organ weights of F1 rats exposed to CPM for 13 weeks

Organs (g)	CPM dose (mg/kg)			
	0	1	10	100
F1 female body weight	262.2 ± 11.7	274.7 ± 13.4	276.5 ± 18.3	250.8 ± 15.8
Liver (%)	8.59 ± 1.49 (3.27 ± 0.48)	8.29 ± 0.82 (3.02 ± 0.25)	8.54 ± 0.66 (3.09 ± 0.20)	8.36 ± 1.01 (3.33 ± 0.34)
Spleen (%)	0.594 ± 0.052 (0.226 ± 0.014)	0.591 ± 0.061 (0.215 ± 0.022)	0.630 ± 0.059 (0.228 ± 0.019)	0.601 ± 0.063 (0.240 ± 0.021)
Kidney (%)	0.757 ± 0.089 (0.2887 ± 0.0008)	0.757 ± 0.048 (0.2758 ± 0.0002)	0.765 ± 0.046 (0.2777 ± 0.0005)	0.744 ± 0.077 (0.2968 ± 0.0008)
Adrenal gland (%)	0.0268 ± 0.0023 (0.0102 ± 0.0009)	0.0286 ± 0.0019 (0.0104 ± 0.0007)	0.0346 ± 0.0035** (0.0125 ± 0.0010**)	0.0356 ± 0.0038** (0.0142 ± 0.0014**)
Thyroid gland (%)	0.0136 ± 0.0026 (0.0052 ± 0.0010)	0.0159 ± 0.0028* (0.0058 ± 0.0011)	0.0147 ± 0.0032 (0.0053 ± 0.0012)	0.0143 ± 0.0023 (0.0057 ± 0.0008)
Ovary (%)	0.0430 ± 0.0071 (0.0164 ± 0.0023)	0.0473 ± 0.0073 (0.0172 ± 0.0021)	0.0468 ± 0.0056 (0.0170 ± 0.0021)	0.0455 ± 0.0053 (0.0182 ± 0.0018)
Uterus (%)	0.381 ± 0.047 (0.145 ± 0.019)	0.464 ± 0.203 (0.169 ± 0.073)	0.364 ± 0.051 (0.132 ± 0.022)	0.512 ± 0.342 (0.206 ± 0.142)
Vagina (%)	0.115 ± 0.018 (0.044 ± 0.007)	0.126 ± 0.021 (0.046 ± 0.008)	0.122 ± 0.028 (0.040 ± 0.016)	0.119 ± 0.021 (0.048 ± 0.009)
Brain (%)	1.709 ± 0.133 (0.652 ± 0.042)	1.754 ± 0.062 (0.639 ± 0.024)	1.727 ± 0.061 (0.626 ± 0.030)	1.713 ± 0.030 (0.685 ± 0.045*)
Pituitary gland (%)	0.0130 ± 0.0022 (0.0050 ± 0.0009)	0.0117 ± 0.0010 (0.0043 ± 0.0003*)	0.0131 ± 0.0011 (0.0047 ± 0.0004)	0.0118 ± 0.0029 (0.0047 ± 0.0012)
F1 male body weight	420.1 ± 18.7	428.4 ± 29.4	432.2 ± 17.4	403.1 ± 21.7
Liver (%)	13.71 ± 0.91 (3.26 ± 0.09)	13.57 ± 1.00 (3.17 ± 0.16)	14.35 ± 0.89 (3.32 ± 0.19)	14.58 ± 1.35 (3.62 ± 0.28**)
Spleen (%)	0.727 ± 0.046 (0.173 ± 0.010)	0.758 ± 0.088 (0.177 ± 0.015)	0.762 ± 0.086 (0.176 ± 0.016)	0.787 ± 0.107 (0.195 ± 0.020**)
Kidney (%)	1.213 ± 0.053 (0.289 ± 0.012)	1.242 ± 0.086 (0.290 ± 0.018)	1.305 ± 0.111* (0.302 ± 0.022)	1.258 ± 0.107 (0.312 ± 0.025**)
Adrenal gland (%)	0.0232 ± 0.0013 (0.0055 ± 0.0003)	0.0229 ± 0.0025 (0.0054 ± 0.0006)	0.0291 ± 0.0040** (0.0067 ± 0.0008**)	0.0319 ± 0.0032** (0.0079 ± 0.0010**)
Thyroid gland (%)	0.0185 ± 0.0031 (0.0044 ± 0.0006)	0.0186 ± 0.0025 (0.0044 ± 0.0006)	0.0173 ± 0.0017 (0.0040 ± 0.0004)	0.0154 ± 0.0025* (0.0038 ± 0.0005*)
Testes (%)	1.899 ± 0.078 (0.452 ± 0.019)	1.866 ± 0.136 (0.436 ± 0.026)	1.904 ± 0.075 (0.441 ± 0.023)	1.805 ± 0.094* (0.449 ± 0.025)
Epididymis (%)	0.586 ± 0.028 (0.139 ± 0.005)	0.594 ± 0.037 (0.139 ± 0.007)	0.600 ± 0.046 (0.139 ± 0.012)	0.559 ± 0.026 (0.139 ± 0.009)
Ventral prostate (%)	0.526 ± 0.076 (0.125 ± 0.018)	0.521 ± 0.087 (0.122 ± 0.018)	0.495 ± 0.092 (0.115 ± 0.021)	0.422 ± 0.078** (0.105 ± 0.020*)
Seminal vesicle (%)	1.486 ± 0.120 (0.354 ± 0.030)	1.486 ± 0.166 (0.348 ± 0.045)	1.448 ± 0.198 (0.335 ± 0.041)	1.388 ± 0.124 (0.345 ± 0.030)
Brain (%)	1.806 ± 0.086 (0.430 ± 0.016)	1.884 ± 0.062** (0.441 ± 0.025)	1.869 ± 0.064* (0.433 ± 0.023)	1.835 ± 0.061 (0.456 ± 0.025**)
Pituitary gland (%)	0.0114 ± 0.0011 (0.0027 ± 0.0002)	0.0124 ± 0.0013 (0.0029 ± 0.0002)	0.0109 ± 0.0026 (0.0025 ± 0.0006)	0.0114 ± 0.0020 (0.0028 ± 0.0005)

Values are mean ± S.D. of 12 treated rats. (%) Relative weight represented the percentage of organ weight per body weight.
* Significantly different from control at $p < 0.05$.
** Significantly different from control at $p < 0.01$.

d-d-T80-prallethrin

Reference: Seki et al. (1987)

Study Details: d-d-T80-prallethrin (0, 120, 600, or 3000 ppm) was administered via the diet to adult male and female SD rats for 26 or 52 weeks of exposure.

Primary Mode of Action: Unknown, possibly through thyroid receptor.

NDMR Observation: A statistically significant decrease in the relative thyroid weight was seen at the low dose for male rats following 26 weeks of treatment to d-d-T80-prallethrin, while no change was seen in the mid dose group, and a statistically significant increase the relative thyroid weights was seen at the high dose. In females, a statistically significant decrease in thyroid weight was found in at the low and mid dose groups, while the high dose resulted in an increase in relative thyroid weight following 26 weeks of exposure. After 52 weeks of exposure, a statistically significant decrease was found in relative thyroid weight of males at the low dose and an increase at the high dose; however, no change was seen at the middle dose.

Decision/Comments: **Exclude Filter 3.** The thyroid weight effects seen after 26 weeks of exposure are not consistent with the 52 week exposure results and inconsistent between the sexes. The NMDRs observed for changes in relative thyroid weight are not the sole determinants of the study-wide LOEL. Other effects were observed in blood biochemistry panel at 120 ppm.

Table 7-1 Relative organ weight in rats after 26-week treatment of *d*-*d*-T80-prallethrin.

Sex	Dose (ppm)		BRN g %	LUG g %	HRT g %	SPL g %	KID g %	LIV g %	THR mg %	PIT mg %	ADR mg %	TST g %	PRT g %	OVY mg %
Male	0	N	12	12	12	12	12	12	12	12	12	12	12	
		AV	.3749	.2873	.2788	.1381	.6116	2.281	4.395	2.848	9.380	.5762	.1624	
		SE	.0096	.0071	.0059	.0046	.0139	.0371	.1556	.0744	.4841	.0168	.0113	
	120	N	12	12	12	12	12	12	12	12	12	12	12	
		AV	.3817	.2970	.2709	.1398	.5962	2.356	3.596	2.874	9.307	.5765	.1395	
		SE	.0103	.0081	.0060	.0024	.0133	.0358	.2452*	.0955	.3334	.0181	.0080	
	600	N	12	12	12	12	12	12	12	12	12	12	12	
		AV	.3754	.2901	.2714	.1420	.5906	2.449	4.205	2.642	8.903	.5674	.1634	
		SE	.0103	.0071	.0061	.0039	.0145	.0450**	.1337	.1048	.4615	.0222	.0116	
	3,000	N	12	12	12	12	12	12	12	12	12	12	12	
		AV	.4004	.3058	.2940	.1382	.6747	2.906	5.327	2.697	9.127	.5696	.1494	
		SE	.0103	.0116	.0086	.0054	.0198*	.0638**	.3324*	.0515	.4544	.0345	.0134	
Female	0	N	12	12	12	12	12	12	12	12	12			12
		AV	.6485	.4456	.3366	.1651	.6783	2.333	5.895	8.313	21.35			17.93
		SE	.0174	.0246	.0059	.0064	.0262	.0609	.2195	.9979	1.737			2.000
	120	N	12	12	12	12	12	12	12	12	12			12
		AV	.6216	.4248	.3321	.1640	.6255	2.299	4.829	8.003	21.61			17.77
		SE	.0165	.0115	.0089	.0053	.0178	.0708	.2723**	.6759	.9815			1.871
	600	N	12	12	12	12	12	12	12	12	12			12
		AV	.6782	.3992	.3554	.1600	.6501	2.317	5.123	7.966	22.14			17.11
		SE	.0212	.0131	.0083	.0064	.0130	.0781	.1900**	.6264	1.007			1.317
	3,000	N	12	12	12	12	12	12	12	12	12			11
		AV	.7105	.4272	.3533	.1630	.7387	2.770	7.099	8.354	20.93			15.62
		SE	.0238*	.0083	.0112	.0041	.0221	.0863**	.4058*	.8906	1.384			1.155

Significant differences from control * ; $p<0.05$, ** ; $p<0.01$
BRN ; brain LUG ; lung HRT ; heart SPL ; spleen KID ; both kidneys LIV ; liver THR ; thyroid PIT ; pituitary ADR ; both adrenals
TST ; both testes PRT ; prostate OVY ; both ovaries
Relative organ weights are expressed as % or x 10^{-1} % (mg %)

Table 7-2 Relative organ weight in rats after 52-week treatment of *dd*-T80-prallethrin.

Sex	Dose (ppm)		BRN g %	LUG g %	HRT g %	SPL g %	KID g %	LIV g %	THR mg %	PIT mg %	ADR mg %	TST g %	PRT g %	OVY mg %
Male	0	N	23	23	23	23	23	23	23	23	23	23	23	
		AV	.3454	.2678	.2486	.1649	.6009	2.326	4.577	2.638	8.688	.4771	.0914	
		SE	.0065	.0067	.0048	.0130	.0157	.0674	.1310	.0806	.2862	.0243	.0074	
	120	N	23	23	23	23	23	23	23	23	23	23	23	
		AV	.3284	.2681	.2475	.1459	.5831	2.349	4.122	2.755	7.856	.4869	.0816	
		SE	.0072	.0068	.0047	.0045	.0101	.0438	.1352*	.2013	.2966 *	.0136	.0072	
	600	N	23	23	23	23	23	23	23	23	23	23	23	
		AV	.3292	.2564	.2387	.1365	.5709	2.251	4.437	2.574	8.131	.4654	.0914	
		SE	.0079	.0048	.0038	.0030*	.0126	.0329	.1313	.1258	.4143	.0175	.0066	
	3,000	N	23	23	23	23	23	23	23	23	23	23	23	
		AV	.3318	.2588	.2439	.1385	.6209	2.811	5.445	2.722	7.862	.5005	.1044	
		SE	.0051	.0054	.0037	.0038	.0102	.0530**	.1692**	.2457	.2356*	.0135	.0081	
Female	0	N	24	24	24	24	24	24	24	24	24			24
		AV	.5449	.3484	.2846	.1581	.5776	2.145	6.559	6.936	18.69			14.35
		SE	.0124	.0099	.0054	.0051	.0238	.0357	.2153	.4185	.6050			1.090
	120	N	24	24	24	24	24	24	24	24	24			24
		AV	.5119	.3313	.2784	.1465	.6006	2.230	6.039	6.860	18.37			12.06
		SE	.0153	.0089	.0060	.0037	.0145	.0448	.2308	.5096	.7285			.8332
	600	N	24	24	24	24	24	24	24	24	24			24
		AV	.5290	.3315	.2890	.1472	.5938	2.199	6.699	7.068	18.38			14.79
		SE	.0154	.0088	.0061	.0047	.0152	.0356	.2506	.3367	1.017			1.764
	3,000	N	23	23	23	23	23	23	23	23	23			23
		AV	.5698	.3529	.2905	.1444	.6072	2.548	6.997	7.029	17.22			12.77
		SE	.0160	.0120	.0074	.0048	.0115	.0554**	.1950	.4156	.6226			1.056

Significant differences from control * p; <0.05, **; p<0.01.
BRN ; brain LUG ; lung HRT ; heart SPL ; spleen KID ; both kidneys LIV ; liver THR ; thyroid PIT ; pituitary ADR ; both adrenals
TST ; both testes PRT ; prostate OVY ; both ovaries
Relative organ weights are expressed as % or x 10^{-3} % (mg %)

Dibromoacetonitrile

Reference: Poon et al. (2003)

Study Details: Dibromoacetonitrile (0, 0.1, 1, 10, 100 ppm) was administered to adult male and female SD rats in drinking water for 13 weeks. Measurements were taken at the end of the study.

Primary Mode of Action: Unknown, possible effect on liver metabolism, metabolite (cyanide/thiocyanate) may inhibit sodium/iodide symporter.

NDMR Observation: The thyroid measure "collapse/angularity" exhibited an NMDR for incidence and severity in males only, with effects at lowest two doses and the highest dose; however, no effect was seen at second highest dose (10 ppm). Thyroid cytoplasmic vacuolation also had an NMDR with a decrease in vacuolation at the lowest and second highest dose, while no effect was seen at the other two doses.

Decision/Comments: **Exclude Filter 3.** The NMDRs for the thyroid measures are not the determinant of the study-wide LOEL. A similar dose response curve was not found for thyroid effects in female rats. Effects on a bone marrow endpoint occurred at the lowest dose tested. Statistics were not performed on these results.

Table 7
Histopathological changes following 13-week exposure to dibromoacetonitrile in drinking water

Dibromoacetonitrile in drinking water (ppm)	Male					Female				
	Cont.	0.1 ppm	1 ppm	10 ppm	100 ppm	Cont.	0.1 ppm	1 ppm	10 ppm	100 ppm
Thyroid										
Collapse/Angularity	1[a] (0.05)[b]	8 (0.5)	5 (0.35)	1 (0.1)	8 (0.75)	2 (0.08)	1 (0.05)	1 (0.05)	1 (0.17)	9 (0.80)
Increased epithelial height	5 (0.48)	8 (0.65)	10 (1.4)	10 (1.4)	9 (1.40)	5 (0.55)	6 (0.40)	10 (0.7)	8 (1.05)	9 (1.55)
Cytoplasmic vacuolation	5 (0.38)	0	7 (0.7)	2 (0.35)	7 (0.35)	0	0	4 (0.18)	4 (0.20)	10 (0.80)
Vesiculation of nuclei	0	1 (0.15)	8 (0.58)	9 (1.48)	6 (0.50)	0	5 (0.20)	10 (0.65)	8 (0.62)	10 (1.65)
Bone Marrow										
Increased myeloid/erythroid	0	7 (1.1)	7 (0.95)	4 (0.65)	8 (1.4)	2 (0.3)	2 (0.05)	8 (0.75)	5 (0.52)	7 (1.1)
Renal tubule outer cortex										
Cytoplasmic inclusion	9 (0.75)	n.d.[c]	n.d.	n.d.	10 (2.0)	0	n.d.	n.d.	n.d.	0

[a] Number of animals out of 10 per group showing changes.
[b] Average Severity Index, where 1 = minimal, 2 = mild, 3 = moderate and 4 = severe. The scores were obtained by dividing the sum of total scores by the number of tissues examined. For tissue changes that are focal, locally extensive and multifocal, a score of less than integer is assigned as follows: minimal focal = 0.25, minimal, locally extensive = 0.5, minimal multifocal = 0.75, mild focal = 1.25, mild, locally extensive = 1.50, mild multifocal = 1.75.
[c] n.d., not done.

Diethylstilbestrol (DES)

Reference: Shin et al. (2009)

Primary Mode of Action: Estrogen agonist.

Study Details: Diethylstibestrol (DES 0 10, 20, 40 µg/kg/day) was administered to juvenile male SD rats by oral gavage for 20 days. Animals were sacrificed 24 hours after the last dose and blood and tissues collected.

NMDR Observations: A statistically significant increase in thyroid gland weight at the lowest dose tested with no significant change at the two higher dose levels.

Decision/Comments: **Exclude Filter 3**. The NMDR for thyroid weight was not the determinant of the study-wide NOEL. Significant declines in liver weight and serum levels of luteinizing hormone were observed at all dose levels tested. No significant changes in serum T4 were detected.

Table 2. Absolute (A) and relative (R) organ weights in control and DES treated male rats

Group		Liver	Heart	Combined adrenals	Combined kidneys	Thyroid glands	Hypophysis
Control	A	9.61 ± 0.07	1.01 ± 0.07	0.046 ± 0.007	2.44 ± 0.10	0.013 ± 0.003	0.011 ± 0.001
	R	3.09 ± 0.18	0.33 ± 0.02	0.015 ± 0.002	0.79 ± 0.05	0.004 ± 0.001	0.003 ± 0.001
DES 10 µ/kg	A	12.12 ± 0.65*	1.04 ± 0.07	0.069 ± 0.006*	2.42 ± 0.31	0.017 ± 0.003*	0.011 ± 0.002
	R	4.01 ± 0.16*	0.34 ± 0.02	0.023 ± 0.002*	0.80 ± 0.10	0.006 ± 0.001*	0.004 ± 0.001
DES 20 µ/kg	A	12.94 ± 0.58*	1.02 ± 0.05	0.071 ± 0.011*	2.31 ± 0.12	0.010 ± 0.003	0.010 ± 0.003
	R	4.26 ± 0.21*	0.34 ± 0.01	0.024 ± 0.003*	0.77 ± 0.04	0.003 ± 0.001	0.004 ± 0.001
DES 40 µ/kg	A	9.84 ± 0.73	0.87 ± 0.03*	0.073 ± 0.005*	2.20 ± 0.21	0.013 ± 0.001	0.011 ± 0.001
	R	3.85 ± 0.17*	0.34 ± 0.02	0.029 ± 0.002*	0.86 ± 0.05	0.005 ± 0.001	0.004 ± 0.001*

Values are mean ± SD; n=10. *Significantly different from control (P<0.05).

Table 3. Serum hormone levels in control and DES treated male rats

Group		Testosterone (ng/ml)	Estradiol (pg/ml)	Thyroxine (ng/ml)	LH (pg/ml)
Control		2.1 ± 0.31	28.7 ± 8.89	56.6 ± 5.51	23.3 ± 8.520
DES	10 µ/kg	0.5 ± 0.19*	22.4 ± 3.11	75.6 ± 17.43	7.9 ± 1.033*
	20 µ/kg	0.6 ± 0.69*	22.9 ± 11.57	69.1 ± 13.05	10.7 ± 5.175*
	40 µ/kg	0.3 ± 0.21*	23.5 ± 4.92	54.1 ± 13.48	5.1 ± 0.54*

Values are mean ± SD; n=10. *Significantly different from control (P<0.05).

Ethylenethiourea (ETU)

References: Graham et al. (1975); Graham et al. (1973)

Note: Both papers report data from the same study.

Study Details: Ethylene thiourea (ETU; 0, 5, 25, 125, 250, 500 ppm) was fed to male and female Charles River rats in the diet for 2, 6, 12, 18 or 24 months, beginning when the animals were approximately 5 weeks old. At the end of the feeding period, rats were administered radioactive iodine, then fasted for 24 hours and the thyroids excised and radioactivity measured.

Primary Mode of Action: Inhibition of TPO.

NDMR Observation: A statistical NMDR in thyroid iodine uptake was found following 2, 18 and 24 months of exposure in male rats only. After 2 months of exposure, a statistically significant increase in ^{131}I uptake was found at the 3 lowest doses, and no change at the two highest doses. After 18 months of exposure, a statistically significant increase in thyroid iodine uptake was found for the middle and next to lowest dose, while no change was seen at the lowest and next to highest dose. At the highest dose a statistically significant decrease in uptake was observed. After 24 months of exposure a statistically significant increase in 131I uptake was found at the lowest dose and a decrease at the highest dose, with no change at any of the middle doses.

Decision/Comments: **Exclude Filter 4c.** A similar, but not statistically significant NMDR was observed in females at 18 months of exposure; however, the inflection point was at 125 ppm instead of 25 ppm. Thyroid weight changes are statistically significant at 250 and 500 ppm. Changes in iodine uptake could be the result of compensatory changes in thyroid gland. Graham et al. (1975) reported a high incidence of thyroid tumors in the two high dose groups, which may account for the decrease in thyroid iodine uptake. Tumors do not take up iodine, so it is expected that there would be less uptake the high doses where one see tumors but more uptake at the lower doses where one sees only hyperplasia. The increases in ^{131}I uptake were not reproduced by O'Neil and Marshall (1984) who fed rats 75 or 100ppm ETU in the diet for 46 or 91 days and performed similar measurements in male and female SD rats. At dose levels and time points roughly comparable across the studies (2 months) no increases in ^{131}I thyroid uptake were observed (O'Neil and Marshall, 1984).

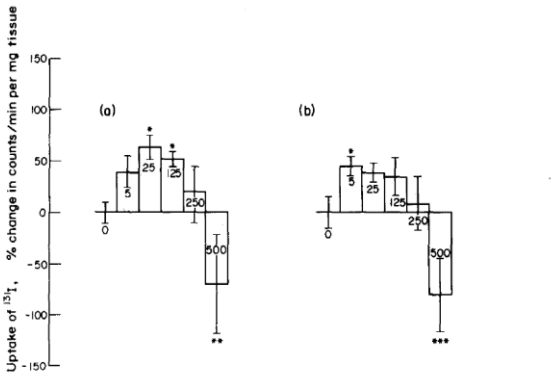


Fig. 2. Mean uptake of ^{131}I by the thyroids of groups of five male rats fed 0–500 ppm ETU for (a) 18 or (b) 24 months. Vertical bars represent the SEM and asterisks indicate results differing significantly from the control: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

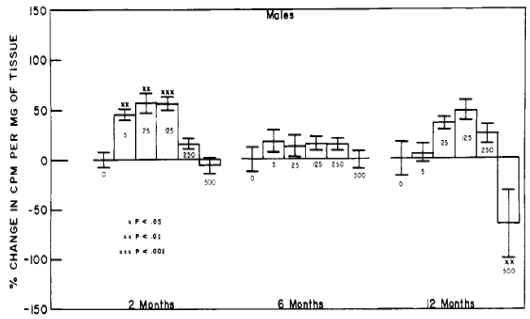


Figure 2. The uptake of ^{131}I by the thyroids (expressed as percent change in cpm/mg of tissue) of male rats. Vertical bars are the SE.

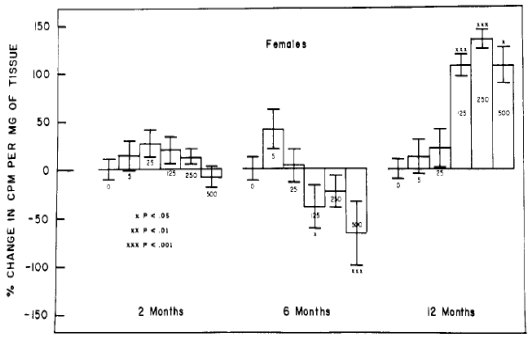


Figure 3. The uptake of ^{131}I by the thyroids (expressed as percent change in cpm/mg of tissue) of female rats.

Furan

Reference: Gill et al. (2010)

Study Details: Furan (0.0, 0.03, 0.12, 0.5, 2.0, 8.0 mg/kg in corn oil) was given to 6-7 week old male and female Fischer-344 rats 5 days/week for a 90-day study.

Primary Mode of Action: Unknown, possible effect on liver metabolism.

NDMR Observation: In males, an increase in serum T3 was seen at 0.12, 2.0, and 8.0 mg/kg-day, while no change from control levels was noted in the lowest or middle dose group. In females, an increase in serum T3 was seen at 2.0 mg/kg-day and no other changes in serum T3 were found.

Decision/Comments: **Exclude Filter 3**. The NMDR for serum T3 is not the sole determinant of the study-wide LOAEL. A monotonic dose response effect was observed for serum T4 in males and was significant at 0.12 mg/kg-day.

TABLE 5A.—Clinical biochemistry parameters in male rats.

	Furan dose (mg/kg bw/day)						
	0	0.03	0.12	0.5	2.0	8.0	*p* value for trend
Amylase	2702 ± 146	2686 ± 189	2518 ± 106.3	2627 ± 263	2270 ± 114*	2184 ± 170*	<.001[a]
Albumin	37.9 ± 0.67	38.20 ± 0.72	38.20 ± 0.57	38.5 ± 1.2	38.5 ± 0.70	39.33 ± 1.0*	<.001[a]
Globulin	19.9 ± 1.2	19.8 ± 1.2	19.7 ± 1.1	19.2 ± 1.2	17.65 ± 0.7*	17.92 ± 0.6*	<.001[a]
Albumin globulin ratio	1.9 ± 0.10	2.0 ± 0.15	2.0 ± 0.12	2.03 ± 0.12	2.19 ± 0.07*	2.21 ± 0.07*	<.001[a]
Glucose	13.9 ± 1.2	13.3 ± 1.4	12.2 ± 1.1*	12.4 ± 1.2	11.8 ± 1.1**	10.8 ± 1.0*	<.001[a]
Total protein	57.8 ± 1.5	58.0 ± 1.2	57.9 ± 1.3	57.9 ± 2.0	56.2 ± 1.1	57.25 ± 1.3	.015[a]
Cholesterol	1.7 ± 0.15	1.7 ± 0.14	1.8 ± 0.12	1.8 ± 0.12	1.9 ± 0.1	1.9 ± 0.16*	<.001[a]
Triglycerides	1.96 ± 0.66	1.9 ± 0.18	1.57 ± 0.32	1.43 ± 0.30*	0.85 ± 0.15*	0.82 ± 0.16*	<.001[a]
Conjugated bilirubin	0.24 ± 0.18	0.22 ± 0.07	0.22 ± 0.12	0.28 ± 0.16	0.33 ± 0.14	0.32 ± 0.1	<.001[a]
Total bilirubin	1.2 ± 0.16	1.1 ± 0.3	1.0 ± 0.3	1.1 ± 0.3	1.3 ± 0.3	1.4 ± 0.163	.029[a]
Calcium	2.7 ± 0.05	2.7 ± 0.05	2.7 ± 0.05	2.7 ± 0.02	2.7 ± 0.05	2.8 ± 0.06	.138
Chloride	97.9 ± 0.9	98.9 ± 1.2	98.3 ± 0.80	98.7 ± 0.8	98.8 ± 0.9	98.8 ± 1.0	.0554
Magnesium	0.93 ± 0.03	0.89 ± 0.03*	0.91 ± 0.03	0.89 ± 0.04	0.89 ± 0.04	0.88 ± 0.04**	.0154[a]
Potassium	4.21 ± 0.26	4.43 ± 0.23	4.33 ± 0.26	4.318 ± 0.33	4.26 ± 0.31	4.38 ± 0.26	.890
Phosphorus	2.1 ± 0.16	2.1 ± 0.17	2.1 ± 0.22	2.2 ± 0.25	2.4 ± 0.1*	2.7 ± 0.11*	.0001[a]
Triiodothyronine-T3 (nmol/L)	1.38 ± 0.29	1.67 ± 0.30	1.84 ± 0.37**	1.62 ± 0.39	1.89 ± 0.42*	1.79 ± 0.25**	.004[a]
Thyroxine-T4 (nmol/L)	54.39 ± 8.65	65.94 ± 16.31	71.03 ± 13.8**	72.18 ± 14.77**	83.65 ± 12.49*	81.73 ± 14.46*	.0001[a]

TABLE 5B.—Clinical biochemistry parameters in female rats

	Furan Dose (mg/kg bw/day)						
	0	0.03	0.12	0.5	2.0	8.0	*P* value for trend
Amylase (U/L)	1732 ± 262	1622 ± 120	1548 ± 98	1632 ± 149	1499 ± 168**	1542 ± 168	0.0038[a]
Albumin (g/L)	38.9 ± 0.9	39.0 ± 1.2	38.7 ± 1.4	40.25 ± 1.5	41.25 ± 2.7**	44.83 ± 2.2*	0.0001[a]
Globulin (g/L)	17.4 ± 0.8	18.0 ± 1.2	17.9 ± 1.04	17.58 ± 0.8	18.25 ± 2.9	18.42 ± 1.6	0.1673
Albumin Globulin ratio	2.3 ± 0.09	2.2 ± 0.17	2.17 ± 0.10	2.3 ± 0.12	2.3 ± 0.36	2.5 ± 0.27	0.0034[a]
Glucose (mmol/L)	11.8 ± 0.8	12.4 ± 0.9	11.3 ± 1.0	11.3 ± 0.9	10.1 ± 0.8*	10.4 ± 0.9*	0.0001[a]
Total protein (g/L)	56.33 ± 1.4	57.0 ± 1.2	56.6 ± 2.1	57.8 ± 2.03	59.7 ± 2.1*	63.3 ± 2.3*	0.0001[a]
Cholesterol (mmol/L)	2.4 ± 0.15	2.3 ± 0.14	2.2 ± 0.19	2.3 ± 0.17	2.3 ± 0.28	2.4 ± 0.26	0.865
Triglycerides (mmol/L)	1.3 ± 0.38	1.3 ± 0.60	0.95 ± 0.30	0.92 ± 0.17	0.61 ± 0.09*	0.68 ± 0.33*	0.0001[a]
Conjugated bilirubin (umol/L)	0.21 ± 0.07	0.19 ± 0.1	0.23 ± 0.08	0.23 ± 0.08	0.23 ± 0.05	0.25 ± 0.13	0.184
Total bilirubin (umol/L)	1.2 ± 0.16	1.1 ± 0.28	1.1 ± 0.30	1.1 ± 0.34	1.3 ± 0.27	1.4 ± 0.16	0.029[a]
Calcium (mmol/L)	2.7 ± 0.03	2.7 ± 0.04	2.7 ± 0.06	2.7 ± 0.04	2.7 ± 0.06	2.8 ± 0.05*	0.0001[a]
Chloride (mmol/L)	100.8 ± 1.4	101.3 ± 0.9	100.6 ± 1.8	100.6 ± 0.7	100.6 ± 1.1	99.58 ± 1.2	0.0048[a]
Magnesium (mmol/L)	0.94 ± 0.06	0.96 ± 0.06	0.94 ± 0.04	0.92 ± 0.04	0.95 ± 0.04	0.96 ± 0.03	0.792
Potassium (mmol/L)	3.75 ± 0.24	3.7 ± 0.20	3.8 ± 0.21	3.8 ± 0.20	3.9 ± 0.35	3.9 ± 0.35	0.0313[a]
Phosphorus (mmol/L)	1.9 ± 0.25	1.91 ± 0.22	2.1 ± 0.34	2.1 ± 0.27	2.5 ± 0.21*	2.7 ± 0.19*	0.0001[a]
Triiodothyronine-T3 (nmol/L)	1.56 ± 0.53	1.74 ± 0.63	1.70 ± 0.40	1.97 ± 0.38	2.14 ± 0.56**	2.1 ± 0.35	0.0012[a]
Thyroxine-T4 (nmol/L)	50.59 ± 9.9	47.06 ± 10.7	49.06 ± 17.1	55.77 ± 12.43	56.83 ± 15.35	54.93 ± 9.12	0.0699

* Data are significantly different from corresponding control using one-way ANOVA and using TUKEY column comparison (P <0.01).
** Data are significantly different from corresponding control using one-way ANOVA and using TUKEY column comparison (P <0.05).
[a] significant linear trend

Hexachlorobenzene (HCB)

Reference: van Raaij et al. (1993)

Study Details: Hexachlorobenzene (HCB; 0, 3, 10, 30, 100, 300, 1000 ppm in an emulsion of water and Tween-20) was administered to adult male Wistar rats (200-300g) via gavage 3 days/week for 5 weeks. Measurements were obtained two days post dosing.

Primary Mode of Action: Effect on liver metabolism and possible effect of metabolite on serum binding proteins.

NDMR Observation: A statistically significant decrease in serum free T4 was seen at the next to highest dose. No other changes in serum fT4 were noted.

Decision/Comments: **Exclude Filter 3.** The NMDR for the serum free T4 is not the determinant of the study-wide LOEAL. A monotonic dose response effect was observed in total T4 and was significant at the next to highest dose (2.6 mmol/kg) tested. The statistical significance of free T4 in the male rats is likely due to the lower standard deviation for that group.

Table 1. Effect of HCB on thyroid hormone status

HCB (mmol/kg)*	N	Expt (weeks)	TT4 (nmol/L)	FT4 (pmol/L)	TT3 (nmol/L)	TSH (ng/mL)
0.0	4–5	2	21.4 ± 2.1	14.7 ± 2.2	0.44 ± 0.06	3.5 ± 0.5
0.9	3–5	2	23.7 ± 2.6	17.2 ± 2.2	0.44 ± 0.08	4.9 ± 1.1
1.7	3–5	2	19.2 ± 2.7	13.3 ± 1.9	0.42 ± 0.08	5.1 ± 1.6
2.6	5	2	16.1 ± 3.7†	11.8 ± 0.7†	0.33 ± 0.13	4.6 ± 1.6
3.5	4–5	2	13.5 ± 1.2†	12.1 ± 1.2	0.38 ± 0.07	4.8 ± 1.8
0.0	3–5	4	35.3 ± 3.8	9.2 ± 1.3	0.48 ± 0.06	7.6 ± 0.4
3.5	4–5	4	20.9 ± 3.4†	2.7 ± 0.6†	0.50 ± 0.17	11.9 ± 2.9†

Groups of rats (N = 3–5) were orally dosed three times a week with different doses of HCB for a period of 2 or 4 weeks. Within 24 hr after the last dose, blood was collected from the tail, and thyroid hormone parameters were determined.

* The doses of HCB expressed in mg/kg are 0, 250, 500, 750 and 1000, respectively. Statistical significance: †$P < 0.05$.

Imidazole

Reference: Comer et al. (1985)
Study Details: SC-37211 (0, 20, 60, 200 ppm) was given in the drinking water to male CD rats in the diet for 21 days.
Primary Mode of Action: Unknown, possible effect on liver metabolism.
NDMR Observation: A statistically significant decrease in serum T4 was seen at the middle dose following 2 weeks of treatment. No other statistical changes were found for serum T4.
Decision/Comments: **Exclude Filter 3**. The NMDR for serum T4 is not the determinant of the study-wide LOEL. A monotonic dose response effect was observed for serum T3 and was significant at the lowest dose tested. Also, the standard deviation in serum T4 is greater for the highest dose compared to the middle dose. The NMDR effect is likely statistical only and not biological.

TABLE 1

SERUM TRIIODOTHYRONINE (T_3) AND THYROXINE (T_4) CONCENTRATIONS[a]

SC-37211 (mg/kg/day)	T_3 (ng/dl)	T_4 (μg/dl)
	2 weeks of treatment	
0	94.4 ± 19.1	4.6 ± 1.2
20	74.5 ± 11.2[b]	4.0 ± 0.6
60	67.7 ± 14.8[b]	3.5 ± 0.7[b]
200	70.3 ± 10.6[b]	3.7 ± 0.9
	2 weeks of recovery	
0	85.0 ± 15.4	4.8 ± 0.2
20	78.3 ± 23.4	4.9 ± 0.9
60	83.5 ± 15.5	5.3 ± 1.4
200	77.2 ± 12.1	5.5 ± 1.0

[a] $\bar{x}$ ± SD of 8 to 10 animals after 2 weeks of treatment and 5 animals after 2 weeks of recovery.
[b] t test against control significant at the 5% level.

Methimazole (MMI)

Reference: Hood et al. (1999)

Study Details: MMI (0, 3, 10, 30, 100, 300, 1000 ppm) or PTU (0, 1, 3, 10, 30, 100, 300 ppm) were administered to adult male LE rats in the diet for 21 days. Measurements were obtained at 3 days before and at 3, 4, 14, and 21 days of exposure.

Primary Mode of Action: TPO inhibition (MMI & PTU); deiodinase inhibitor (PTU).

NMDR Observation: Statistically significant increase in serum total T4 and free T3 following exposure to 3ppm MMI for 21 days, with reductions at higher doses.

Decision/Comments: **Filter 4 Include** NMDR observed at low-dose level which would be used at the LOEL for this study. No additional studies were located for this dose or lower. Increases in TT4 and fT3 may be due to compensatory mechanisms to maintain serum T3, including deiodinase activation, recovery of T3 metabolites and enterohepatic circulation.

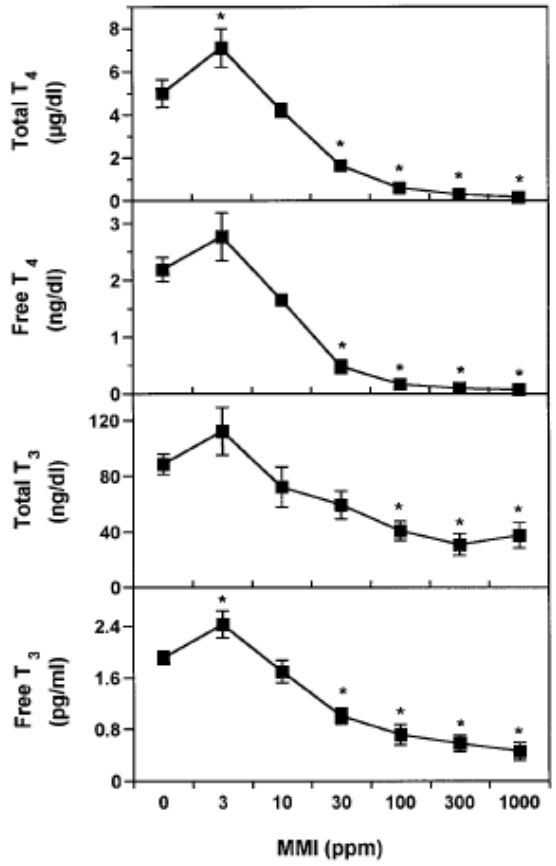


FIG. 5. Dietary concentration-dependent effects of MMI on serum thyroid hormone concentrations. Total T_4 (µg/dl), free T_4 (ng/dl), total T_3 (ng/dl) and free T_3 (pg/ml) were measured on treatment day 21. *Significantly different ($p < 0.05$) from controls.

Methoxychlor

Reference: Okazaki et al. (2002)

Study Details: Methoxyclor (0, 20, 100, 500 mg/kg) was administered via oral gavage to five week old male and female CrJ:CD(SD)IGS rats daily for 28 days. Male rats were sacrificed the day after the 28th administration, while female rats were killed on the diestrus day during the 4 days after the 28th administration.

Primary Mode of Action: Unknown, possible effect on liver metabolism.

NDMR Observation: A statistically significant increase in serum T4 was found in male rats dosed with 20 and 100 mg/kg, and no significant effect from control was found in the animals dosed with the highest dose.

Decision/Comments: **Exclude Filter 3.** The NMDR for serum T4 is not the sole determinant of the study-wide LOEL. A monotonic dose response effect was observed in other blood biochemistry parameters where the effect was seen at the lowest dose (e.g., cholesterol and albumin). *Note*: There appears a typo in the table such that the control T4 concentration for male rats should be 4.7, not 47 ug/dL. This is evident based on the statistics reported, too. There were no changes in thyroid pathology in males or females at any doses. Gender was not included in the statistical models.

Table 3 Serum hormone levels in male and female rats treated with methoxychlor for 28–31 days

Sex	Dose mg/kg	No. of animals	T3 (ng/ml)	T4 (μg/dl)	TSH (ng/ml)	Testosterone (ng/ml)	Estradiol (pg/ml)	FSH (ng/ml)	LH (ng/ml)	Prolactin (ng/ml)
Male	0	10	1.09 ± 0.09	47 ± 0.7	8.0 ± 3.2	5.0 ± 3.3	207 ± 29	171 ± 32	17.9 ± 2.4	36.8 ± 30.4
	20	10	1.12 ± 0.13	5.7 + 1.1*	10.3 ± 2.9	5.0 ± 3.5	190 ± 45	167 ± 28	15.1 ± 1.9	74.1 ± 55.7
	100	10	1.21 ± 0.09	5.8 ± 0.4**	10.1 ± 3.5	2.9 ± 1.7	234 ± 83	206 ± 31	11.7 ± 2.2**	127.4 ± 50.7**
	500	9	1.26 ± 0.14**	5.4 ± 0.8	15.8 + 7.8**	2.1 ± 0.8*	232 ± 55	257 ± 93*	14.8 ± 4.3	115.2 ± 61.0**
Female	0	10	1.01 ± 0.18	4.5 ± 0.9	13.1 ± 5.2	0.8 ± 0.5	185 ± 89	186 ± 27	15.4 ± 2.0	32.6 ± 19.6
	20	10	1.04 ± 0.14	4.7 ± 0.7	12.8 ± 4.2	1.3 ± 0.9	164 ± 70	156 ± 23	14.1 ± 2.4	34.7 ± 23.8
	100	10	1.25 ± 0.15**	5.5 ± 1.0	13.0 ± 4.9	0.8 ± 0.2	245 ± 151	168 ± 31	12.4 ± 2.1**	43.1 ± 27.6
	500	10	1.25 ± 0.11**	5.9 ± 0.8**	12.1 ± 5.93	1.2 ± 0.4	209 ± 108	186 ± 43	11.0 ± 1.4**	42.8 ± 16.3

*$P < 0.05$, **$P < 0.01$ (Significant difference from the control group)
Values are mean ± SD. (*T3* triiodothyronine, *T4* thyroxine, *TSH* thyroid-stimulating hormone, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone)

Parabens

Reference: Vo et al. (2010)

Study Details: The antimicrobials, propylparaben, isopropylparaben, butylparaben, and isobutylparabaen (0, 62.5, 250, 1000 mg/kg/day) were administered by oral gavage in corn oil to juvenile male and female SD rats from PND22 to PND41. Animals were sacrificed and tissue collected on PND42.

Primary Mode of Action: Unknown; possible effect on thyroid receptor

NMDR Observation: Statistically significant decrease in serum T4 at 250 mg/kg of propylparaben and isopropylparaben but not at higher or lower doses. A statistically significant decrease in serum T4 at the lowest dose of isobutylparaben but not a higher dose levels. A statistically significant increase in thyroid weight at the lowest dose of butylparaben.

Decision/Comments: **Filter 3 Exclude** The NMDR for the serum T4 for butylparaben, isobutylparaben, isopropylparaben are not the determinant of the study-wide NOEL. A statistically significant increase in liver weight was seen for all doses for butylparaben; a statistically significant increase in uterine thickness was observed at all doses for isobutylparaben. A delay in vaginal opening was seen at the two highest doses of isopropylparaben. **Filter 4 Include** NMDR effect on serum T4 for propylparaben was not accompanied by change in any other parameter assessed. No other studies of propylparaben found.

Table 2
Effects of parabens on body weight and organ weight (uterine, pituitary, ovary, adrenal gland, thyroid gland, kidney, liver) in peripubertal female rats.

Groups	Body weight (g)	Uterus weight (mg/g BW)	Pituitary weight (mg/g BW)	Ovary weight (mg/g BW)	Thyroid weight (mg/g BW)	Kidney weight (mg/g BW)	Adrenal weight (mg/g BW)	Liver weight (mg/g BW)
(A)								
VE	118.69 ± 6.4	1.29 ± 0.11	0.043 ± 0.008	0.51 ± 0.06	0.86 ± 0.07	8.31 ± 0.57	0.27 ± 0.01	42.90 ± 2.17
EE (mg/kg BW/day)								
1	61.56 ± 4.85[b]	3.40 ± 0.30[b]	0.077 ± 0.012 [b]	0.45 ± 0.05	1.23 ± 0.1[b]	9.94 ± 0.63[b]	0.38 ± 0.03[b]	52.38 ± 2.77 [b]
Methyl paraben (mg/kg BW/day)								
62.5	115.54 ± 8.07	1.38 ± 0.7	0.046 ± 0.006	0.5 ± 0.08	0.9 ± 0.08	7.88 ± 0.51	0.32 ± 0.04 (a)	44.35 ± 3.57
250	123.815 ± 12	1.23 ± 0.3	0.045 ± 0.008	0.43 ± 0.08	1.01 ± 0.12	7.52 ± 0.45	0.28 ± 0.02	42.03 ± 2.86
1000	110.3 ± 20.59	0.86 ± 0.26	0.041 ± 0.004	0.29 ± 0.05[a]	1.05 ± 0.14[a]	7.77 ± 0.42	0.36 ± 0.05[a]	50.03 ± 1.84[a]
Ethyl paraben (mg/kg BW/day)								
62.5	125.66 ± 9.22	1.34 ± 0.28	0.041 ± 0.007	0.48 ± 0.07	0.82 ± 0.10	7.76 ± 0.65	0.27 ± 0.03	44.75 ± 2.17
250	125.85 ± 13.78	1.22 ± 0.32	0.041 ± 0.005	0.48 ± 0.06	0.89 ± 0.07	7.72 ± 0.34	0.27 ± 0.03	45.39 ± 2.29
1000	112.36 ± 7.84	1.33 ± 0.27	0.049 ± 0.006	0.47 ± 0.08	0.98 ± 0.11	7.3 ± 0.58[a]	0.32 ± 0.03[a]	39.56 ± 2.26
Propyl paraben (mg/kg BW/day)								
62.5	108.75 ± 4.16	1.41 ± 0.07	0.050 ± 0.006	0.48 ± 0.08	0.95 ± 0.08	8.09 ± 0.61	0.26 ± 0.01	39.64 ± 1.89
250	113.36 ± 13.51	1.42 ± 0.12	0.045 ± 0.008	0.49 ± 0.07	0.94 ± 0.08	7.69 ± 0.33	0.25 ± 0.03	38.54 ± 1.97
1000	111.69 ± 5.67	1.46 ± 0.10	0.055 ± 0.008	0.42 ± 0.09	0.99 ± 0.12	8.26 ± 0.47	0.32 ± 0.03[a]	44.58 ± 2.57
(B)								
Isopropylparaben (mg/kg BW/day)								
62.5	110.67 ± 7.85	1.19 ± 0.30	0.045 ± 0.005	0.41 ± 0.06	0.85 ± 0.07	8.04 ± 0.44	0.29 ± 0.03	41.22 ± 3.00
250	113.85 ± 5.87	1.15 ± 0.44	0.047 ± 0.009	0.04 ± 0.07	0.82 ± 0.06	7.66 ± 0.47	0.27 ± 0.02	40.58 ± 3.19
1000	102.45 ± 4.38	0.87 ± 0.22	0.044 ± 0.003	0.32 ± 0.05[a]	0.88 ± 0.08	7.25 ± 0.35[a]	0.3 ± 0.02	41.75 ± 2.04
Butyl paraben (mg/kg BW/day)								
62.5	112.09 ± 9.35	1.25 ± 0.15	0.054 ± 0.01	0.49 ± 0.08	1.29 ± 0.13[b]	8.48 ± 0.35	0.30 ± 0.03	51.91 ± 2.77[a]
250	122.9 ± 5.3	1.45 ± 0.09	0.054 ± 0.007	0.52 ± 0.05	0.95 ± 0.12	8.03 ± 0.45	0.27 ± 0.02	48.61 ± 2.63[a]
1000	115.02 ± 12.28	1.46 ± 0.13	0.050 ± 0.01	0.50 ± 0.04	0.93 ± 0.08	8.66 ± 0.62	0.28 ± 0.03	49.34 ± 2.98[a]
Isobutylparaben (mg/kg BW/day)								
62.5	114.07 ± 11.53	1.44 ± 0.19	0.048 ± 0.007	0.53 ± 0.05	0.87 ± 0.11	7.66 ± 0.38	0.26 ± 0.03	46.97 ± 3.19
250	117.66 ± 3.9	1.22 ± 0.1	0.042 ± 0.005	0.47 ± 0.07	0.81 ± 0.08	8.05 ± 0.49	0.27 ± 0.03	42.72 ± 2.56
1000	115.72 ± 11.29	1.28 ± 0.40	0.040 ± 0.005	0.52 ± 0.12	0.89 ± 0.12	8.16 ± 0.69	0.3 ± 0.01	45.88 ± 2.57

Mean ± SD; $n = 10$ prepubertal female rats/group.
[a] $p < 0.05$ vs. vehicle (VE) (Tukey's multiple regression test at $p < 0.05$).
[b] $p < 0.01$ vs. vehicle (VE) (Tukey's multiple regression test at $p < 0.05$).

Table 4
Effects of parabens on circulating estradiol, prolactin, and T4 levels in peripubertal female rats.

Groups	Estradiol (pg/ml)	Prolactin (ng/ml)	T4 (ng/ml)
VE	47.07 ± 14.72	9.81 ± 3.12	3.00 ± 0.32
EE (mg/kg BW/day)			
1	55.37 ± 14.77	238.93 ± 35.00[b]	2.73 ± 0.50
Methyl paraben (mg/kg BW/day)			
62.5	23.21 ± 8.15	22.83 ± 7.93	2.71 ± 0.19
250	20.62 ± 12.38	67.26 ± 42.54	2.31 ± 0.33
1000	19.74 ± 8.76	30.35 ± 19.98	1.38 ± 0.07[b]
Ethyl paraben (mg/kg BW/day)			
62.5	27.41 ± 9.90	10.01 ± 1.97	2.88 ± 0.16
250	18.46 ± 3.75	27.56 ± 20.67	2.72 ± 0.03
1000	13.43 ± 6.96[b]	85.46 ± 46.86	2.40 ± 0.12
Propyl paraben (mg/kg BW/day)			
62.5	20.30 ± 6.47	61.73 ± 67.59	2.34 ± 0.24
250	24.69 ± 5.74	41.26 ± 13.29	1.74 ± 0.20[b]
1000	40.08 ± 9.00	13.97 ± 3.78	2.54 ± 0.45
Isopropylparaben (mg/kg BW/day)			
62.5	30.53 ± 15.91	45.10 ± 13.12	2.70 ± 0.39
250	25.20 ± 6.05	49.76 ± 58.31	1.73 ± 0.34[b]
1000	16.23 ± 6.86[a]	24.12 ± 6.46	3.06 ± 0.19
Butyl paraben (mg/kg BW/day)			
62.5	29.22 ± 2.35	9.65 ± 1.15	2.58 ± 0.13
250	20.07 ± 3.12	16.03 ± 8.25	2.64 ± 0.07
1000	23.81 ± 4.69	15.54 ± 6.04	2.71 ± 0.41
Isobutylparaben (mg/kg BW/day)			
62.5	26.00 ± 6.00	5.67 ± 1.64	1.67 ± 0.02[b]
250	20.08 ± 0.18	14.72 ± 8.55	2.30 ± 0.38
1000	33.34 ± 1.07	42.44 ± 55.85	2.88 ± 0.38

Mean ± SD; $n = 10$ prepubertal female rats/group.
[a] $p < 0.05$ vs. vehicle (VE) (Tukey's multiple regression test at $p < 0.05$).
[b] $p < 0.01$ vs. vehicle (VE) (Tukey's multiple regression test at $p < 0.05$).

Pentabromodiphenyl ether (DE-71)

Reference: Fowles et al. (1994)
Study Details: DE-71 (0, 0.8, 4.0, 20, 100, 500 mg/kg in peanut oil) was administered to 8 week old female C57BL/6 mice via oral gavage. Time of sacrifice in relation to the dose was not stated in the manuscript.
Primary Mode of Action: Effects on hepatic metabolism of thyroid hormones.
NDMR Observation: A statistically significant decrease in total T4 was observed for the 3 lowest doses and the highest dose, while the next to highest dose (100 mg/kg) dose was not significantly different from controls following a single exposure.
Decision/Comments: **Exclude Filter 4a.** The inflection in the dose response curve that resulted in an NMDR for this endpoint is in the high dose range. Additionally, the results of this paper are not consistent with known effects of DE-71 and other PBDEs. No effects on serum T4 were found at 3 mg/kg-day for 5 or 20 day exposures in rats (Stoker et al., 2004), or 1 or 3 mg/kg-day for 4 days in female rats (Zhou et al., 2001). The latter contained an extensive dose response from 1 – 1000 mg/kg-day for 4 days.

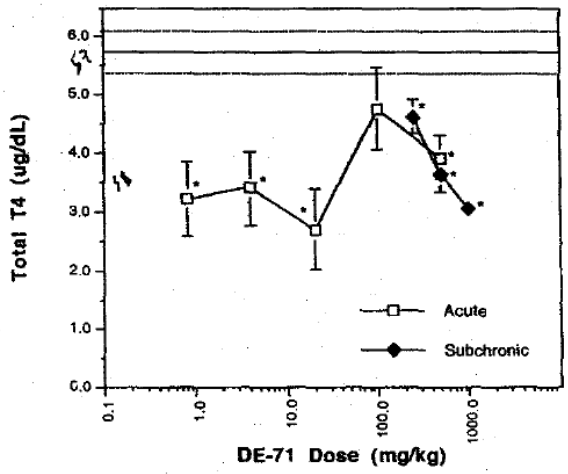


Fig. 1. Total T4 in female C57BL/6 mice (5–8/dose) treated by gavage with 0, 0.8, 4.0, 20, 100, or 500 mg/kg DE-71 in an acute exposure, or with 0, 250, 500, or 1000 mg/kg over a 14 day period (1 experimental iteration for each exposure regime). Data are presented as mean ± S.E.M. * indicates a significant difference from control (represented by horizontal lines for mean ± S.E.M. of 5.68 ± 0.32, n= 14.

Pentachlorodiphenyl ethers (PCDE)

Reference: Rosiak et al. (1997)

Study Details: 2,2',4,5,6'-pentachlorodiphenyl ether (PCDE 35 0, 25, 50, 100 mg/kg/day) or 2',3,4,6'-tetrachlorodiphenyl ether (PCDE 37 0, 50, 75, 100 mg/kg/day) were administered orally by gavage in corn oil vehicle to pregnant SD rats from GD6-15. On PN16, pups were sacrificed for tissue collection.

Primary Mode of Action: Unknown, possible effect on liver metabolism.

NMDR Observation: PCDE35 produced reductions in serum T4 at 25 and 100 mg/kg but not at 50mk/kg dose level PN16 pups. Increases in thyroid weight were also seen 25mg/kg but not higher dose levels. PCDE37: Reductions in serum T4 at 50 and 75 mg/kg but not at 100 mg/kg dose level.

Decision/Comments: **Exclude Filter 4c**. These observations were excluded based on study quality concerns. Serum T4 in many dose groups was reported from a small number of litters (1-4 litters for critical NMDR observations).

TABLE 2

Relative Thyroid Weights, Thyroxine Concentrations (T_4), and Triiodothyronine Concentrations (T_3) of Postnatal day 16 Pups Exposed to PCDE Congeners or Corn Oil Vehicle. Results Expressed as Mean +/- S.E. N Indicates the Number of Pups; d Indicates Data are Significantly

Treatment (mg/kg/d)	# of litters (pups)	Mean Body Wt (g) ♂♂	Mean Body Wt (g) ♀♀	Relative Thyroid Wts (mg/g)	# of litters	T_4 (μg/dl)	# of litters	T_3 (ng/dl)
CONTROL	12 (24)	34.9±1.4	33.6±1.2	14.8±0.8	12	5.42±0.23	9	93.05±6.48
PCDE 32: 25	4 (8)	46.5±3.5[d]	44.3±3.3[d]	12.9±0.9	4	1.76±0.16[d]	4	64.65±4.71[d]
50	7 (14)	33.7±3.3	30.4±2.6	14.3±0.1	7	1.79±0.13[d]	7	84.18±5.18
100	2 (4)	32.8±0.3	32.2±0.1	16.9±1.8	2	1.99±0.18[d]	--	--
PCDE 35: 25	4 (8)	44.8±4.1[d]	43.0±4.5[d]	11.1±0.4[d]	4	3.82±0.66[d]	4	101.21±5.86
50	7 (14)	44.6±2.8[d]	40.0±1.7	14.4±0.6	7	5.14±0.38	7	124.90±5.40[d]
100	1 (2)	41.1± --	36.2± --	9.1±7.4	1	3.68±0.01[d]	--	--
PCDE 37: 50	6 (12)	31.8±2.5	30.9±2.8	16.8±0.1	6	3.45±0.40[d]	6	97.17±5.00
75	4 (8)	34.7±0.7	32.4±1.9	14.8±1.0	4	2.58±0.36[d]	4	74.25 ±3.03
100	3 (6)	27.7±3.1	32.0±2.9	15.4±1.8	3	5.36±0.07	--	--

Perchlorate (ClO_4^-)

Reference: Thuett et al. (2002)

Study Details: Ammonium perchlorate (0, 1nM, 1uM, 1mM) was administered via drinking water to male and female mice during mating and throughout gestation and lactation. Pups were euthanized at PND21.

Primary Mode of Action: Competitive inhibition of sodium/iodide symporter

NDMR Observation: A statistically significant increase in plasma T4 was observed in the low and mid dose groups, and no change was observed at high dose of PND21 mice. Thyroid histopathology analysis found a decrease in active follicles at the low and high dose.

Decision/Comments: **Exclude Filter 4c.** The effects reported here are at very low levels of perchlorate exposure (117ppt, 117 ppb and 117ppm, ~ 0.01, 0.1, and 1.5 µg/kg-day (Thuett et al., 2002). Increases in serum T4 by perchlorate are counter to many other published reports in rat and rabbit and the known mode of action of perchlorate to inhibit the NIS (NAS, 2005). Study design is not well described and it is unclear that appropriate litter-based analysis was performed on serum hormone data. The increases in T4 were based on very small sample sizes (n=4-5), insufficient for reliable detection of small changes in serum hormone using RIA. The increase in serum T4 at the low and mid dose group is not consistent with changes in the thyroid follicle observed in this same study.

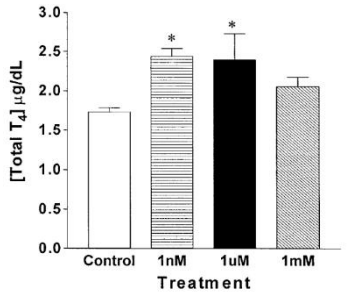


FIGURE 1. Total T_4 concentration in deer mouse plasma at postnatal day 21. Asterisk indicates significantly different ($p < .05$) from control (nonparametric ANOVA/GLM and Duncan's multiple-range test); $n = 3$ for 1 µM, 1 mM, and control; $n = 4$ for 1 nM.

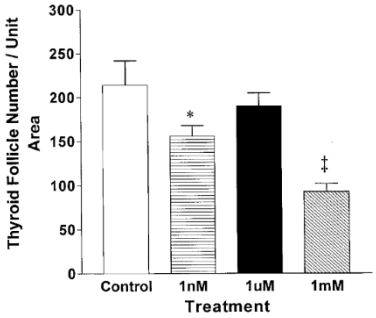


FIGURE 3. The number of active thyroid follicles per unit area for deer mice at postnatal day 21 as determined by analysis of individual pup data. Asterisk indicates significantly different from control; double dagger, significantly different from control, 1 nM, and 1 µM (nonparametric ANOVA/GLM and Duncan's multiple range test); $N = 5$ for controls; $n = 8$ for 1 nM; $n = 6$ for 1 µM and 1 mM.

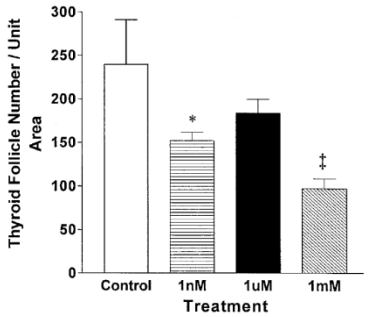


FIGURE 4. The number of active thyroid follicles per unit area for deer mice at postnatal day 21 as determined by analysis of litter mean data. Asterisk indicates significantly different from control; double dagger, significantly different from control, 1 nM, and 1 µM (nonparametric ANOVA/GLM and Duncan's multiple-range test); $n = 3$ for controls; $n = 4$ for 1 nM; $n = 5$ for 1 µM; $n = 2$ for 1 mM.

Reference: Männistö et al. (1979)

Study Details: Potassium perchlorate (0, 10, 50, 100, 500 mg/L) was administered via drinking water to adult males. All animals were sacrificed on day 5.

Primary Mode of Action: Competitive inhibition of sodium/iodide symporter.

NDMR Observation: Intermediate drinking water concentrations (50 and 100 mg/L) resulted in a statistically significant decrease in serum T3. No changes in serum T3 were seen following exposure to the lowest or highest dose.

Decision/Comments: **Exclude Filter 3.** The NMDR decrease in serum T3 is not the determinant of the study-wide NOEL. A monotonic dose response effect was observed in serum T4 and was significant at the same dose where the decrease in serum T3 was first significant (50 mg/L).

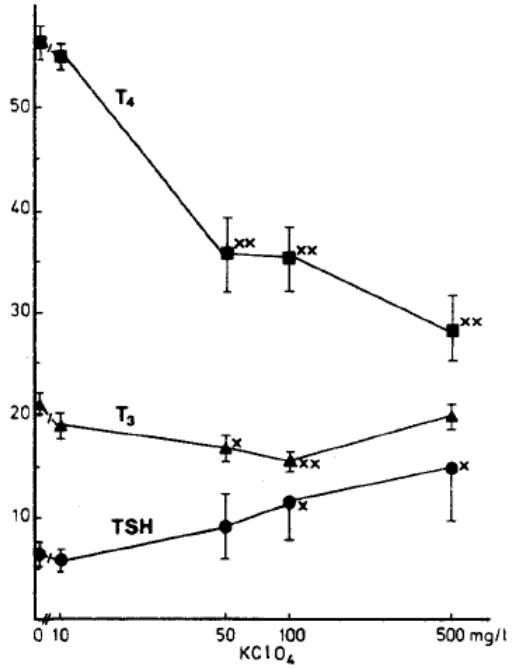


Fig. 3.

Serum T_3, T_4 and TSH concentrations as a function of the $KClO_4$ dose (mg/l in drinking water; log scale). For further information, see Fig. 1.

Reference: York et al. (2001)

Study Details: Ammonium perchlorate (0, 0.3, 3.0, 30.0 mg/kg-day) was administered via drinking water to adult male and female SD rats through mating, gestation, and lactation. The F1 generation was given the same doses in water beginning at weaning and continuing until sacrifice. F2 generation pups were sacrificed on lactation day 21; other sacrifice times were not clearly stated.

Primary Mode of Action: Competitive inhibition of sodium/iodide symporter.

NDMR Observation: Several NMDRs were observed in this study. For the adult males, an increase in serum T3 was seen at the low and mid doses, but no change was observed at the high dose. The adult females had an increase in serum T4 at the low and mid doses, but no change at the high dose. The F1 male pups showed a decrease in serum TSH was at the low and mid dose, with no change at the high dose. F1 female pups had an increase in serum T4 at the low dose, and no other changes in serum T4 were observed. The F1 adult males had an increase in serum T4 at the low and mid doses and a decrease in serum T4 at the high dose. The only change in thyroid hormones in the F2 male pups was the increase in serum T3 at the mid dose, while the female pups only had an increase in T4 at the mid dose.

Decision/Comments: **Exclude Filter 3.** The NMDRs were not the determinant of the study-wide NOEL. The study authors based the NOEL (0.3 mg/kg-day) on the thyroid histopathology results that showed a monotonic dose-response for hypertrophy/hyperplasia. The NMDRs were not consistent between gender or generation. The authors also commented on the nonmonotonic nature of the data, attributing the results to the data being a "snapshot in time" of a dynamic system, where TSH regulation could "overshoot" causing an increase in T3/T4 relative to controls.

TABLE 5
Summary of thyroid effects observed in P, F1, and F2 generations *(Continued)*

	Male				Female			
Effect	0 mg/kg-day	0.3 mg/kg-day	3.0 mg/kg-day	30.0 mg/kg-day	0 mg/kg-day	0.3 mg/kg-day	3.0 mg/kg-day	30.0 mg/kg-day
				Hormone levels (mean ± *SD*)				
P adult (*N*)	29	30	30	29	29	30	29	30
T_3 (ng/dl)	72.6 ± 11.2	87.4 ± 16.3*	88.4 ± 18.6*	78.6 ± 14.4	57.8 ± 28.2	64.8 ± 29.3	56.4 ± 14.0	60.4 ± 22.0
T_4 (μg/dl)	4.64 ± 0.58	4.73 ± 0.82	4.74 ± 0.79	3.58 ± 0.86*	2.13 ± 0.68	2.90 ± 0.04*	2.92 ± 0.84*	2.42 ± 0.79
TSH (ng/ml)	1.53 ± 0.96	1.35 ± 0.64	1.49 ± 0.82	3.87 ± 3.50*	2.05 ± 0.87	2.21 ± 0.99	1.99 ± 0.77	2.17 ± 0.74
F1 pup (*N*)	27	21	25	23	28	22	25	23
T_3 (ng/dl)	105.9 ± 10.0	111.2 ± 16.4	109.8 ± 15.7	107.4 ± 16.1	106.0 ± 13.1	109.9 ± 13.1	109.3 ± 13.6	97.6 ± 11.0*
T_4 (μg/dl)	4.40 ± 1.01	4.62 ± 0.98	4.53 ± 0.79	4.52 ± 1.09	4.27 ± 1.02	4.86 ± 0.95*	4.32 ± 0.78	3.91 ± 0.98
TSH (ng/ml)	1.24 ± 0.45	0.94 ± 0.34*	0.88 ± 0.25*	1.27 ± 0.38	1.12 ± 0.51	1.19 ± 0.35	1.14 ± 0.38	1.30 ± 0.35
F1 adult (*N*)	30	30	30	30	30	29	30	29
T_3 (ng/dl)	82.5 ± 8.7	81.3 ± 15.4	83.2 ± 16.5	83.0 ± 13.4	61.5 ± 25.2	51.2 ± 21.9	53.4 ± 19.6	56.8 ± 18.9
T_4 (μg/dl)	3.78 ± 0.55	4.21 ± 0.86*	4.20 ± 0.87*	2.78 ± 0.72**	2.22 ± 1.03	2.03 ± 0.84	2.27 ± 1.05	2.13 ± 0.86
TSH (ng/ml)	2.51 ± 1.01	2.16 ± 1.04	2.30 ± 1.73	5.18 ± 2.52**	1.62 ± 1.01	1.22 ± 0.66	1.65 ± 0.88	2.12 ± 0.69*
F2 pup (*N*)	20	26	28	25	20	26	28	25
T_3 (ng/dl)	106.3 ± 18.3	108.0 ± 14.6	119.5 ± 20.1*	107.1 ± 21.4	108.4 ± 21.1	107.4 ± 13.0	107.9 ± 20.7	98.8 ± 24.0
T_4 (μg/dl)	3.2 ± 0.84	3.3 ± 0.86	3.8 ± 0.88	3.4 ± 0.80	3.4 ± 0.72	3.3 ± 0.79	4.2 ± 1.0*	3.8 ± 0.83
TSH (ng/ml)	0.82 ± 0.19	0.88 ± 0.26	0.95 ± 0.28	0.96 ± 0.21	0.94 ± 0.28	0.91 ± 0.29	0.96 ± 0.22	0.97 ± 0.22

*Significantly different from the carrier group value ($p \leq .05$).
**Significantly different from the carrier group value ($p \leq .01$).

Reference: York et al. (2004)

Study Details: Ammonium perchlorate (0, 0.1, 1.0, 30, 10.0 mg/kg-day) was administered in drinking water to adult female SD rats from gestation day 0 through lactation day 10.

Primary Mode of Action: Competitive inhibition of sodium/iodide symporter.

NDMR Observation: A statistically significant decrease in follicular lumen area was observed at the low (0.1 mg/kg-day), 2nd intermediate (3.0 mg/kg-day), and high (10 mg/kg-day) dose in F1 male pups; however, no change in follicular lumen area was found at the 1st intermediate dose (1.0 mg/kg-day).

Decision/Comments: **Exclude Filter 4c.** The standard deviation for the 1st intermediate dose (1.0 mg/kg-day) that did not show a decrease in follicular lumen was very large, almost 3-times the SDs for the other dose groups. This NMDR effect occurred in male F1 pups only, not in females. No change in thyroid weights was reported for F1 male pups. Data from this study and several others were previously subjected to re-analysis by outside experts. The data presented in this paper is not consistent with the re-review results available in the U.S. EPA's 2002 perchlorate risk assessment document. The reanalysis found a significant main effect of treatment on lumen size for all doses at PND5 (U.S. EPA (2005); Figure 5-8).

TABLE 3
Thyroid hormone, morphology and histopathology of F1 culled pups (PPD 5)

Parameters	Group I (Carrier)	Group II (0.1 mg/kg-day)	Group III (1.0 mg/kg-day)	Group IV (3.0 mg/kg-day)	Group V (10.0 mg/kg-day)
Pooled serum					
TSH (ng/ml)	4.51 ± 0.46[a] [17]	4.52 ± 0.44 [14]	4.75 ± 0.48 [18]	4.77 ± 0.48 [17]	5.52 ± 0.58** [19]
T3 (ng/dl)	88 ± 5.94 [10]	85 ± 7.57 [10]	79 ± 7.08* [10]	39 ± 3.47*** [12]	38 ± 3.76*** [12]
T4 (μg/dl)	3.41 ± 0.37 [15]	3.32 ± 0.31 [11]	3.14 ± 0.27 [13]	2.68 ± 0.25*** [11]	2.53 ± 0.23*** [12]
Males					
Follicular cell hypertrophy	5 [10]	9 [10]	9 [10]	9 [10]	10 [10]
Hypertrophy severity	0.5	1.0	1.2	1.3	1.4*
Follicular lumen diameter (μm)	21.2 ± 2.4 [10]	18.8 ± 2.3 [10]	17.7 ± 2.7* [10]	17.2 ± 1.6* [10]	16.4 ± 2.1* [10]
Follicular epithelial height (μm)	6.3 ± 0.8 [10]	6.2 ± 0.8 [10]	6.8 ± 0.7 [10]	6.7 ± 0.9 [10]	7.2 ± 1.0 [10]
Follicular lumen area (μm^2)	315.0 ± 50.45 [10]	255.0 ± 38.19* [10]	290.8 ± 143.21 [10]	208.4 ± 46.14* [10]	209.7 ± 73.77* [10]
Females					
Follicular cell hypertrophy	4 [10]	5 [10]	7 [10]	8 [10]	9 [10]
Hypertrophy severity	0.4	0.5	0.8	1.3*	1.8*
Follicular lumen diameter (μm)	20.5 ± 3.8 [10]	18.7 ± 1.7 [10]	17.5 ± 1.9 [10]	17.1 ± 3.0* [10]	16.6 ± 3.1* [10]
Follicular epithelial height (μm)	6.6 ± 0.8 [10]	6.2 ± 1.0 [10]	6.8 ± 0.9 [10]	7.2 ± 0.8 [10]	7.7 ± 1.1* [10]
Follicular lumen area (μm^2)	320.7 ± 82.56 [10]	264.7 ± 63.18 [10]	255.2 ± 74.69 [10]	235.6 ± 132.05 [10]	211.4 ± 119.96* [10]

PPD = days postpartum, [a]mean ± *SD*; [*N*] = number; average severity scored 0 (normal) to 3 (severe).
*Significantly different from carrier group, $p \leq .05$.
**Significantly different from carrier group, $p \leq .01$.
***Significantly different from carrier group, $p \leq .001$.

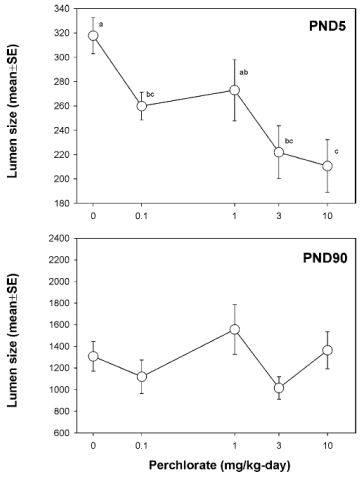


Figure 5-8. Effects from maternal drinking water administration of ammonium perchlorate to SD rats on thyroid gland follicular lumen size in F1-generation offspring on PND5 as recalculated in Crofton and Marcus (2001). Data of Channel (1998c) and Argus Research Laboratories, Inc. (1998a). Means with different letters were significantly different ($p < 0.05$). Daily dose was estimated from water consumption data.

Reference: Gilbert and Sui (2008)

Study Details: Perchlorate (0, 30, 300, 1000 ppm) was administered in drinking water from GD6 until weaning. Blood samples were obtained from pups on PNDs 4, 14, 21, and 80–90, and from dams at weaning on PND30. Behavioral and electrophysiologic measurements were performed on adult male offspring.

Primary Mode of Action: Competitive inhibition of sodium/iodide symporter.

NDMR Observation: A statistically significant increase was seen in TSH of PND14 pups at the low and mid dose and no difference from control at the high dose.

Decision/Comments: **Exclude Filter 3.** The NMDR was not the determinant of the study-wide NOEL. A monotonic decrease in serum T4 was seen beginning with the lowest dose in dams. The serum TSH NMDR in PND14 pups was not seen in PND4, PND21, or dams. All functional physiology effects observed were monotonic in nature, consistent with PTU observations.

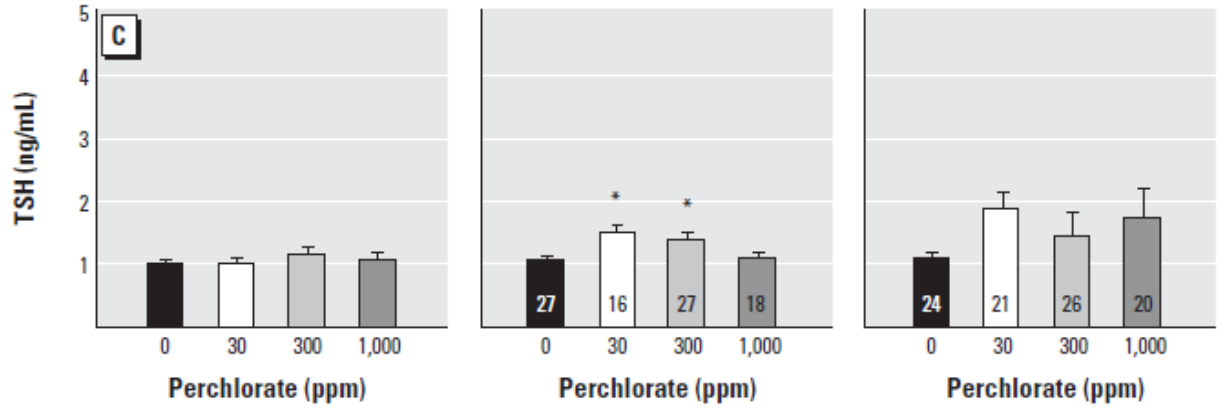


Figure 3. Thyroid hormone concentrations (mean ± SE) in pups exposed to perchlorate beginning on GD6 and sacrificed on PNDs 4, 14, or 21. (*A*) T_3. (*B*) T_4. (*C*) TSH. Data from PND4 represent males and females because samples were pooled to provide sufficient serum for the assays. No differences in serum hormones were detected between sexes on PND14 and PND21 ($p > 0.05$), so data were collapsed across, and mean value per litter at each age was analyzed. Numbers within the bars represent sample sizes.
*$p < 0.05$ by Dunnett's *t*.

Polychlorinated Biphenyl (PCB)

Reference: Li et al. (2001)
Study Details: 2,2',3,4',5',6-hexachlorophenyl (PCB149 0, 8, 32, 96 mg/kg/day) was administered ip in corn oil to juvenile female SD rats on PND21 and 22 and sacrificed on PND24.
Primary Mode of Action: Liver metabolism.
NMDR Observation: Statistically significant reduction in serum T4 at 32 but not 96 mg/kg dose level.
Decision/Comments: **Filter 4c Exclude.** Lack of effect on serum T4 at highest dose attributable to high variability likely stemming from small sample size (n=5) for serum hormone assays. The NMDRC is not consistent with findings from extensive dose response curves for 12 different PCBs tested at lower dose ranges in a 4-day oral dosing paradigm in juvenile female rats. (Crofton et al., 2005)

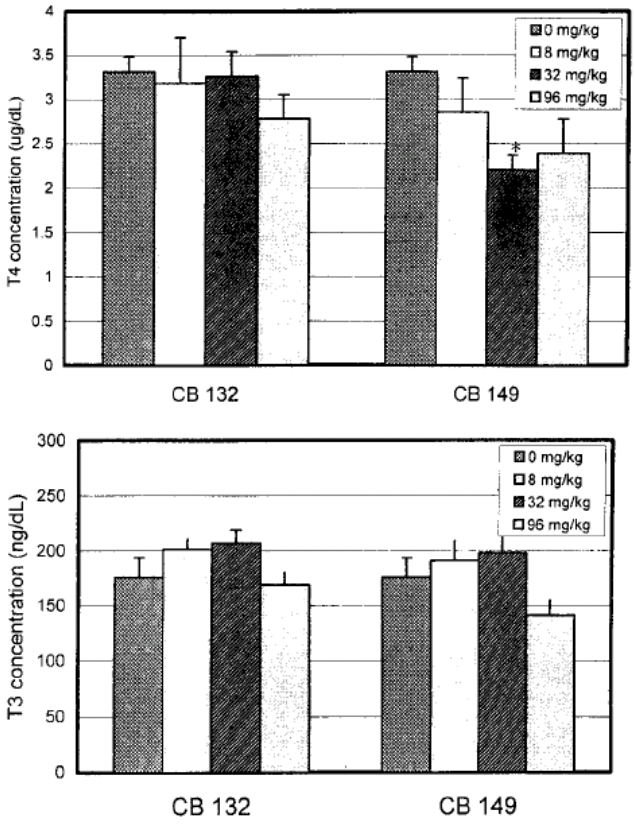


Fig. 1. Thyroid hormones status in prepubertal female rats administered CB 132 or CB149. *Significantly different from controls by Dunnett's *t* test ($p \leq 0.05$)

Reference: Desaulniers et al. (1997)

Study Details: PCB77 (0, 10, 100, 1000, 10,000 ppb) was administered in the diet to young female SD rats for 13 weeks. Animals were sacrificed at the end of the exposure period.

Primary Mode of Action: Liver metabolism, T3 receptor activation

NMDR Observation: Statistically significant increase in serum T4 at 10, 100, 1000 with declines at the highest dose tested.

Decision/Comments: **Include Filter 4.** Although an NMDR was not seen with a related PCB (PCB 28) assessed in the same study, the increase in serum T4 at the equivalent of 0.06, 0.6 and 6 ug/kg/day is the lowest dose for which an effect on thyroid or any other endpoint in vivo has been reported.

TABLE 1. Serum Concentrations (Mean ± Standard Error) of TSH and T4, and Hepatic UDP-GT Activity in Female Rats Following 90-Day Dietary Exposure to 0, 10, 100, 1000, and 10 000 ppb of PCB 77 or 0, 50, 500, 5000, and 50 000 ppb of PCB 28

PCB congeners	ppb	TSH ng/mL	T4 µg/dL	UDP-GT[1] nmoles/min/mg prot
PCB 77	0	1.0 ± 0.2b (7)[2]	2.7 ± 0.3c (8)	0.65 ± 0.08b (10)
	10	1.3 ± 0.1ab (10)	4.8 ± 0.3a (10)	0.84 ± 0.16b (10)
	100	1.3 ± 0.2ab (10)	4.2 ± 0.2ab (10)	0.75 ± 0.13b (10)
	1,000	1.0 ± 0.1b (10)	3.4 ± 0.3b (10)	1.16 ± 0.13b (10)
	10,000	1.7 ± 0.2a (3)	1.3 ± 0.1d (10)	2.01 ± 0.39a (10)
	p value[3]	0.09	0.0001	0.0002
PCB 28	0	0.9 ± 0.2 (5)	3.1 ± 0.2ab (10)	3.74 ±0.85 (10)
	50	1.3 ± 0.1 (6)	3.8 ± 0.4a (10)	3.29 ± 0.51 (10)
	500	1.2 ± 0.1 (5)	3.1 ± 0.4ab (6)	3.51 ± 0.55 (10)
	5,000	1.6 ± 0.2 (5)	4.0 ± 0.5a (5)	3.45 ± 0.54 (10)
	50,000	1.5 ± 0.4 (6)	2.5 ± 0.3b (6)	4.08 ± 0.45 (10)
	p value	0.27	0.06	0.89

[1]UDP-GT activity measured from the liver homogenate of rats treated with PCB 77 and the liver homogenate S9 fractions for rats treated with PCB 28.
[2]number of rats per group; partial results are presented in some groups due to limited volumes of serum samples.
[3]*p* value from one way analysis of variance.
a.b.c.d: within colums, means with the same letter are not significantly different (Duncan's multiple range test, $p > 0.05$).

Reference: Zoeller et al. (2000)

Study Details: Aroclor 1254 (0, 1, 4, 8 mg/kg/day) were administered to pregnant SD rats from GD6 to PND21 in food and pups sacrificed for tissue collection on PNDs 5, 15 and 30. In situ hybridization in brains of pups was performed. Myelin basic protein (MBP) was examined in the medulla and cerebellum at all 3 ages. Neurogranin (RC3) was examined in the retrosplenial cortex on PND15.

NMDR Observations: A transient and statistically significant reduction in MBP was observed in medulla on PND5 at 4 but not 8 mg/kg dose level. On PND15, MBP was reduced in the cerebellum and medulla at 1 mg/kg but not 4 or 8mg/kg. A monotonic increase in RC3 expression was seen in the cortex and was significant at 4 and 8 mg/kg dose levels.

Decision/Comments: **Exclude Filter 3.** The NMDR for expression of MBP in the neonatal brain was not the determinant of the study-wide NOEL. A monotonic decline in serum T4 was observed and was significant at all dose levels.

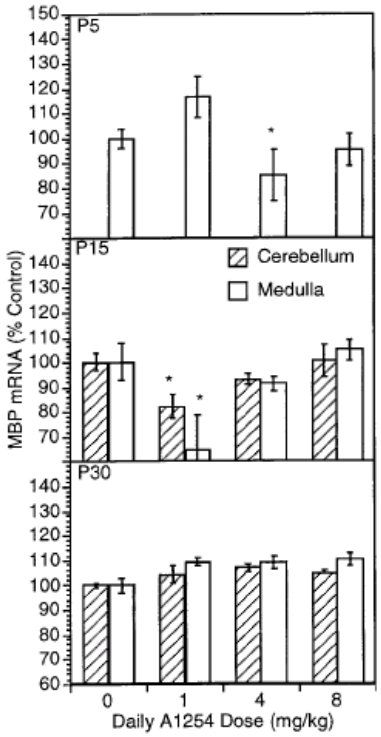


FIG. 7. MBP mRNA levels in the cerebellum and medulla of pups derived from dams treated with different doses of A1254. *Bars* represent mean ± SEM of film density, displayed as percent control. Measurements were taken from different pups within each litter on P5, P15, and P30. Treatment effects on MBP mRNA levels in the cerebellum were restricted to P15, where 1 mg/kg A1254 induced a significant decrease in MBP mRNA levels ($F_{3,23} = 3.291$; $P < 0.05$). MBP mRNA was also reduced in the medulla, at this time, by 1 mg/kg A1254 ($F_{3,23} = 4.926$; $P < 0.01$). Interestingly, only the integrated density of the MBP signal was affected in the pons/medulla. On P5, MBP expression was not detected in the cerebellum.

Reference: Li et al. (1998)

Study Details: A PCB mixture (PCB110 + PCB126) or PCB110 alone (0, 8, 32, 48, 96 mg/kg) was administered ip in corn oil vehicle to juvenile female SD rats on PND21 and 22. Animals were sacrificed on PND23 for tissue collection.

Primary Mode of Action: Liver metabolism.

NMDR Observation: A statistically significant increase in serum T4 was observed in PCB110 group at the lowest dose, followed by a monotonic decrease in T4 at higher dose levels. A monotonic decline in serum T4 was seen in the PCB110+PCB126 mixture.

Decision/Comments: **Include Filter 4.** Hepatic microsomal enzymes (PROD) were not induced at lower dose of PCB110 which may have permitted mobilized T4 to reach higher serum levels. This conclusion is supported by induction of metabolic pathways in the PCB110+126 group where a monotonic dose-response pattern was observed for serum T4.

PCBs in Prepubertal Female Rats 101

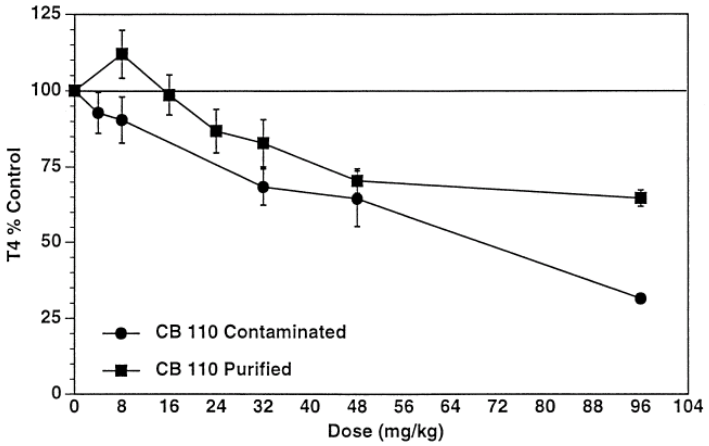


Fig. 2. Serum total T_4 level in prepubertal female rats dosed with CB 110 purified to remove Ah-receptor agonist (CB 110P) compared to the preparation before removal of Ah-receptor agonists (CB 110C). Values (mean ± SE) have been converted to percent of the same litter control. Control levels were 2.02 ± 0.12 μg/dcl or 100 ± 5.9%. T4 levels are significantly different ($p < 0.05$) between dose groups at 8 and 96 mg/kg and significantly lower than controls at 48 and 96 mg/kg

Reference: Collins and Capen (1980)

Study Details: Aroclor 1254 (0, 5, 50, 500 ppm) was administered to adult male O-M rats in the diet for 4 weeks. Animals were sacrificed at the end of exposure.

Primary Mode of Action: Liver metabolism.

NMDR Observation: Statistically significant increase in serum T3 was observed following exposure to 5 ppm PCB with reduction at the 500ppm dose.

Decision/Comments: **Exclude Filter 4b.** An increase in serum T3 is inconsistent with the majority of PCB literature. T4 was monotonically reduced at 50 and 500ppm. A lower LOEL was seen for serum T4 after 15-weeks of exposure to 0.1 mg/kg/day A1254, equivalent to dietary exposure of ~1.7 ppm (Gray et al., 1993).

228 W.T. Collins and C.C. Capen

Table 1. Serum thyroxine (T_4) and triiodothyronine (T_3) concentrations in rats administered PCB, thyroxine, or fed iodide deficient or excess diets for 4 weeks

Group	T_4 (μg/dl)	T_3 (ng/dl)
Control rats	3.71 ± 0.04	86.80 ± 2.0
5 ppm PCB	3.56 ± 0.10	105.96 ± 3.0***
50 ppm PCB	2.14 ± 0.10***	82.13 ± 8.7
500 ppm PCB	0.78 ± 0.04***	72.18 ± 3.7*
1% KI	3.22 ± 0.10*	87.06 ± 5.6
I-deficiency	2.74 ± 0.40*	125.15 ± 6.8**
T_4-suppression	8.55 ± 0.9***	384.23 ± 30.9***

$N = 6$/group
Mean ± Standard error of mean
*$P < 0.025$; **$P < 0.005$; ***$P < 0.001$

Potassium Bromate ($KBrO_3$)

Reference: Wolf et al. (1998)
Study Details: Potassium bromide ($KBrO_3$: 0, 0.02, 0.1, 0.2, 0.4 g/L) was dissolved in the drinking water administered to 30-day old male F344 rats for 12, 26, 52, 78, or 100 weeks.
Primary Mode of Action: Competitive inhibition of sodium/iodide symporter.
NDMR Observation: After 12 weeks of treatment, serum T3 concentrations were reduced relative to controls for all dose groups, and Group 3 (0.1 g/L) showed an increase relative to higher and lower dose groups though additional statistics and standard deviations were not reported.
Decision/Comments: **Exclude Filter 3**. The NMDR for serum T3 is not the sole determinant of the study-wide LOEL. A monotonic dose response effect was observed for thyroid tumors following 100 weeks of exposure.

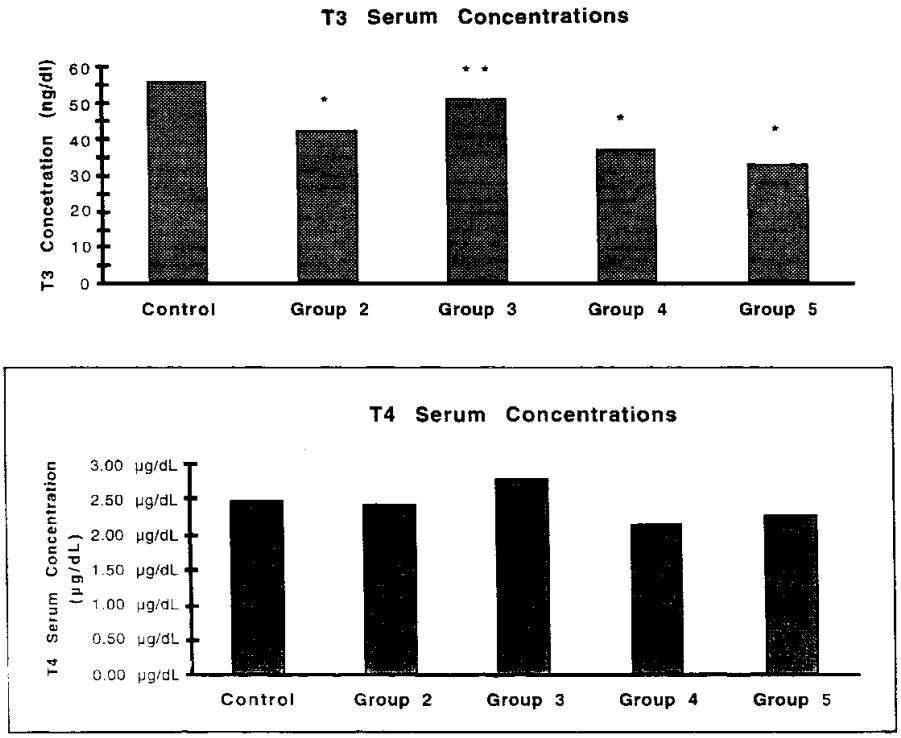


FIG. 5.—Serum concentrations of T_3 and T_4 in control and $KBrO_3$-treated male F344 rats after 12 wk of treatment. Serum T_3 concentrations were decreased in a treatment-dependent but not dose-dependent manner. T_4 concentrations were unaffected by $KBrO_3$ treatment. * $p < 0.05$; ** $p = 0.07$.

Propazine

Reference: Laws et al. (2003)

Study Details: Diamino-S-chlorotriazine (DACT 0, 16.7, 33.8, 67.5, 135 mg/kg/day), an atrazine metabolite, was administered to juvenile female SD rats from PND22-PND41. Animals were monitored daily for pubertal development and sacrificed on PND41 for tissue collection.
Primary Mode of Action: Aromatase inhibition.
NMDR Observation: Statistically significant increase in serum T4 at 67.5 mg/kg with no effect at the higher 135 mg/kg dose. No other thyroid serum parameters altered at any dose. Significant reductions in female pubertal endpoints at lower doses.
Decision/Comments: **Filter 3 Exclude.** The NMDR for increases in serum T4 is not the determinant of the study-wide NOEL. A monotonic dose-response effect was observed for delay in vaginal opening which was significant at 33.8 mg/kg/day and above.

TABLE 7
Serum Thyroid Hormone Concentrations at Necropsy

Chemical	Dose (mg/kg)[a]	Dose (AED)[b]	T_4 (ng/ml)	T_3 (ng/ml)	TSH (ng/ml)
DACT	0	0	50.0 ± 3.2[c]	1.06 ± 0.05	0.858 ± 0.093
	16.7	25	52.9 ± 3.6 (14)	1.19 ± 0.06 (14)	0.960 ± 0.088
	33.8	50	59.7 ± 3.9	1.31 ± 0.07	0.857 ± 0.090
	67.5	100	63.9 ± 3.7[d]	1.23 ± 0.06	0.641 ± 0.081 (14)
	135	200	54.8 ± 3.0	1.18 ± 0.08	0.744 ± 0.085
OH-ATR	0	0	36.6 ± 1.67 (14)	1.35 ± 0.08	1.09 ± 0.108 (14)
	22.8	25	45.3 ± 2.40	1.30 ± 0.06	1.34 ± 0.137
	45.7	50	44.8 ± 2.49	1.27 ± 0.06	1.50 ± 0.106
	91.5	100	39.1 ± 2.44	1.23 ± 0.11	1.10 ± 0.113
	183	200	33.8 ± 2.48	1.17 ± 0.08	1.17 ± 0.100
PRO	0	0	36.7 ± 2.6	1.54 ± 0.08	1.17 ± 0.100
	13	12.5	37.7 ± 2.0	1.75 ± 0.11	1.34 ± 0.116
	26.7	25	40.3 ± 2.4	1.60 ± 0.09	1.43 ± 0.137
	53	50	42.9 ± 2.7	1.43 ± 0.10	1.40 ± 0.084
	106.7	100	40.6 ± 2.4	1.45 ± 0.01	1.28 ± 0.101 (14)

Note. DACT, diamino-s-chlorotriazine; OH-ATR, hydroxyatrazine; PRO, propazine.
[a]Actual dose (mg/kg) of each test chemical used.
[b]Doses used for each chemical were equimolar to doses for ATR (mg/kg, AED)
[c]Mean ± SE (n = 15 unless noted). DACT: Combined data from DACT Studies 1 and 2; OH-ATR: data from Study 1; PRO: data from Study 2.
[d]Significantly treatment effect by ANOVA (GLM) and different from control by Dunnett's multiple comparison test, $p < 0.05$.

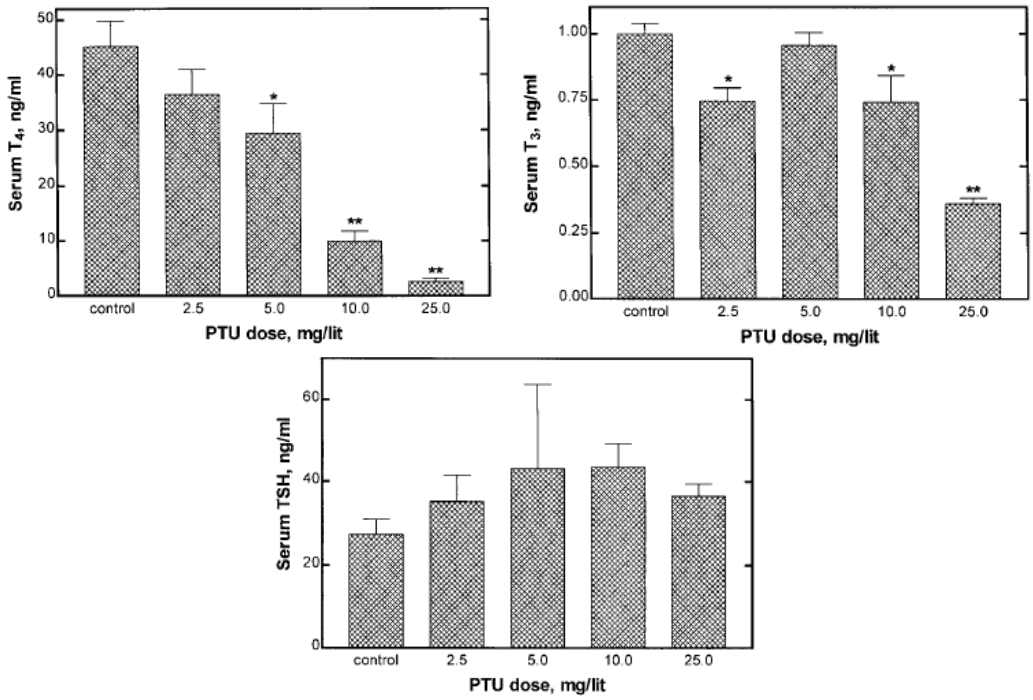
Propylthiouracil (PTU)

Reference: **Gordon et al. (2000)**

Study Details: PTU (0, 2.5, 5, 10, 25 ppm) were administered to adult male LE rats in drinking water for 21-28 days. During the 4ths wk of exposure animals were subjected to heat and cold stress and temperature monitored by radiotelemetry, Animals were sacrificed at the end of exposure and blood collected for hormone measurements.

NMDR Observations: A statistically significant reduction in serum T3 was seen at the lowest and two highest dose levels with no difference from control at the middle dose of 5ppm. Serum T4 was dose dependently reduced with significant declines first evident at 5 ppm.

Decision/Comments: **Exclude Filter 4a.** The NMDR for serum T3 at this dose of PTU is inconsistent with findings for T4 within the same paper and with a number of other published reports using this dose range and dosing duration for PTU.



ig. 5. Effect of 37 days of PTU treatment on serum levels of hyroxine (T_4, *top*), triiodothyronine (T_3, *middle*), and thyroid-stimulating hormone (TSH, *bottom*). ANOVA results: T_4, $F(4,28) = 17.9$,

Reference: Gilbert (2011)

Study Details: PTU (0, 1, 2, 3, 10 ppm) were administered to pregnant LE rats from GD6 to PND21 in drinking water. Pups were sacrificed for serum collection on PNDs 14, 21 and 30; dams sacrificed at weaning. Adult male offspring assessed for hippocampal synaptic function and learning and memory.

NMDR Observations: A statistically significant reduction in freezing behavior detected at two lowest doses, followed by return to control levels at highest dose in a trace fear conditioning paradigm.

Decision/Comments: **Exclude Filter 3.** The NMDR for learning was not the determinant of the study-wide NOEL. A monotonic decline in serum T4 was observed and was significant at all dose levels in dams and pups prior to weaning.

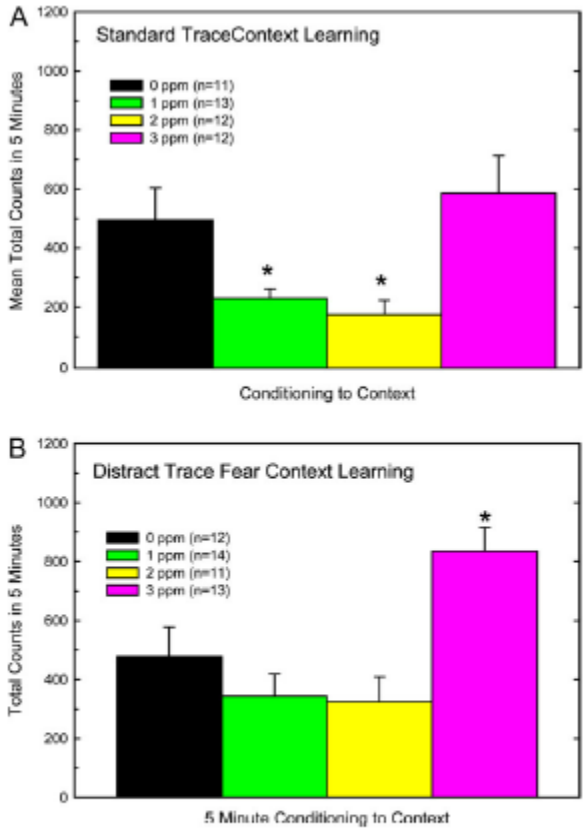


FIG. 8. Context learning. Mean activity counts during the 5 min of context testing were decreased in the lower dose groups but similar to controls at the high dose level 24 h after standard trace fear training (A). In contrast, an increase above control counts was seen in the high-dose group 24 h after distract trace fear training (B) with no significant difference from controls evident in the lower dose groups. (*$p < 0.05$).

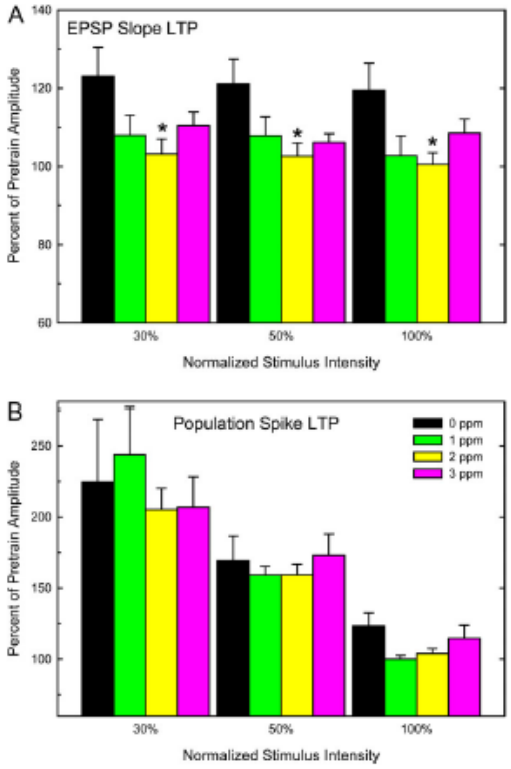


FIG. 6. Individual animal normalization to detect LTP magnitude differences across dose groups. To simplify detection of dose-dependent differences in LTP, the percent increase above pretrain amplitudes was calculated for EPSP slope and PS based on the intensity that produced a PS 30, 50, and 100% of maximal for each individual animal in the pretrain baseline I/O function. This analysis confirmed significant reductions in EPSP slope at all dose levels when collapsed across intensities (A), consistent with the pattern portrayed in Figure 5. Mean contrasts tests at each intensity suggested greater decrements in the 2 ppm dose group. (B) Greater LTP magnitude was seen at lower intensities for PS, but no effect of PTU was evident. Tukey's t-test * $p < 0.05$ LTP of the PS was not affected by PTU (B).

Reference: Lasley and Gilbert (2011)

Study Details: PTU (0 1 2 3 10 ppm) were administered to pregnant LE rats from GD6 to PND21 in drinking water and male and female pups sacrificed for tissue collection on PNDs 14, 21 and 30. Protein levels of brain-derived neurotrophic factor (BDNF) were measured using ELIZA in cortex, hippocampus, and cerebellum.

NMDR Observations: A statistically significant reduction in BDNF was observed in hippocampus and cortex of adult offspring that was greater at 1 and 2 ppm, returning to baseline at 3 and 10 ppm, and in females, exceeding control levels at 10ppm.

Decision/Comments: **Exclude Filter 3.** The NMDR for expression of BDNF was not the determinant of the study-wide NOEL. A monotonic decline in serum T4 was observed and was significant at all dose levels in dams and pups prior to weaning.

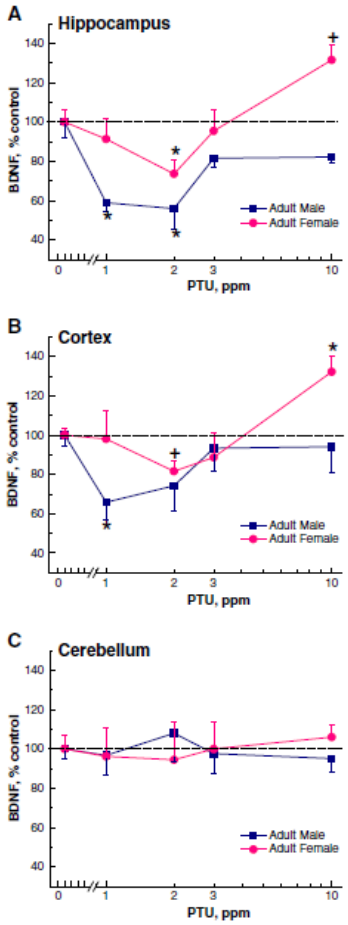


Fig. 5. Dose-effect relationships for BDNF protein expression and PTU dose in adult male and female offspring in each brain region. BDNF values are normalized to the 0 ppm value (= 100) for the respective gender in that brain area. Values are expressed as mean ± SEM in percent control with N = 5–11 for each PTU dose in each gender; *p < 0.05 compared to the 0 ppm value of the same gender. Marginal effects seen in female hippocampus at 10 ppm and cortex at 2 ppm are depicted as + p < 0.06 when contrasted to 0 ppm value in females.

Reference: Sawin et al. (1998)

Study Details: PTU (0 5 15 25 ppm) was administered to pregnant LE rats from GD18 to PND21 in drinking water. Pups were sacrificed for serum and brain tissue collection on PNDs 7, 14, 21, 35, 120; dams sacrificed at weaning.

Primary Mode of Action: TPO Inhibition.

NMDR Observations: A statistically significant reduction in choline acetyltransferase in prefrontal cortex in adult rats at 15 ppm concentration but not at higher or lower levels. A statistically significant increase in brain weight in adult female offspring at the lowest concentration of 5ppm. No difference from controls at higher dose levels.

Decision/Comments: **Exclude Filter 3**. The NMDR for learning was not the determinant of the study-wide NOEL. A monotonic decline in serum T4 was observed and was significant at all dose levels in dams and pups prior to weaning. Brain weight changes were restricted to females at the low dose and not observed in males. Decrements not increases in brain weight are anticipated by developmental hypothyroidism. No differences were evident when data expressed as brain/body weight ratio. Choline acetyltransferase decrements were not observed in the hippocampus.

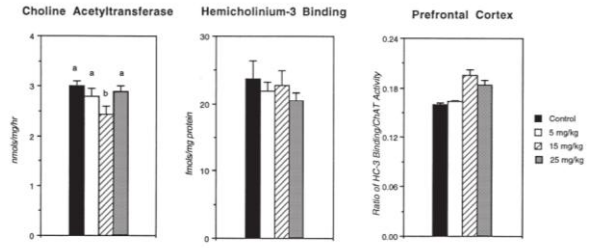


FIG. 7. Choline acetyltransferase activity and hemicholinium-3 binding in prefrontal cortex of adult rats exposed to PTU during preweaning development. Letters denote significant differences ($p < 0.05$) between various treatment groups determined by Duncan's multiple range test.

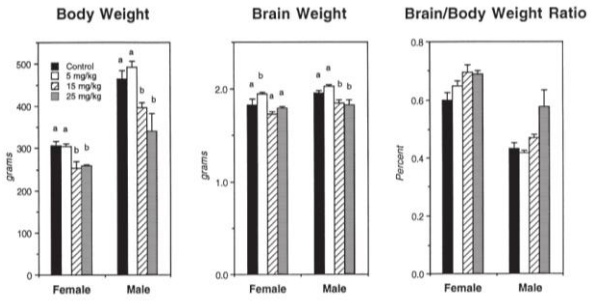


FIG. 4. Body and brain weight in adult rats exposed to PTU during preweaning development. Letters denote significant differences ($p<0.05$) between various treatment groups determined by Duncan's multiple range test.

Saisentong

Reference: Zhang et al. (2010)
Study Details: The thiadizole fungicide, Saisentong (0, 5, 10, 15 mg/kg/day) was administered by oral gavage in soybean oil vehicle to juvenile male SD rats from PN22 for 20 days. Animals were sacrificed 24 hours after the last dose.
Primary Mode of Action: Liver metabolism.
NMDR Observation: Activation of liver microsomal enzyme UDPGT is reduced at middle doses, with return to control levels at the high dose level. No changes in serum T4 or evidence of thyroid histopathology were detected, but significant dose-dependent increases in thyroid and pituitary weights were observed at the two higher doses. Body weight deficits were also seen at the high dose.
Decision/Comments: **Exclude Filter 4c**. The non-monotonicity was evident at the high dose only, a dose which also negatively impacted body weight. The dose labels in this publication are higher than those reported in the methods (0, 20, 40, 80 mg/kg/day). If this is not a typographical error, a lower LOEL is evident in thyroid and body weight decrements. For this reason, this paper was excluded based on study quality issues. No other papers on Saisentong were found.

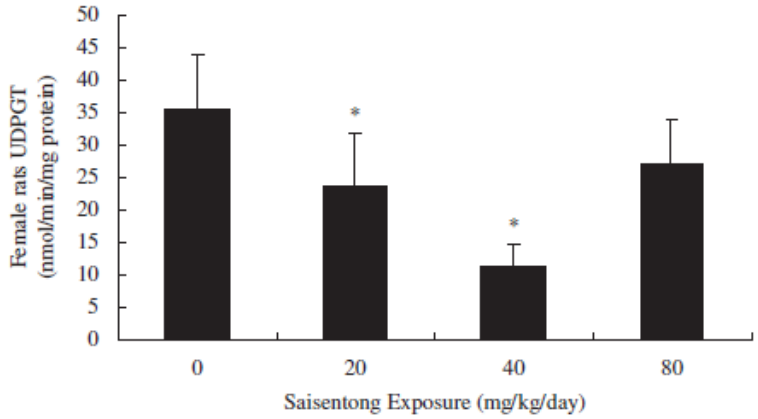


Fig. 3. Effect of pubertal exposure to Saisentong on liver microsomal enzyme, 4-nitrophenol uridinediphosphate-glucuronosyltransferase (UDPGT), activity in female rats. Data are presented as means ± SE. *Denotes value significantly different from the control group at $\alpha = 0.05$.

.

Tamoxifen

Reference: Kim et al. (2002)

Study Details: Tamoxifen (0, 10, 50, 200 µg/kg; n=10) was administered for 20 days to immature female Sprague-Dawley rats by oral gavage dissolved in 95% ethanol and diluted with corn oil vehicle. Animals were euthanized and tissues taken 24 hours after the last dose was administered.

Primary Mode of Action: Unknown.

NMDR Observation: Thyroid gland weights, serum TSH, and serum T_3 displayed NMDR response, with statistically significant increases relative to control at 10 and 50 µg/kg/day but not at 200 µg/kg/day. No effects were observed on serum T4.

Decision/Comments: **Include Filter 4.** Reasons for the NMDR are not known, but tamoxifen is a well known estrogen receptor antagonist. Estrogen and thyroid receptors share a common binding site on their molecular response element (TRE and ERE) so interactions between these two hormone systems is not unprecedented (Zhu et al., 1996) and may contribute to the pattern of effects observed. However, another report in the literature using a very similar dosing regimen did not replicate the pattern of effects observed here. Kennel et al. (2003) reported no effects on serum hormones or thyroid gland weight in male rats any dose of tamoxifen (5, 30 or 200 µg/kg/day for 28 days). Females exhibited a decrease in serum T4 with no changes in other serum markers or in thyroid gland weight.

TABLE 1
Absolute Organ Weights in Sprague-Dawley Rats Treated with Various Endocrine-Relative Compounds in the Female Pubertal Onset Assay

Treatment	Dosage	Initial BW	Necropsy BW	Thyroid gland	Ovary	Uterus
Control	0	52.50 ± 1.13	156.70 ± 1.81	8.91 ± 0.56	54.77 ± 3.04	0.28 ± 0.02
DES						
	0.2 µg/kg	51.00 ± 1.02	164.01 ± 5.49	9.69 ± 1.03	60.28 ± 4.81	0.28 ± 0.02
	1.0 µg/kg	53.60 ± 0.93	158.62 ± 4.43	10.17 ± 1.09	47.21 ± 2.79	0.23 ± 0.01
	5.0 µg/kg	53.78 ± 1.15	160.21 ± 2.55	10.52 ± 1.14*	35.18 ± 3.42*	0.29 ± 0.02
Tamoxifen						
	10 µg/kg	52.00 ± 0.59	160.85 ± 1.26	12.94 ± 0.91*	57.32 ± 2.22	0.30 ± 0.03
	50 µg/kg	51.80 ± 0.51	159.01 ± 2.21	11.66 ± 0.92*	51.96 ± 2.09	0.24 ± 0.03
	200 µg/kg	52.21 ± 0.71	141.31 ± 2.43*	9.78 ± 0.64	25.64 ± 1.81*	0.11 ± 0.01*
Testosterone						
	0.05 mg/kg	49.90 ± 1.26	159.90 ± 3.04	8.31 ± 0.50	37.58 ± 1.70*	0.24 ± 0.02
	0.2 mg/kg	49.90 ± 0.86	163.30 ± 3.80	7.90 ± 1.29	28.37 ± 2.94*	0.22 ± 0.02*
	1.0 mg/kg	50.22 ± 0.91	173.11 ± 3.73*	7.48 ± 0.57	23.24 ± 1.70*	0.16 ± 0.01*
Flutamide						
	1.0 mg/kg	50.50 ± 0.93	157.40 ± 3.76	8.44 ± 0.58	52.26 ± 1.58	0.27 ± 0.02
	5.0 mg/kg	50.80 ± 0.78	164.80 ± 2.53	8.86 ± 0.89	51.51 ± 3.29	0.27 ± 0.02
	25 mg/kg	51.00 ± 0.97	159.70 ± 1.95	8.28 ± 0.77	41.73 ± 2.10*	0.23 ± 0.01

Note. Values are mean ± SE (n = 10 animals per treatment group). BW, body weight; Initial BW, body weight on the first day of treatment (21 days of age). Necropsy BW, body weight at necropsy (41 days of age). Body weights and uterus weights given in g; thyroid and ovary weights given in mg.
*Significantly different from control by Dunnett's test ($p < 0.05$).

TABLE 3
Serum Hormone Concentrations in Sprague-Dawley Rats Treated with Various Endocrine-Relative Compounds in the Female Pubertal Onset Assay

Treatment	Dosage	Estradiol (pg/ml)	TSH (ng/ml)	T_4 (μg/dl)	T_3 (ng/dl)
Control	0	15.81 ± 1.74	0.683 ± 0.056	3.27 ± 0.23[a]	79.88 ± 2.42
DES					
	0.2 μg/kg	21.15 ± 1.42	0.782 ± 0.060	3.80 ± 0.19	106.99 ± 8.24*
	1.0 μg/kg	15.65 ± 1.22	0.469 ± 0.046	3.74 ± 0.33	111.91 ± 9.07*
	5.0 μg/kg	15.58 ± 0.94	0.576 ± 0.079	3.47 ± 0.25	122.59 ± 5.44*
Tamoxifen					
	10 μg/kg	20.75 ± 1.53	1.422 ± 0.088*	3.78 ± 0.33	124.69 ± 10.46*
	50 μg/kg	24.99 ± 2.16*	2.172 ± 0.233*	4.02 ± 0.22	127.48 ± 5.29*
	200 μg/kg	18.07 ± 1.55	1.024 ± 0.136	3.93 ± 0.08	101.59 ± 7.54
Testosterone					
	0.05 mg/kg	17.48 ± 1.28	0.919 ± 0.110	1.80 ± 0.20*	86.15 ± 6.18
	0.2 mg/kg	18.18 ± 1.26	1.294 ± 0.132*	1.95 ± 0.17*	100.84 ± 5.04
	1.0 mg/kg	18.13 ± 1.28	0.674 ± 0.047	2.09 ± 0.17*	111.62 ± 8.19*
Flutamide					
	1.0 mg/kg	19.72 ± 1.05	1.551 ± 0.212*	4.03 ± 0.25	117.06 ± 10.14*
	5.0 mg/kg	15.14 ± 1.02	1.095 ± 0.163	3.42 ± 0.12	114.38 ± 8.51*
	25 mg/kg	16.01 ± 0.87	1.474 ± 0.187*	3.76 ± 0.34	103.68 ± 9.62

Note. Values are mean ± SE (n = 10 animals per treatment group).
*Significantly different from control by Dunnett's test ($p < 0.05$).

Thiazole-Zn

Reference: Yang et al. (2013)
Study Details: The systemic fungicide, thiazole-Zn (0, 40, 100, 200 mg/kg/day) was administered to juvenile female SD rats from PND22 to PND42. Animals were sacrifice on PND43 and tissues collected for analysis.
Primary Mode of Action: Unknown.
NMDR Observations: Statistically significant reduction in serum T3 at the lowest dose of 40 mg/kg, with no effect at 100 or 200 mg/kg dose levels. Serum TSH and thyroid weights were increased at the two highest doses. Serum T4 was monotonically reduced and thyroid histopathology evident at all dose levels.
Decision/Comments: **Filter 3 Exclude.** The NMDR for serum T3 is not the determinant of the study-wide NOEL. A monotonic dose-response effect was observed for serum T4 and thyroid histopathology.

Table 3
Effects of thiazole-Zn on serum hormone levels in the female pubertal assay.

Treatment	Dosage (mg/kg.bw)	T4 (ng/ml)	T3 (pg/ml)	TSH (mIU/L)	E2 (pg/ml)
Control	0	26.7 ± 2.8	5741 ± 328	3.12 ± 0.26	68.0 ± 3.4
Thiazole-Zn	40	32.6 ± 2.8*	2119 ± 839*	3.33 ± 0.18	70.7 ± 5.1
	100	33.9 ± 3.5*	5620 ± 626	3.56 ± 0.18*	64.1 ± 4.9
	200	30.3 ± 1.8*	5841 ± 412	3.40 ± 0.14*	66.2 ± 3.6

Note: Data are expressed as mean ± SD (n = 10 animals per treatment group).
* Significantly different from the vehicle controls ($p < 0.05$).

.

Thiazopyr

Reference: Hotz et al. (1997)

Study Details: The pre-emergent herbicide thiazopyr (0, 10, 30, 100, 300, 1000, 3000 ppm) was administered to adult male SD rats in their diet for 56 days. Animals were sacrificed at the end of treatment.

Primary Mode of Action: Liver metabolism.

NMDR Observation: Significant reductions in serum T3 were observed at the mid-dose of 30ppm and increases at the highest dose tested.

Decision/Comments: **Include Filter 4.** Within this study, increases in serum T3 were not consistently observed at the high dose at 56-days, whereas high dose effects on T4, TSH, liver and thyroid weights were replicated. The decrease in serum T3 at the mid- dose level is not consistent with an upregulation of hepatic metabolism in the absence of an effect on T4. Effects on serum to T4 and TSH were limited to reductions and increases, respectively, at the highest dose of 3000ppm. UDPGT effects at the two highest doses are consistent with a liver metabolism mode of action. No other thiazopyr studies found.

TABLE 2

Dose-Related Effects of Dietary Administration of Thiazopyr on Thyroid Function in Male Rats[a]

Treatment	Body wt (g)	Liver wt (g)	Thyroid wt (mg)	T_4 (μg/dl)	T_3 (ng/dl)	rT_3 (ng/dl)	TSH (ng/ml)
Control	565 ± 9	21.2 ± 0.8	23.2 ± 0.7	4.1 ± 0.2	84 ± 3	0.047 ± 0.004	2.7 ± 0.2
10 ppm	590 ± 9	22.4 ± 0.5	24.4 ± 0.7	4.3 ± 0.3	82 ± 4	—	3.5 ± 0.4
30 ppm	576 ± 12	21.6 ± 0.7	24.5 ± 0.8	3.9 ± 0.2	68 ± 2*	—	2.7 ± 0.1
100 ppm	560 ± 10	21.7 ± 0.6	23.8 ± 0.6	4.1 ± 0.2	84 ± 3	—	3.1 ± 0.4
300 ppm	578 ± 12	24.1 ± 0.8*	25.5 ± 0.7	4.0 ± 0.2	82 ± 3	—	2.9 ± 0.3
1000 ppm	579 ± 11	28.4 ± 1.1*	29.1 ± 0.8*	4.0 ± 0.2	91 ± 4	—	3.1 ± 0.2
3000 ppm	566 ± 9	38.5 ± 0.1*	33.9 ± 1.3*	2.9 ± 0.1*	110 ± 6*	0.071 ± 0.006*	4.3 ± 0.4*

[a] Rats were treated with thiazopyr in the diet for 56 days. Data represent the mean ± standard error of the mean for 19 or 20 rats per group.
* Significantly different from control with Dunnett's test after ANOVA ($p \leq 0.05$).

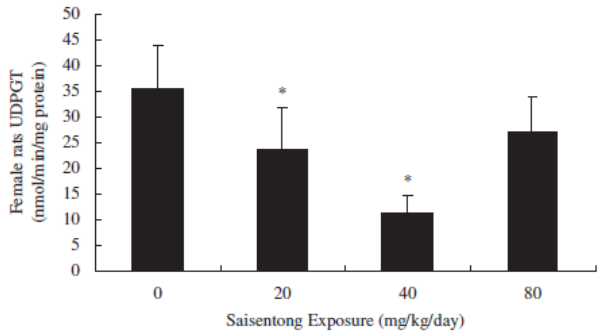


Fig. 3. Effect of pubertal exposure to Saisentong on liver microsomal enzyme, 4-nitrophenol uridinediphosphate-glucuronosyltransferase (UDPGT), activity in female rats. Data are presented as means ± SE. *Denotes value significantly different from the control group at $\alpha = 0.05$.

Triclosan

Reference: Zorrilla et al. (2009)
Study Details: The antibacterial/antifungal triclosan (0, 3, 30, 100, 200, 300 mg/kg/day) was administered by oral gavage to juvenile female SD rats from PND23 to PND53. Animals were sacrificed on PND53 and serum and tissues collected for analysis.
Primary Mode of Action: Liver metabolism.
NMDR Observation: Statistically significant increases in serum T3 following exposure to 3 mg/kg/day triclosan followed by significant declines at 200 and no change from control at 300 mg/kg/day. Monotonic reductions in serum T4 were detected beginning at 30 mg/kg/day dose level. NMDR increase in T3 at lowest dose.
Decision/Comments: **Filter 3 Exclude.** The NMDR for serum T3 is not the sole determinant of the study-wide NOEL. A monotonic dose response reduction in EROD enzyme activity was observed and was significant at the lowest dose tested.

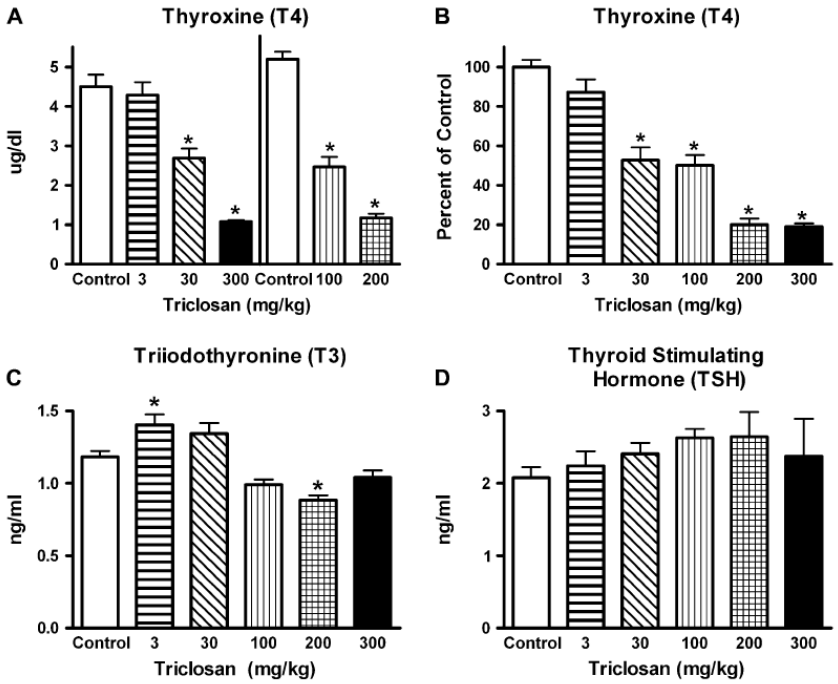


FIG. 6. The effect of a 31-day exposure to triclosan (mg/kg/day) on (A) mean total serum T4, (B) mean total T4 shown as percent of control, (C) mean total T3, and (D) mean serum TSH concentrations in the male Wistar rat. *$p < 0.05$ as compared with control mean.

Bibliography

Atterwill, C; Jones, C; Brown, C. (1992). Thyroid gland IImechanisms of species-dependent thyroid toxicity, hyperplasia and neoplasia induced by xenobiotics. In Endocrine Toxicology. Cambridge, MA: Cambridge University Press.

Ballantyne, B; Norris, JC; Dodd, DE; Klonne, DR; Losco, PE; Neptun, DA; Price, SC; Grasso, P. (1997). Short-term and subchronic repeated exposure studies with 5-ethylidene-2-norbornene vapor in the rat. J Appl Toxicol 17: 197-210. http://dx.doi.org/10.1002/(SICI)1099-1263(199707)17:4<197::AID-JAT429>3.0.CO;2-L

Biegel, LB; Cook, JC; O'Connor, JC; Aschiero, M; Arduengo, AJ; Slone, TW. (1995). Subchronic toxicity study in rats with 1-methyl-3-propylimidazole-2-thione (PTI): effects on the thyroid. Fundam Appl Toxicol 27: 185-194.

Boas, M; Feldt-Rasmussen, U; Skakkebæk, NE; Main, KM. (2006). Environmental chemicals and thyroid function [Review]. Eur J Endocrinol 154: 599-611. http://dx.doi.org/10.1530/eje.1.02128

Brucker-Davis, F. (1998). Effects of environmental synthetic chemicals on thyroid function [Review]. Thyroid 8: 827-856.

Collins, WT, Jr; Capen, CC. (1980). Ultrastructural and functional alterations of the rat thyroid gland produced by polychlorinated biphenyls compared with iodide excess and deficiency, and thyrotropin and thyroxine administration. Virchows Arch B Cell Pathol Incl Mol Pathol 33: 213-231. http://dx.doi.org/10.1007/BF02899183

Comer, CP; Chengelis, CP; Levin, S; Kotsonis, FN. (1985). Changes in thyroidal function and liver UDPglucuronosyltransferase activity in rats following administration of a novel imidazole (SC-37211). Toxicol Appl Pharmacol 80: 427-436.

Crofton, KM; Craft, ES; Hedge, JM; Gennings, C; Simmons, JE; Carchman, RA; Carter, WH, Jr; Devito, MJ. (2005). Thyroid-hormone-disrupting chemicals: Evidence for dose-dependent additivity or synergism. Environ Health Perspect 113: 1549-1554.

Desaulniers, D; Poon, R; Phan, W; Leingartner, K; Foster, WG; Chu, I. (1997). Reproductive and thyroid hormone levels in rats following 90-day dietary exposure to PCB 28 (2,4,4'-trichlorobiphenyl) or PCB 77 (3,3'4,4'-tetrachlorobiphenyl). Toxicol Ind Health 13: 627-638.

Devito, M; Biegel, L; Brouwer, A; Brown, S; Brucker-Davis, F; Cheek, AO; Christensen, R; Colborn, T; Cooke, P; Crissman, J; Crofton, K; Doerge, D; Gray, E; Hauser, P; Hurley, P; Kohn, M; Lazar, J; Mcmaster, S; Mcclain, M; Mcconnell, E; Meier, C; Miller, R; Tietge, J; Tyl, R. (1999). Screening methods for thyroid hormone disruptors [Review]. Environ Health Perspect 107: 407-415.

Fowles, JR; Fairbrother, A; Baecher-Steppan, L; Kerkvliet, NI. (1994). Immunologic and endocrine effects of the flame-retardant pentabromodiphenyl ether (DE-71) in C57BL/6J mice. Toxicology 86: 49-61. http://dx.doi.org/10.1016/0300-483X(94)90052-3

Freitas, J; Cano, P; Craig-Veit, C; Goodson, ML; Furlow, JD; Murk, AJ. (2011). Detection of thyroid hormone receptor disruptors by a novel stable in vitro reporter gene assay. Toxicol In Vitro 25: 257-266. http://dx.doi.org/10.1016/j.tiv.2010.08.013

Gaitan, E; Cooksey, RC. (1989). Chapter 1: General concepts of environmental goitrogenesis. In E Gaitan (Ed.), Environmental goitrogenesis (pp. 3-13). Boca Raton, FL: CRC Press.

Gilbert, ME. (2011). Impact of low-level thyroid hormone disruption induced by propylthiouracil on brain development and function. Toxicol Sci 124: 432-445. http://dx.doi.org/10.1093/toxsci/kfr244

Gilbert, ME; Sui, L. (2008). Developmental exposure to perchlorate alters synaptic transmission in hippocampus of the adult rat. Environ Health Perspect 116: 752-760. http://dx.doi.org/10.1289/ehp.11089

Gill, S; Bondy, G; Lefebvre, D; Becalski, A; Kavanagh, M; Hou, Y; Turcotte, A; Barker, M; Weld, M; Vavasour, E; Cooke, G. (2010). Subchronic oral toxicity study of furan in Fischer-344 rats. Toxicol Pathol 38: 619-630. http://dx.doi.org/10.1177/0192623310368978

Gordon, CJ; Becker, P; Padnos, B. (2000). Comparison of heat and cold stress to assess thermoregulatory dysfunction in hypothyroid rats. Am J Physiol Regul Integr Comp Physiol 279: R2066-R2071.

Graham, SL; Davis, KJ; Hansen, WH; Graham, CH. (1975). Effects of prolonged ethylene thiourea ingestion on the thyroid of the rat. Food Cosmet Toxicol 13: 493-499. http://dx.doi.org/10.1016/0015-6264(75)90001-2

Graham, SL; Hansen, WH; Davis, KJ; Perry, CH. (1973). Effects of one-year administration of ethylenethiourea upon the thyroid of the rat. J Agric Food Chem 21: 324-329. http://dx.doi.org/10.1021/jf60187a036

Gray, LE, Jr; Ostby, J; Marshall, R; Andrews, J. (1993). Reproductive and thyroid effects of low-level polychlorinated biphenyl (Aroclor 1254) exposure. Fundam Appl Toxicol 20: 288-294. http://dx.doi.org/10.1006/faat.1993.1038

Hood, A; Liu, YP; Gattone, VH; Klaassen, CD. (1999). Sensitivity of thyroid gland growth to thyroid stimulating hormone (TSH) in rats treated with antithyroid drugs. Toxicol Sci 49: 263-271.

Hotz, KJ; Wilson, AG; Thake, DC; Roloff, MV; Capen, CC; Kronenberg, JM; Brewster, DW. (1997). Mechanism of thiazopyr-induced effects on thyroid hormone homeostasis in male Sprague-Dawley rats. Toxicol Appl Pharmacol 142: 133-142. http://dx.doi.org/10.1006/taap.1996.8032

Howdeshell, KL. (2002). A model of the development of the brain as a construct of the thyroid system [Review]. Environ Health Perspect 110 Suppl 3: 337-348.

Hurley, PM; Hill, RN; Whiting, RJ. (1998). Mode of carcinogenic action of pesticides inducing thyroid follicular cell tumors in rodents. Environ Health Perspect 106: 437-445.

Jeong, SH; Kim, BY; Kang, HG; Ku, HO; Cho, JH. (2006). Effect of chlorpyrifos-methyl on steroid and thyroid hormones in rat F0- and F1-generations. Toxicology 220: 189-202. http://dx.doi.org/10.1016/j.tox.2006.01.005

Kennel, P; Pallen, C; Barale-Thomas, E; Espuña, G; Bars, R. (2003). Tamoxifen: 28-day oral toxicity study in the rat based on the Enhanced OECD Test Guideline 407 to detect endocrine effects. Arch Toxicol 77: 487-499. http://dx.doi.org/10.1007/s00204-003-0476-5

Kim, HS; Shin, JH; Moon, HJ; Kim, TS; Kang, IH; Seok, JH; Kim, IY; Park, KL; Han, SY. (2002). Evaluation of the 20-day pubertal female assay in Sprague-Dawley rats treated with DES, tamoxifen, testosterone, and flutamide. Toxicol Sci 67: 52-62. http://dx.doi.org/10.1093/toxsci/67.1.52

Köhrle, J. (2008). Environment and endocrinology: the case of thyroidology [Review]. Ann Endocrinol 69: 116-122. http://dx.doi.org/10.1016/j.ando.2008.02.008

Lasley, SM; Gilbert, ME. (2011). Developmental thyroid hormone insufficiency reduces expression of brain-derived neurotrophic factor (BDNF) in adults but not in neonates. Neurotoxicol Teratol 33: 464-472. http://dx.doi.org/10.1016/j.ntt.2011.04.001

Laws, SC; Ferrell, JM; Stoker, TE; Cooper, RL. (2003). Pubertal development in female Wistar rats following exposure to propazine and atrazine biotransformation by-products, diamino-S-chlorotriazine and hydroxyatrazine. Toxicol Sci 76: 190-200. http://dx.doi.org/10.1093/toxsci/kfg223

Li, MH; Hsu, PC; Guo, YL. (2001). Hepatic enzyme induction and acute endocrine effects of 2,2',3,3',4,6'-hexachlorobiphenyl and 2,2',3,4',5',6-hexachlorobiphenyl in prepubertal female rats. Arch Environ Contam Toxicol 41: 381-385. http://dx.doi.org/10.1007/s002440010263

Li, MH; Rhine, C; Hansen, LG. (1998). Hepatic enzyme induction and acute endocrine effects of 2,3,3',4',6-pentachlorobiphenyl in prepubertal female rats. Arch Environ Contam Toxicol 35: 97-103. http://dx.doi.org/10.1007/s002449900355

Männistö, PT; Ranta, T; Leppäluoto, J. (1979). Effects of methylmercaptoimidazole (MMI), propylthiouracil (PTU), potassium perchlorate (KClO4) and potassium iodide (KI) on the serum concentrations of thyrotrophin (TSH) and thyroid hormones in the rat. Acta Endocrinol 91: 271-281. http://dx.doi.org/10.1530/acta.0.0910271

Mcconnell, EE. (1992). Thyroid follicular cell carcinogenesis: results from 343 2-year carcinogenicity studies conducted by the NCI/NTP. Regul Toxicol Pharmacol 16: 177-188.

O'Neil, W; Marshall, W. (1984). Goitrogenic effects of ethylenethiourea on rat thyroid. Pestic Biochem Physiol 21: 92-101. http://dx.doi.org/10.1016/0048-3575(84)90077-4

Okazaki, K; Imazawa, T; Nakamura, H; Furukawa, F; Nishikawa, A; Hirose, M. (2002). A repeated 28-day oral dose toxicity study of 17alpha-methyltestosterone in rats, based on the 'enhanced OECD Test Guideline 407' for screening the endocrine-disrupting chemicals. Arch Toxicol 75: 635-642.

Pickford, DB. (2010). Screening chemicals for thyroid-disrupting activity: A critical comparison of mammalian and amphibian models [Review]. Crit Rev Toxicol 40: 845-892. http://dx.doi.org/10.3109/10408444.2010.494250

Poon, R; Chu, I; Lebel, G; Yagminas, A; Valli, VE. (2003). Effects of dibromoacetonitrile on rats following 13-week drinking water exposure. Food Chem Toxicol 41: 1051-1061.

Potter, CL; Moore, RW; Inhorn, SL; Hagen, TC; Peterson, RE. (1986). Thyroid status and thermogenesis in rats treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol Appl Pharmacol 84: 45-55. http://dx.doi.org/10.1016/0041-008X(86)90415-1

Rosiak, KL; Seo, BW; Chu, I; Francis, BM. (1997). Effects of maternal exposure to chlorinated diphenyl ethers on thyroid hormone concentrations in maternal and juvenile rats. J Environ Sci Health B 32: 377-393. http://dx.doi.org/10.1080/03601239709373093

Sawin, S; Brodish, P; Carter, CS; Stanton, ME; Lau, C. (1998). Development of cholinergic neurons in rat brain regions: Dose-dependent effects of propylthiouracil-induced hypothyroidism. Neurotoxicol Teratol 20: 627-635. http://dx.doi.org/10.1016/S0892-0362(98)00020-8

Seki, T; Ito, S; Adachi, H; Yoshioka, K; Hosokawa, S; Yoshitake, A; Miyamoto, J; Kurata, Y. (1987). [One-year chronic dietary toxicity study of d.d-T80-prallethrin in rats]. J Toxicol Sci 12: 397-428.

Shin, JH; Kim, TS; Kang, IH; Kang, TS; Moon, HJ; Han, SY. (2009). Effects of postnatal administration of diethylstilbestrol on puberty and thyroid function in male rats. J Reprod Dev 55: 461-466. http://dx.doi.org/10.1262/jrd.20169

Stoker, TE; Laws, SC; Crofton, KM; Hedge, JM; Ferrell, JM; Cooper, RL. (2004). Assessment of DE-71, a commercial polybrominated diphenyl ether (PBDE) mixture, in the EDSP male and female pubertal protocols. Toxicol Sci 78: 144-155. http://dx.doi.org/10.1093/toxsci/kfh029

Thuett, KA; Roots, EH; Mitchell, LP; Gentles, BA; Anderson, T; Kendall, RJ; Smith, EE. (2002). Effects of in utero and lactational ammonium perchlorate exposure on thyroid gland histology and thyroid and sex hormones in developing deer mice (peromyscus maniculatus) through postnatal day 21. J Toxicol Environ Health A 65: 2119-2130. http://dx.doi.org/10.1080/00984100290071513

Tyl, RW; Myers, CB; Marr, MC; Sloan, CS; Castillo, NP; Veselica, MM; Seely, JC; Dimond, SS; Van Miller, JP; Shiotsuka, RS; Stropp, GD; Waechter, JM; Hentges, SG. (2008). Two-generation reproductive toxicity evaluation of dietary 17beta-estradiol (E2; CAS No. 50-28-2) in CD-1 (Swiss) mice. Toxicol Sci 102: 392-412. http://dx.doi.org/10.1093/toxsci/kfn002

U.S. EPA (U.S. Environmental Protection Agency). (2005). Health Implications of Perchlorate Ingestion. Committee to Assess the Health Implications of Perchlorate Ingestion, National Research Council. http://www.nap.edu/catalog.php?record_id=11202

van Raaij, JA; Frijters, CM; van den Berg, KJ. (1993). Hexachlorobenzene-induced hypothyroidism. Involvement of different mechanisms by parent compound and metabolite. Biochem Pharmacol 46: 1385-1391.

Vo, TT; Yoo, YM; Choi, KC; Jeung, EB. (2010). Potential estrogenic effect(s) of parabens at the prepubertal stage of a postnatal female rat model. Reprod Toxicol 29: 306-316. http://dx.doi.org/10.1016/j.reprotox.2010.01.013

Wolf, DC; Crosby, LM; George, MH; Kilburn, S. R.; Moore, TM; Miller, RT; Deangelo, AB. (1998). Time- and dose-dependent development of potassium bromate-induced tumors in male Fischer 344 rats. Toxicol Pathol 26: 724-729.

Yamasaki, K; Ishii, S; Kikuno, T; Minobe, Y. (2012). Endocrine-mediated effects of two benzene related compounds, 1-chloro-4-(chloromethyl)benzene and 1,3-diethyl benzene, based on subacute oral toxicity studies using rats. Food Chem Toxicol 50: 2635-2642. http://dx.doi.org/10.1016/j.fct.2012.05.035

Yamasaki, K; Miyata, K; Shiraishi, K; Muroi, T; Higashihara, N; Oshima, H; Minobe, Y. (2008). Uterotrophic assay, Hershberger assay, and subacute oral toxicity study of 4,4'-butylidenebis(2-tert-butyl-5-methylphenol) and 3-(dibutylamino)phenol, based on the OECD draft protocols. Arch Toxicol 82: 301-311. http://dx.doi.org/10.1007/s00204-007-0250-1

Yang, H; Zhang, W; Kong, Q; Liu, H; Sun, R; Lin, B; Zhang, H; Xi, Z. (2013). Effects of pubertal exposure to thiazole-Zn on thyroid function and development in female rats. Food Chem Toxicol 53: 100-104. http://dx.doi.org/10.1016/j.fct.2012.11.003

York, RG; Barnett, J; Brown, WR; Garman, RH; Mattie, DR; Dodd, D. (2004). A rat neurodevelopmental evaluation of offspring, including evaluation of adult and neonatal thyroid, from mothers treated with ammonium perchlorate in drinking water. Int J Toxicol 23: 191-214. http://dx.doi.org/10.1080/10915810490475835

York, RG; Brown, WR; Girard, MF; Dollarhide, JS. (2001). Two-generation reproduction study of ammonium perchlorate in drinking water in rats evaluates thyroid toxicity. Int J Toxicol 20: 183-197. http://dx.doi.org/10.1080/109158101750408019

Zhang, L; Wang, J; Zhu, GN. (2010). Pubertal exposure to saisentong: Effects on thyroid and hepatic enzyme activity in juvenile female rats. Exp Toxicol Pathol 62: 127-132. http://dx.doi.org/10.1016/j.etp.2009.03.001

Zhou, T; Ross, DG; DeVito, MJ; Crofton, KM. (2001). Effects of short-term in vivo exposure to polybrominated diphenyl ethers on thyroid hormones and hepatic enzyme activities in weanling rats. Toxicol Sci 61: 76-82.

Zhu, YS; Yen, PM; Chin, WW; Pfaff, DW. (1996). Estrogen and thyroid hormone interaction on regulation of gene expression. PNAS 93: 12587-12592.

Zoeller, RT; Dowling, AL; Vas, AA. (2000). Developmental exposure to polychlorinated biphenyls exerts thyroid hormone-like effects on the expression of RC3/neurogranin and myelin basic protein messenger

ribonucleic acids in the developing rat brain. Endocrinology 141: 181-189. http://dx.doi.org/10.1210/en.141.1.181

Zorrilla, LM; Gibson, EK; Jeffay, SC; Crofton, KM; Setzer, WR; Cooper, RL; Stoker, TE. (2009). The effects of triclosan on puberty and thyroid hormones in male Wistar rats. Toxicol Sci 107: 56-64. http://dx.doi.org/10.1093/toxsci/kfn225