McLanahan et al, 2007

Guidelines/Criteria	
Reference:	McLanahan ED, Campbell JL Jr, Ferguson DC, Harmon B, Hedge JM, Crofton KM, Mattie DR, Braverman L, Keys DA, Mumtaz M, Fisher JW. 2007. Low-dose effects of ammonium perchlorate on the hypothalamic-pituitary-thyroid axis of adult male rats pretreated with PCB 126. Toxicol Sci 97(2):308-317.
In vivo **Study Type** Route of Administration Species & age of animals	 PCB by gavage, perchlorate via drinking water SD rats, male, 160-180 g bw
Study Duration	1-5 days
Type of Mixture Binary >2 components Similar acting or dissimilar What Mode of Action was investigated?	 subsequent exposure: first PCB126, then ClO4- dissimilar increased T4 clearance by enzyme induction versus competition for thyroid iodine uptake
Parameters/End points Measured Target organs/Critical effects Pharmacological changes or adverse effects	 hypothalamic-pituitary-thyroid axis liver weight, serum freeT4, serum total T4, serum TSH, hepatic UDPGT activity
Individual Components Characterisation of individual compounds Name, exact chemical name, CAS no. Were dose responses established for individual components? Were no effect levels established? Were doses below the NO(A)ELs investigated?	 PCB126 and AP salt, no further details more or less - two to 3 dose levels yes yes, mostly
Mixtures Investigated Number of dose levels How does the mixture make-up compare to individual components? (e.g. low dose) equivalents used?) No. of technical replicates per exposure condition (*in vitro*) No. of animals per dose group (*in vivo*)	 two different experiments - see snapshot below see below 8
Observations/Findings	Experiment 1: Lower PCB dose of 7.5ug/kg was NOEL for all endpoints examined except serum TSH, other dose of 75ug/kg showed clear effect on all endpoints. Of the three ClO4- doses, the highest was an effect dose for all endpoints when administered as single compound, the lowest was a NOEL and the mid dose had a statistically significant effect on one endpoint. Coexposures: the 0.01 mg/kg ClO4- plus 7.5ug/kg PCB group was the NOEL for all endpoints except for serum TSH. Experiment 2: One ClO4- dose only (0.01 mg/kg), for 1 day or 4 days, evoked no statistically significant effect on any endpoint. Single doses of PBC: 0.075 / 0.75 / 7.5ug/kg: at 2 and 5 days after exposure, only hepatic UDGPT activity was increased at mid (day 2 only) and high dose (both timepoints). Coexposures: no significant differences from control for coexposed animals were detected. Conclusion by authors: In conclusion, these studies demonstrate that HPT axis disturbances following exposure to ClO4 are less than additive when pretreated with relatively high doses of PCB126. At relatively low doses, at or near the no-observed-effect-level for PCB126 and ClO4, no interactions between the chemicals occur.

Overall opinion (e.g. sufficient numbers of groups investigated, group sizes adequate, observations reproducible, low dose levels used investigated)	Despite the somewhat confusing design, this is a good study, agree to conclusions. Could have used some even lower doses, but for most endpoints, NOELS were established. No surprising findings.

TABLE 1
Study design and dosing schedule for dosing study I

Group	PCB126 dose (μg/kg)	Perchlorate dose (mg/kg day)	*n*
	Day 0	Days 9–22	
1	0	0	8
1	0	0.01	8
1	0	0.1	8
1	0	1.0	8
1	7.5	0	8
1	7.5	0.01	8
1	7.5	0.1	8
1	7.5	1.0	8
2	0	0	8
2	0	0.01	8
2	0	0.1	8
2	0	1.0	8
2	75	0	8
2	75	0.01	8
2	75	0.1	8
2	75	1.0	8

Note. Animals were dosed and euthanized in two groups, which were separated by 1 day, as indicated by groups 1 and 2. A single oral gavage dose of PCB126 in corn oil was administered on day 0. AP was added to the drinking water to obtain the target doses indicated, beginning on day 9 and continuing until the end of study, day 22. Eight animals (*n*) were used for each dose combination.

respectively. AP salt (99.8% pure) was obtained from Aldrich (Milwaukee, WI).

TABLE 2
Study design and dosing schedule for dosing study II

PCB126 dose (μg/kg)	Perchlorate dose (mg/kg day)	End of study (day)	*n*
Day 0	Day 1—end of study		
0	NA[a]	0.5	8
0.075	NA	0.5	8
0.75	NA	0.5	8
7.5	NA	0.5	8
0	NA	1	8
0.075	NA	1	8
0.75	NA	1	8
7.5	NA	1	8
0	0	2	8
0.075	0	2	8
0.75	0	2	8
7.5	0	2	8
0	0.01	2	8
0.075	0.01	2	8
0.75	0.01	2	8
7.5	0.01	2	8
0	0	5	8
0.075	0	5	8
0.75	0	5	8
7.5	0	5	8
0	0.01	5	8
0.075	0.01	5	8
0.75	0.01	5	8
7.5	0.01	5	8