	Grouping	Ref.	OECD TG (level)	Lines of evidence	Species	Exposure weeks	Route of Exposure	Effect dose [mg/L]	Tested doses	MTD	Observed effect (+ and -)	Assessment of each line of evidence	Assessment of the integrated line of evidence	Modality
Integrated line of evidence for endocrine acitvity	*In vitro* mechanistic	[redacted] 2018e		Thyroid peroxidase	Porcine thyroid microsomes				0.01 - 100 µM		No inhibition of porcine thyroid peroxidase up to 100 µM.	Inhibition of thyroid peroxidase as a possible MOA can be excluded.	T4 serum levels are reduced through enhanced conjugation with glucuronic acid (see results T4 UDPGT induction under general toxicity) and excretion via the bile. This is compensated by enhanced biosynthesis of TSH by the pituitary. Continuous stimulation of the thyroid by TSH leads to hypertrophy, hyperplasia and ultimately neoplasia of the follicular epithelium. The MOA based on thyroid peroxidase inhibition is excluded.	T
	In vivo mechanistic	[redacted], 2002a		T3/T4 serum levels	Rat	2 weeks	Oral	10000 ppm	0, 200, 10000 ppm		From day 7 statiscally significant decrease in total and free T4 but not in total and free T3 in serum.	Decrease in T4 serum levels in mice and rats in 2 studies and increase in the mouse in one study. This may relate to feedback control mechanisms over-compensating for reductions in systemic T4 levels occurring at earlier time-points. No change in T3 serum levels.		T
		[redacted], 2002b			Mouse	2 weeks	Oral	5000 ppm	0, 100, 5000 ppm		From day 7 statistically significant decrease in total and free T4 but not in total and free T3 in serum.			
		[redacted] 2018a			Mouse	4 weeks	Oral	500, 5000 ppm	0, 500, 5000 ppm		Statistically significant increase in T4 serum levels at 500 and 5000 ppm after 1 and 4 weeks. No substance related effect on T3 serum levels at any dose tested after 1 and 4 weeks.			
		[redacted], 2002a		TSH serum levels	Rat	2 weeks	Oral	10000 ppm	0, 200, 10000 ppm		Non-statistically significant increase with dose at 10000 ppm after 2 weeks.	Although an increase in TSH serum levels was observed in rats and mice in some studies, the results were not always consistent.		
		[redacted], 2002b			Mouse	2 weeks	Oral	/	0, 100, 5000 ppm		No substance related effect at any dose tested after 1 and 2 weeks.			
		[redacted], 2003			Mouse	16 weeks	Oral	5000 ppm	0, 100, 5000 ppm		Statistically significant increase in TSH serum levels at 5000 ppm after 16 weeks. No substance related effect at any dose tested after 2, 4 and 8 weeks.			
		[redacted] 2018a			Mouse	4 weeks	Oral	500, 5000 ppm	0, 500, 5000 ppm		Non statistically significant increase in TSH serum levels at 500 and 5000 ppm after 1 week and non statistically significant decrease in TSH serum levels at 500 and 5000 ppm after 4 weeks.			
		[redacted] 2018a		Pituitary histopathology	Mouse	4 weeks	Oral		0, 500, 5000 ppm		Increased incidence of hypertrophic basophilic cells. Statistically significant increase of the expression of Tshb and Trhr genes in pituitary after 4 weeks.	The increase of hypertrophic basophilic cells in the anterior pituitary and the increase of expression of Tshb and Trhr genes is indicative of enhanced biosynthesis of TSH.		
Integrated line of evidence for adversity	EATS mediated parameter	[redacted] 1998b	OECD 408 (level 4)	Thyroid histopathology	Rat	13 weeks (+ 4 weeks recovery)	Oral	/	0, 50, 200, 5000, 20000 ppm	>20000 ppm	No substance related effect at any of the doses tested.	In a short term study in the mouse an increase in follicular cell proliferation was observed. This is the key event leading to follicular hyperplasia and adenoma observed in male mice after 104 weeks of treatment. No such effect was demonstrated in dogs. In the rat follicular cell hyperplasia was noted after 1 year of treatment but was not confirmed after 2 years.	Thyroid histopathology revealed follicular cell proliferation after 4 weeks and follicular hyperplasia and adenoma after 104 weeks in the mouse. However, this did not translate into a significant increase in thyroid weight which is indicative of a rather weak effect. Since the MOA is based on increased activity of T4 glucuronidation and subsequent biliary elimination it is considered not relevant to man.	T
		[redacted] 2001a	OECD 453		Rat	104 weeks	Oral	5000, 10000 ppm	0, 50, 200, 5000, 10000 ppm	5000 ppm	Statistically significant increase in follicular cell hyperplasia in males and females at 5000 and 10000 ppm after 52 weeks but not after 78 and 104 weeks.			
		[redacted], 2002a			Rat	2 weeks	Oral	/	0, 200 and 10000 ppm		No substance related effect at any dose tested.			
		[redacted], 1999	OECD 416 (level 4)		Rat	2-gen reprotox	Oral	/	0, 100, 1000, 10000 ppm		No substance related effect in F0 and F1 generations at any of the doses tested.			
		[redacted] 1998a	OECD 408 (level 4)		Mouse	13 weeks	Oral	/	0, 50, 200, 7000 and 20000 ppm	7000 ppm	No substance related effect at any of the doses tested.			
		[redacted] 2001b	OECD 453 (level 4)		Mouse	104 weeks	Oral	2500, 5000 ppm	0, 20, 100, 2500, 5000 ppm	2500 ppm	Statistically significant increase in follicular cell adenoma in males at 5000 ppm after 104 weeks. Statistically significant increase in follicular cell hyperplasia and dilated follicles in males and females at 2500 and/or 5000 ppm after 104 weeks.			
		[redacted], 2002b			Mouse	2 weeks	Oral	/	0, 100, 5000 ppm		No substance related effect at any of the doses tested.			
		[redacted] 2018a			Mouse	4 weeks	Oral	500, 5000 ppm	0, 500, 5000 ppm		Statistically significant increase in follicular cell proliferation at 500 and 5000 ppm after 4 weeks. Accumulation of thyroglobulin in follicular cells.			
		[redacted], 1998	≈OECD 407 (level 4)		Dog	4 weeks	Oral	/	0, 100, 300, 1000 mg/kg bw/day		No substance related effect at any dose level tested.			
		[redacted] 1999	OECD 409 (level 4)		Dog	13 weeks	Oral	/	0, 40, 200, 1000 mg/kg bw/day	>1000 mg/kg bw	No substance related effect at any of the doses tested.			
		[redacted] 2001	OECD 452 (level 4)		Dog	52 weeks	Oral	/	0, 4, 40 and 400 mg/kg bw/day	>400 mg/kg bw	No substance related effect at any of the doses tested.			
		[redacted], 2002a		Thyroid weight	Rat	2 weeks	Oral	/	0, 200 and 10000 ppm		No substance related effect on absolute and relative thyroid weight at any of the doses tested.	No effect on thyroid weight was observed.		T
		[redacted], 2002b			Mouse	2 weeks	Oral	/	0, 100 and 5000 ppm		No substance related effect on absolute and relative thyroid weight at any of the doses tested.			
		[redacted], 1998	≈OECD 407 (level 4)		Dog	4 weeks	Oral	/	0, 100, 300, 1000 mg/kg bw/day		No substance related effect on absolute and relative thyroid weight.			
		[redacted] 1999	OECD 409 (level 4)		Dog	13 weeks	Oral	/	0, 40, 200, 1000 mg/kg bw/day	>1000 mg/kg bw	No substance related effect on absolute and relative thyroid weight at any of doses tested.			
		[redacted] 2001	OECD 452 (level 4)		Dog	52 weeks	Oral	/	0, 4, 40, 400 mg/kg bw/day	>400 mg/kg bw	No substance related effect on absolute and relative thyroid weight at any of the doses tested.			
	Parameter sensitive to, but not diagnostic of, EATS	[redacted] 2000a	OECD 414 (level 4)	Fetal development	Rat	GD7-19	Oral	/	0, 10, 100, 1000mg/kg		No substance related effect at any of the doses tested.	The increased incidence of nanofetuses in the rabbit was due to a high number of small fetuses in one litter and is therefore ascribed to the bad condition of the dam and is thus considered not substance related.	Overall no significant indication on the parameters sensitive to but not diagnostic of EATS.	N
		[redacted], 1999	OECD 416 (level 4)		Rat	2-gen reprotox	Oral	10000 ppm	0, 100, 1000, 10000 ppm		One dwarf pup (out of 308 live pups) was observed at 10000 ppm in the F1 generation. No substance related effects noted in the other treatment groups.			
		[redacted], 2004	OECD 414 (level 4)		Rat	GD5-19	Oral	/	0, 10, 100, 1000 mg/kg bw/day		No substance related effect at any of the doses tested.			
		[redacted], 2000b	OECD 414 (level 4)		Rabbit	GD6-28	Oral	40 mg/kg bw/day	0, 10, 20, 40 mg/kg bw/day		Non statistically significant increase in the incidence of nanofetuses at 40 mg/kg bw/day with 10/12 nanofetuses in one litter. Not considered to be substance related.			