

Sertraline (CAS no. 79617-96-2)

Tier 1 *in vivo* Test

Amphibian Metamorphosis Assay (OECD TG 231: AMA) using larval African clawed frog (*Xenopus laevis*) (Nieuwkoop and Faber stage 51)
Sertraline HCl salt (CAS no. 79559-97-0) was used.

(1) Results

Tadpoles were exposed to concentrations of 8.61, 26.1 and 79.6 µg/L (measured). No significant differences were observed in the numbers of tadpoles with thyroid gland hypertrophy, follicular cell hypertrophy or follicular cell hyperplasia.

At 8.61 µg/L and higher, a significant decrease was observed in snout-vent length after 7 days of exposure.

At 26.1 µg/L and higher, significant decreases were observed in hind limb length and body weight after 7 days of exposure and at the end of exposure (21 days of exposure), and significant decreases were also observed in developmental stage and snout-vent length after 21 days of exposure. At 26.1 µg/L, a significant increase was also observed in the numbers of tadpoles with thyroid gland atrophy.

At 79.6 µg/L µg/L, a significant decrease was observed in developmental stage after 7 days of exposure.

Feed intake had decreased continuously after 3rd day of exposure as shown by feed sedimentation at the bottom.

(2) Summary

Antithyroid hormone activity of sertraline has been indicated from literature and Tier 1 *in vitro* tests. In this study, delayed developmental stage and thyroid gland atrophy were observed at a sublethal concentration (26.1 µg/L) to suggest antithyroid hormone effect.

It was difficult to attribute delayed developmental stage at 79.6 µg/L to delayed growth caused by decreased feed intake or antithyroid hormone effect.

The adverse exposure level of 26.1 µg/L was ca. 7,250 times as high as the highest environmental water concentration of 0.0036 µg/L that was measured in MOE's Environmental Survey and Monitoring of Chemicals in FY 2016.

The no observed adverse effect level of 8.61 µg/L was ca. 2,400 times as high as the highest environmental water concentration of 0.0036 µg/L for MOE's Environmental Survey and Monitoring of Chemicals in FY 2016.

Table 1-A Results

After 7 days of exposure				
Measured concentration (µg/L)	Developmental stage	Hind limb length (mm)	snout-vent length (mm)	Body weight (wet) mg
Control	54.0	2.87±0.14	17.1±0.29	374±24.6
8.61	54.0	2.64±0.22	16.0±0.49*	299±36.1
26.1	53.5	2.50±0.18*	14.9±0.24*	258±9.2*
79.6	53.0*	1.65±0.12*	12.1±0.31*	143±9.3*
After 21 days of exposure (At the end of exposure)				
Measured concentration (µg/L)	Developmental stage	Hind limb length (mm)	snout-vent length (mm)	Body weight (wet) mg
Control	60.0	17.4±1.14	27.0±0.27	1,593±70.0
8.61	59.0	16.6±0.64	26.5±0.46	1,463±40.1
26.1	58.5*	14.0±1.01*	25.5±0.39*	1,280±55.6*
79.6	57.0*	6.70±0.56*	20.4±0.81*	636±62.1*

Table 1-B Results (continued)

Thyroid gland hypertrophy				
Measured concentration (µg/L)	Severity in histological observation of thyroid gland After 21 days of exposure (At the end of exposure)			
	Grade 0	Grade 1 and above	Grade 2 and above	Grade 3 and above
Control	20/20	0/20	0/20	0/20
26.1	20/20	0/20	0/20	0/20
Thyroid gland atrophy				
Measured concentration (µg/L)	Severity in histological observation of thyroid gland After 21 days of exposure (At the end of exposure)			
	Grade 0	Grade 1 and above	Grade 2 and above	Grade 3 and above
Control	20/20	0/20	0/20	0/20
26.1	17/20	3/20*	0/20	0/20
Follicular cell hypertrophy				
Measured concentration (µg/L)	Severity in histological observation of thyroid gland After 21 days of exposure (At the end of exposure)			
	Grade 0	Grade 1 and above	Grade 2 and above	Grade 3 and above
Control	20/20	0/20	0/20	0/20
26.1	19/20	1/20	0/20	0/20
Follicular cell hyperplasia				
Measured concentration (µg/L)	Severity in histological observation of thyroid gland After 21 days of exposure (At the end of exposure)			
	Grade 0	Grade 1 and above	Grade 2 and above	Grade 3 and above
Control	20/20	0/20	0/20	0/20
26.1	20/20	0/20	0/20	0/20

Table 1-C Results (continued)

Measured concentration (µg/L)	Number of tested tadpoles	Mortality rate (%)	Observations
Control	80	0	Not found
8.61	80	0	Not found
26.1	80	0.8	Not found
79.6	80	0	One tadpole lost equilibrium and stayed at the bottom after the 1 st day of exposure. Lethargic swimming was also observed after 9 to 10 days of exposure. While these symptoms were temporal, feed intake had decreased continuously after 3 rd day of exposure as shown by feed sedimentation at the bottom.

Data show mean ± SD (standard deviation) of each vessel except developmental stage (mean median of each vessel)
 Statistically significant differences from control group (**p<0.01, *p<0.05)