

Supporting information (SI)

A case study application of the Aggregate Exposure Pathway (AEP) and Adverse Outcome Pathway (AOP) frameworks to facilitate the integration of human health and ecological endpoints for Cumulative Risk Assessment (CRA)

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The information presented here documents the endpoints that correspond to different key events in the AOP network for the case study of the perchlorate anion presented in this work (Table SI1; page S2). Additionally, this document provides a figure and legend that highlights the relative observed activation dose of perchlorate reported for key event in vertebrate species (Figure SI1; page S3).

Table SI1: The measurement endpoints for dose-response data that are aggregated into nine KEs of the AOP network. Species with data included in this study for at least one of the endpoints at each KE are shown in the Empirical Data column. Abbreviations: adverse outcome (AOs), key events (KEs), lethal concentration 50%, (LC50), molecular initiating event (MIE), sodium-iodide symporter (NIS), triiodothyronine (T3), thyroxine (T4), thyroid hormone (TH), thyroid stimulating hormone (TSH).

Position	KE	Endpoints	Empirical Data
MIE	NIS inhibition	NIS inhibition	Human Rat
Intermediate KEs	TH depletion in thyroid	T4 decrease (thyroid tissue) Colloid depletion	Rat Vole Quail Rabbit Zebrafish Mosquito fish African clawed frog
	TH decrease in serum	T4 decrease (plasma) T3 decrease (plasma) T4 decrease (whole body)	Rat Vole Quail Rabbit Zebrafish Mosquito fish African clawed frog
	TSH increase	TSH increase (whole body) TSH gene upregulation	Rat Zebrafish African clawed frog
	Other thyroid histology changes	Angiogenesis Follicle cell height decrease Hyperplasia Hypertrophy Total thyroid weight	Rat Vole Quail Rabbit Zebrafish Mosquito fish African clawed frog
AOs	Impaired growth	Total body weight Length Condition factor Limb size Altered metamorphosis Altered feeding	Zebrafish African clawed frog Mosquito larvae Sand Dollars Water fleas
	Decreased fecundity	Decreased egg volume Altered sex ratio Altered pubertal development Decreased cocoon production Decreased reproductive output	Zebrafish African clawed frog Earthworms Water fleas
	Developmental neurotoxicity	Altered behavior Altered larval development Altered brain morphometry	Rat Zebrafish African clawed frog
	Decreased survival	LC50 Decreased survival	Mosquito fish Earthworms Mosquito larvae

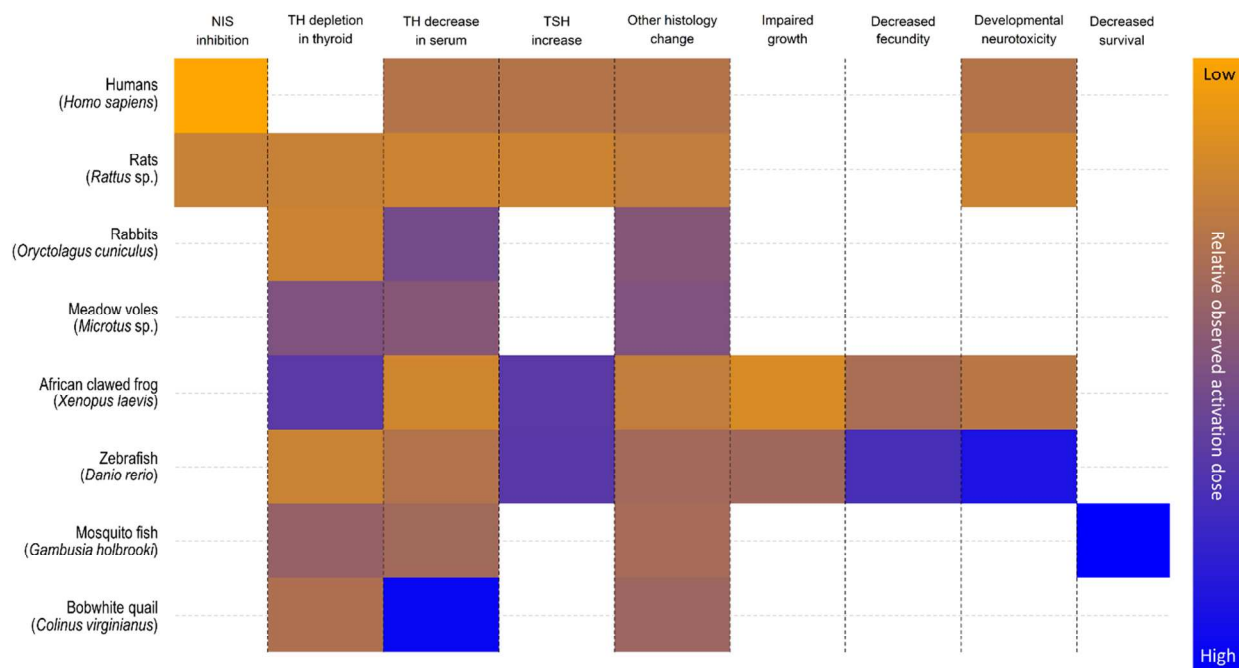


Figure S11: Heatmap showing the relative observed activation dose of different vertebrate species to each KE in the ClO₄⁻ AOP network. Colors correspond to the lowest reported values to activate each KE, with orange indicating lower doses of ClO₄⁻ necessary for activation. Blank spaces indicate data gaps for each species. Abbreviations: sodium-iodide symporter (NIS), thyroid hormone (TH), thyroid stimulating hormone (TSH).