NEUROSOME

Exploring The Neurological Exposome

Adverse Outcome Pathways Activated From Exposure To Flame Retardants And Cadmium

S. Karakitsios[1,2], A. Stratidakis[3], D. Sarigiannis[1,2,3]

1HERACLES Research Center on the Exposome and Health, Center for Interdisciplinary Research and Innovation, Aristotle University of Thessaloniki, Greece
2Aristotle University of Thessaloniki, Department of Chemical Engineering, Environmental Engineering Laboratory, Thessaloniki, Greece
3School for Advanced Study (IUSS), Science, Technology and Society Department, Pavia, Italy

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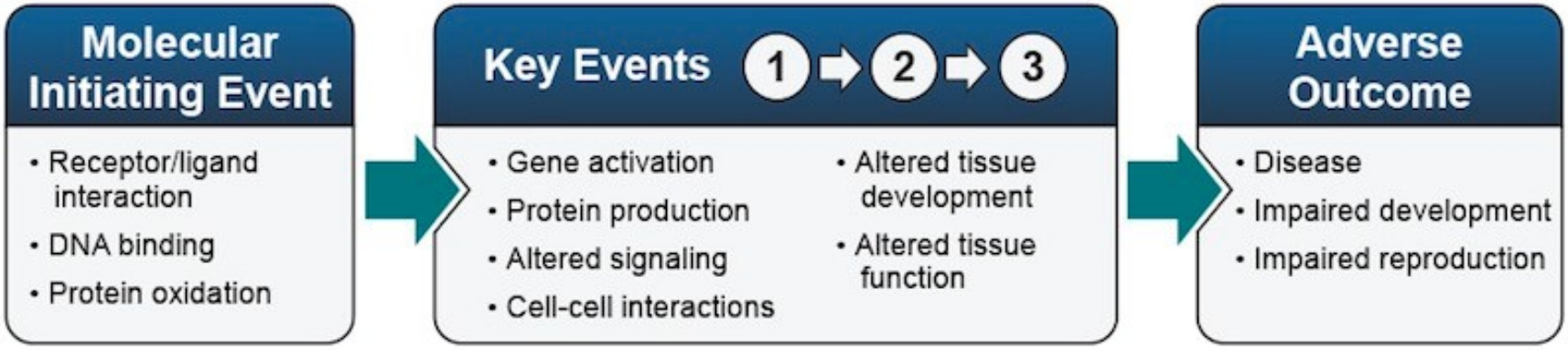
- Allen, T. E., et al. (2014): '*The adverse outcome pathway (AOP) conceptual framework has been presented as a logical sequence of events or processes within biological systems which can be used to understand adverse effects and refine current risk assessment practices in ecotoxicology.'*[1]

- Ankley, G. T., et al. (2010): '*An AOP is a conceptual construct that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome at a biological level of organization relevant to risk assessment.'*[2]

- Bal-Price, A., et al. (2015): '*The Adverse Outcome Pathway (AOP) framework provides a template that facilitates understanding of complex biological systems and the pathways of toxicity that result in adverse outcomes (AOs).'*[3]

- Becker, R. A., et al. (2015): '*An Adverse Outcome Pathway (AOP) represents the existing knowledge of a biological pathway leading from initial molecular interactions of a toxicant and progressing through a series of key events (KEs), culminating with an apical adverse outcome (AO) that has to be of regulatory relevance.'*[4]



AOPs are made up of specific elements:

•A **molecular initiating event** is an interaction between the toxic substance and an organism, such as binding of the substance to a receptor or protein. This interaction begins the toxicity process.

•**Key events** after the molecular initiating event characterize the progression of the toxicity. Early key events can include changes in protein production or molecular signaling that occur in individual cells. Later key events can include altered tissue or organ function. The links between key events are described by **key event relationships**.

•**Adverse outcomes** may occur at individual or population levels. An adverse outcome for an individual organism can include disease, impaired development, or impaired reproduction. Population adverse outcomes can include changes in population structure or local extinction of a species

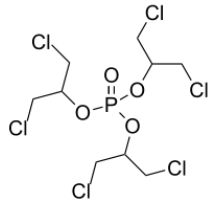
FLAME RETARDANTS

- Flame retardants are chemicals which are added to many materials to increase their fire safety.
- Many plastics are highly flammable and therefore their fire resistance is increased by adding flame retardants in order to reduce the risk of fire.

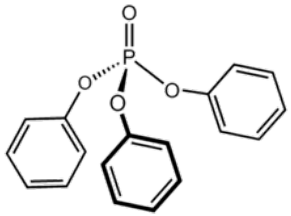
- List of well known and examined Flame Retardants:
  - TDCPP: Tris(1,3-dichloroisopropyl)phosphate
  - TPhP: Triphenyl phosphate
  - TBBPA: Tetrabromobisphenol A
  - TCEP: tris(2-carboxyethyl)phosphine
  - TNBP: Tri-n-butyl phosphate
  - TCIPP: tris (1-chloro-2-propyl) phosphate
  - TBOEP: Tris (2-butoxyethyl) phosphate
  - EHDP: Ethane-1-hydroxy-1,1-diphosphonate
  - TMPP: tris(methylphenyl) phosphate

- The selection of flame retardants was made on the basis of those for which enough toxicological data were found and the present toxicological concern

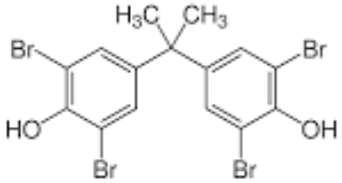
- **TDCPP**: Tris(1,3-dichloroisopropyl)phosphate



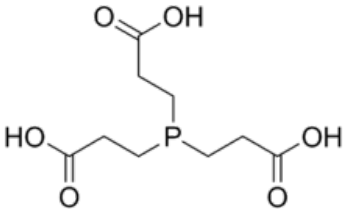
TPhP: Triphenyl phosphate



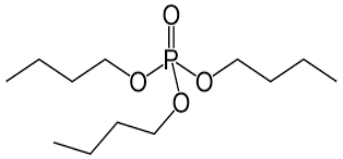
- **TBBPA**: Tetrabromobisphenol A



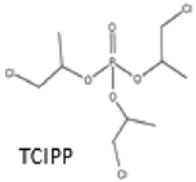
TCEP: tris(2-carboxyethyl)phosphine



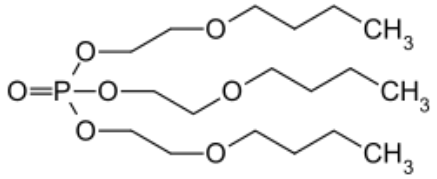
TNBP: Tri-n-butyl phosphate



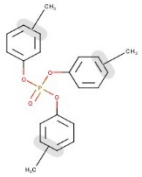
TCIPP: tris (1-chloro-2-propyl) phosphate



TBOEP: Tris (2-butoxyethyl) phosphate



- **TMPP**: tris(methylphenyl) phosphate



AOs OF HIGH IMPORTANCE FOR FLAME RETARDANTS

The AOs that were identified of high importance included:

- Hepatotoxicity and liver cancer
- Reproductive toxicity (male tract formation and semen quality)
- Neurotoxicity (locomotor activity, neurobehavior/cognition in children)

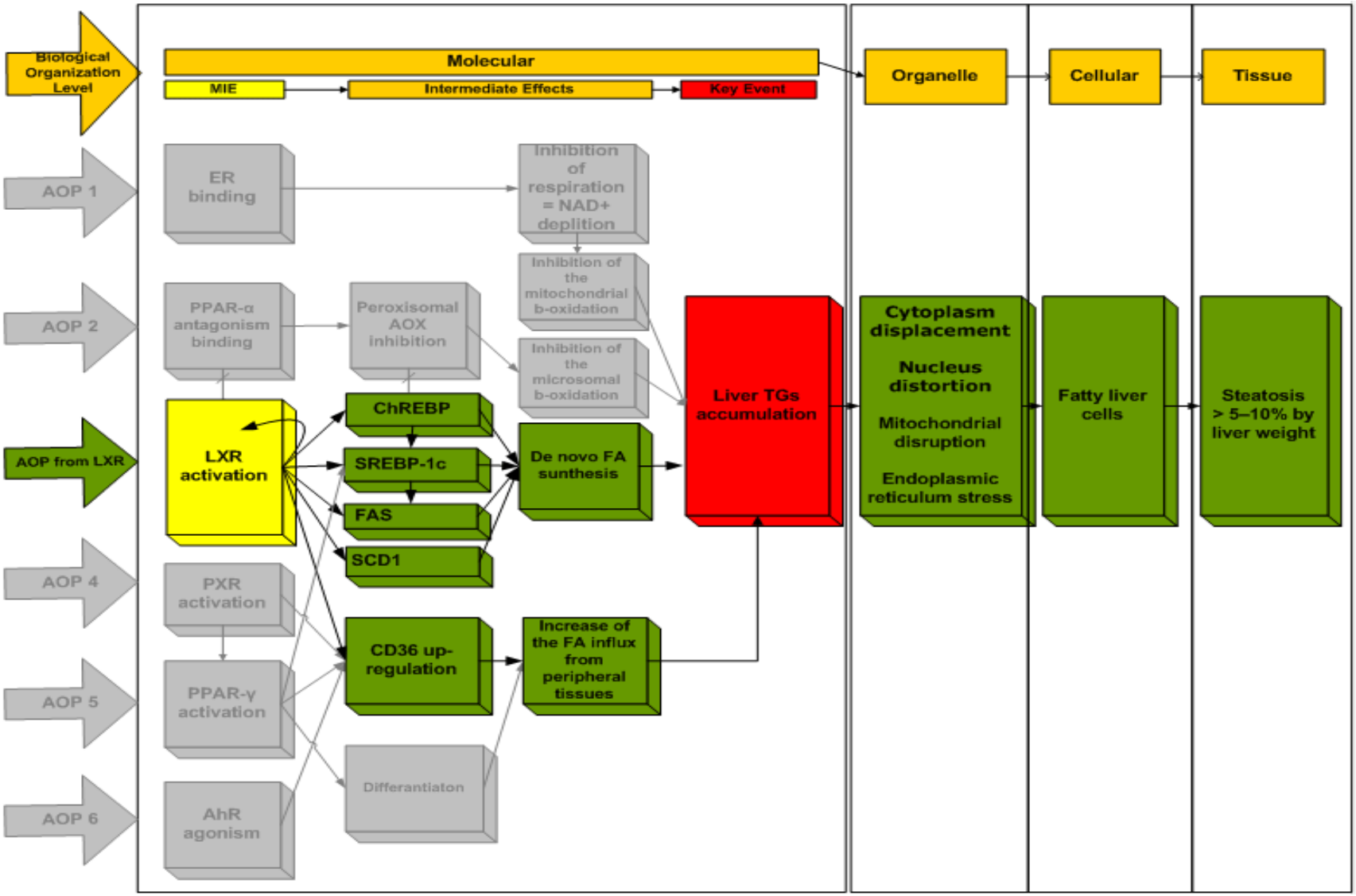
*A plausible mechanism for **TPhP-**, **TBBPA-**, **TDCIPP-** and **TCEP-**induced effects on neurobehavior/cognition.*

SEQUENCE	TYPE	EVENT ID	SHORT NAME
1	MIE	957	Binding, Transthyretin in serum
2	KE	958	Displacement, Serum thyroxine (T4) from transthyretin
3	KE	959	Increased, Free serum thyroxine (T4)
4	KE	960	Increased, Uptake of thyroxine into tissue
5	KE	961	Increased, Clearance of thyroxine from tissues
6	KE	281	T4 in serum, Decreased
7	KE	280	T4 in neuronal tissue, Decreased
8	KE	756	Hippocampal gene expression, Altered
9	KE	757	Hippocampal anatomy, Altered
10	KE	758	Hippocampal Physiology, Altered
11	AO	402	Cognitive Function, Decreased

AOs OF HIGH IMPORTANCE FOR FLAME RETARDANTS

- Only particular development of AOPs of **TNBP**, **TCIPP, TBOEP, EHDP**, **TMPP** has been found till now and an AOP scheme could not be developed.

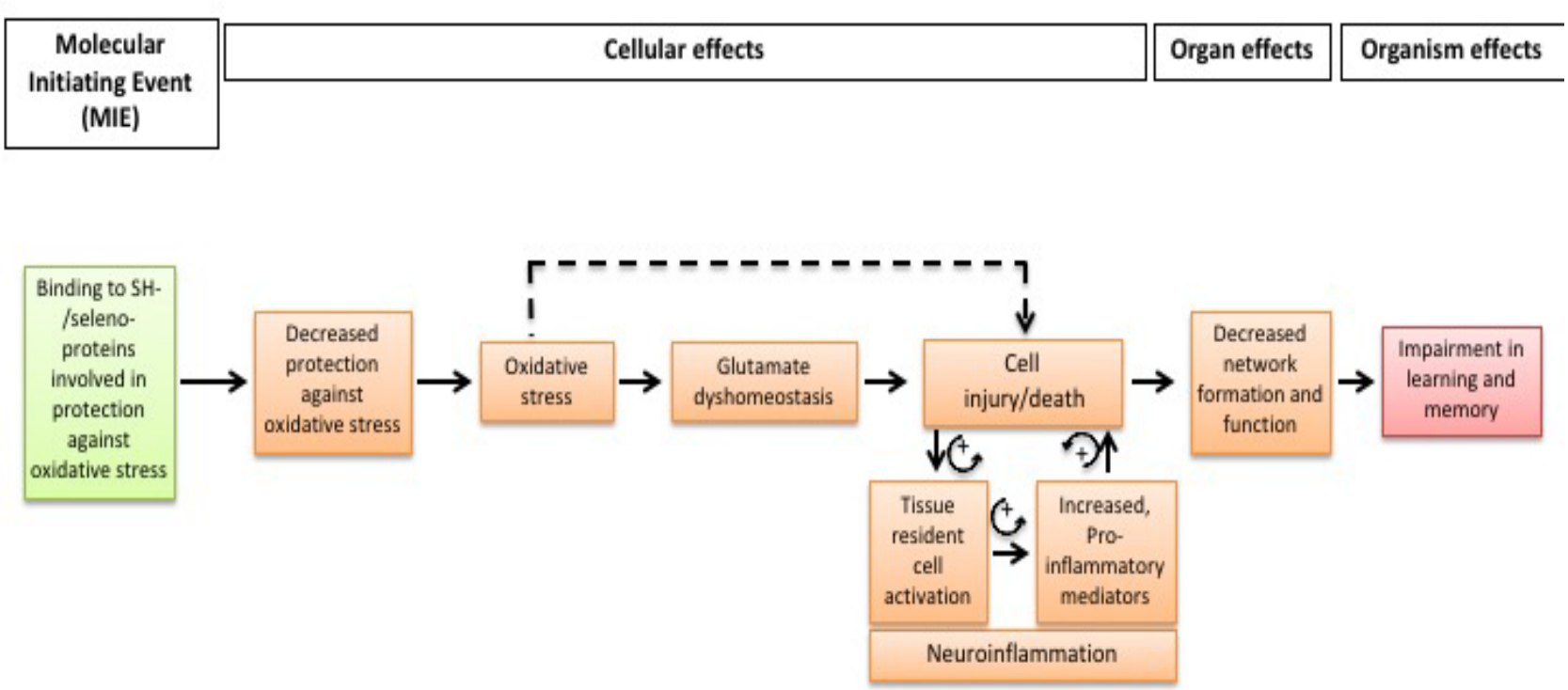
- Several animal studies analyzing the neurotoxic effects of TBBPA reached contradictory conclusions, ranging from LOAELs of 0.1 mg/kg/d in mice or 0.0064 μM in zebrafish to NOAELs of 1000 mg/kg/d in rats.


Biological Organization Level
Molecular
MIE
Intermediate Effects
Key Event
Organelle
Cellular
Tissue
AOP 1
ER binding
Inhibition of respiration = NAD+ deplition
Inhibition of the mitochondrial b-oxidation
AOP 2
PPAR-α antagonism binding
Peroxisomal AOX inhibition
Inhibition of the microsomal b-oxidation
Liver TGs accumulation
Cytoplasm displacement
Nucleus distortion
Mitochondrial disruption
Endoplasmic reticulum stress
Fatty liver cells
Steatosis > 5–10% by liver weight
AOP from LXR
LXR activation
ChREBP
SREBP-1c
FAS
SCD1
De novo FA sunthesis
AOP 4
PXR activation
CD36 up-regulation
Increase of the FA influx from peripheral tissues
AOP 5
PPAR-γ activation
Differantiaton
AOP 6
AhR agonism

NEUROTOXICITY LINKED TO CADMIUM

- Current studies related to Cd neurotoxicity support the Cd relation to several key events (KEs) that are part of AOP 17 (Oxidative stress and Developmental impairment in learning and memory) and AOP 48 (ionotropic glutamatergic receptors and cognition) mostly related to impaired learning and memory.

- The molecular initiating event (MIE) in this case is Cd binding to thiol/seleno-proteins involved in physiological protection against oxidative stress. Key events along the AOPs are induction of oxidative stress; decreased protection against oxidative stress; cell injury/death; glutamate dyshomeostasis; increased generation of pre-inflammatory mediators; mitochondrial dysfunction; neuroinflammation and neurodegeneration; and increased intracellular Ca overload


Molecular Initiating Event (MIE)
Cellular effects
Organ effects
Organism effects
Binding to SH-/seleno-proteins involved in protection against oxidative stress
Decreased protection against oxidative stress
Oxidative stress
Glutamate dyshomeostasis
Cell injury/death
Decreased network formation and function
Impairment in learning and memory
Tissue resident cell activation
Increased, Pro-inflammatory mediators
Neuroinflammation

NEUROTOXICITY LINKED TO CADMIUM
AOP 48:Ionotropic glutamatergic receptors and cognition

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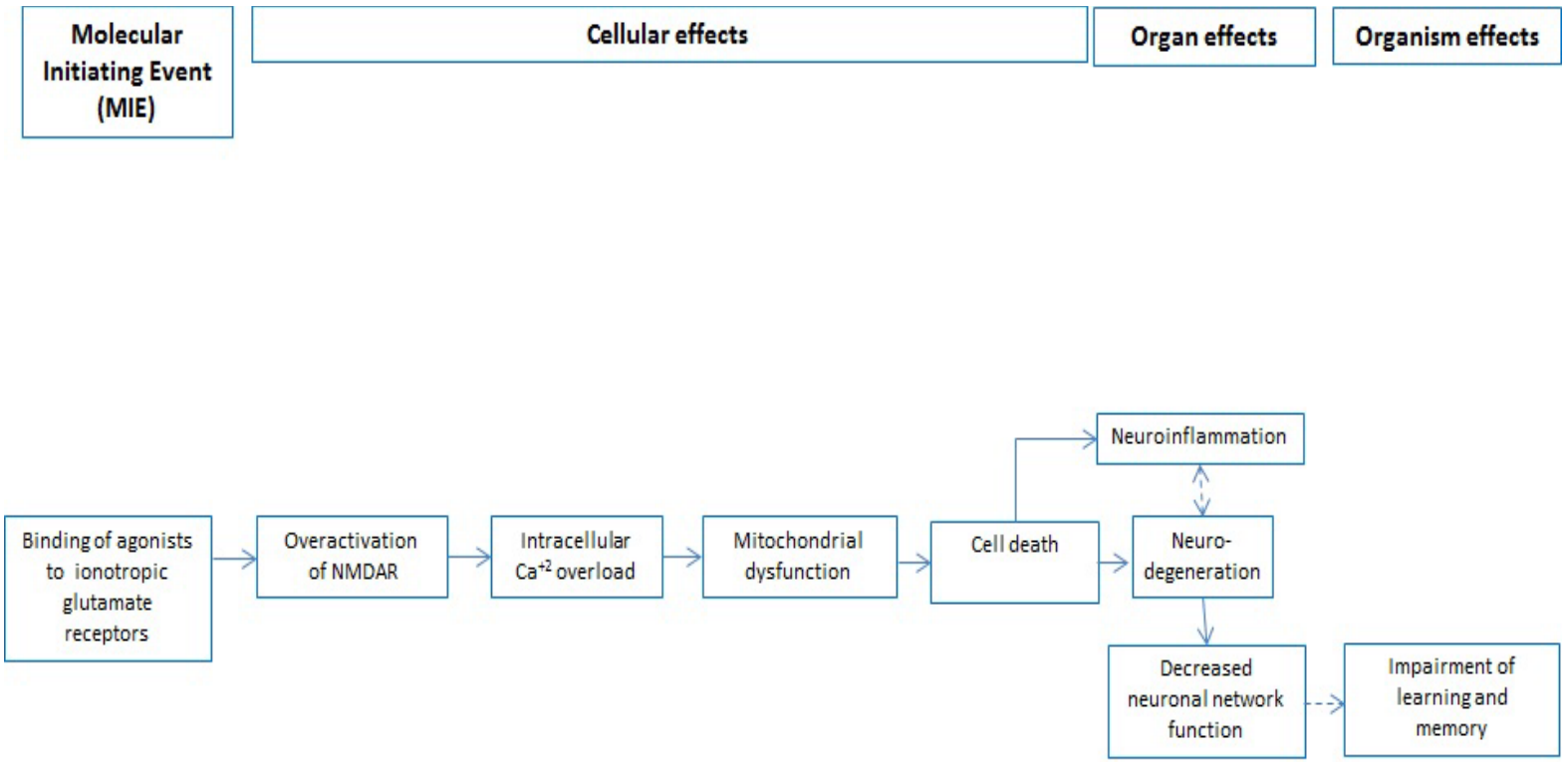

NEUROTOXICITY LINKED TO CADMIUM

SEQUENCE	TYPE	EVENT ID	SHORT NAME
1	MIE	957	Cd binding to thiol/seleno-proteins involved in physiological protection against oxidative stress
2	KE	958	induction of oxidative stress
3	KE	959	decreased protection against oxidative stress
4	KE	960	cell injury/death
5	KE	961	glutamate dyshomeostasis
6	KE	281	increased generation of pre-inflammatory mediators
7	KE	280	mitochondrial dysfunction
8	KE	756	neuroinflammation and neurodegeneration
9	KE	757	and increased intracellular Ca overload
10	AO	402	Impaired learning and memory

1. Allen, T. E., et al. (2014). "Defining molecular initiating events in the adverse outcome pathway framework for risk assessment.
- " Chem Res Toxicol 27(12): 2100-2112.
- 2. Ankley, G. T., et al. (2010). "Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment.
- " Environ Toxicol Chem 29(3): 730-741.
- 3. Bal-Price, A., et al. (2015). 'Putative adverse ourtcome pathways relevant to neurotoxicity.' Crit Rev Toxicol 45(1): 83-91.
- 4. Becker, R. A., et al. (2015). "The adverse outcome pathway for rodent liver tumor promotion by sustained activation of the aryl hydrocarbon receptor." Regul Toxicol Pharmacol 73(1): 172-190.
- 5. National Toxicology Program. U.S. Department of Health and Human Services https://ntp.niehs.nih.gov/pubhealth/evalatm/test-method-evaluations/comptox/ct-aop/aop.html
- 6. Liu, X., Ji, K., Jo, A., Moon, H. B. and Choi, K. (2013). Effects of TDCPP or TPP on gene transcriptions and hormones of HPG axis, and their consequences on reproduction in adult zebrafish (Danio rerio). *Aquat. Toxicol.* 134–135, 104–111.
- 7. Wang, Q., Lam, J. C. W., Han, J., Wang, X., Guo, Y., Lam, P. K. S. and Zhou, B. (2015). Developmental exposure to the organophosphorus flame retardant tris(1,3-dichloro-2-propyl) phosphate: Estrogenic activity, endocrine disruption and reproductive effects on zebrafish. *Aquat. Toxicol.* 160, 163–171.
- 8. Zhu, Y., Ma, X., Su, G., Yu, L., Letcher, R. J., Hou, J., Yu, H., Giesy, J. P. and Liu, C. (2015). Environmentally Relevant Concentrations of the Flame Retardant Tris(1,3-dichloro-2-propyl) Phosphate Inhibit Growth of Female Zebrafish and Decrease Fecundity. *Environ. Sci. Technol.* 49, 14579–14587.

THANK YOU FOR YOUR ATTENTION