SNAPSHOT

AOP ID and Title:

AOP 4: Ecdysone receptor agonism leading to mortality
Short Title: EcR agonism leading to mortality

Authors

You Song[1] and Knut Erik Tollefsen[1,2]
[1] Norwegian Institute for Water Research (NIVA), Section of Ecotoxicology and Risk Assessment, Gaustadalléen 21, N-0349 Oslo, Norway
[2] Norwegian University of Life Sciences (NMBU), Faculty of Environmental Science and Technology, Department of Environmental Sciences (IMV). P.O. Box 5003, N-1432 Ås, Norway
Contact: knut.erik.tollefsen@niva.no

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Abstract

Molting is a natural biological process in arthropods. During a molt cycle, the animals generate new exoskeletons by the epidermis and shed the old ones in order to grow. Successful molting is key to survival, development and reproduction. Over half a century research on arthropod endocrinology reveals that molting is precisely controlled by complex multi-hormone systems, with 20-hydroxyecdysone (20E) being the key effective hormone to mediate different biological processes that are necessary for molting. The hormonal actions of 20E are exerted through binding and modulation of the ecdysone receptors (EcR), which are nuclear transcriptional factors that regulate a wide range of physiological and behavioral changes. Based on this knowledge, endocrine disrupting chemicals (EDCs) targeting at the EcRs are developed as pesticides and anti-parasite pharmaceuticals in order to disrupt the molting cycles of “harmful” arthropods and protect the agriculture and aquaculture. However, environmental residues of these EDCs may also affect non-target species, such as a number of crustaceans (e.g. crabs and lobsters) with great ecological and economical values, due to highly conserved endocrine systems in arthropods. Substantial efforts are therefore needed to assess the environmental hazards and risks of EDCs on non-target species. Due to the high number (over a million described) of species in the phylum of *Arthopoda*, it is not feasible to perform toxicity testing for each species as well as EDC. Construction of universal models on basis of systems (eco)toxicology and phylogenetic similarities for understanding the environmental endocrine disruption (ED) effects may serve as a potential solution. The current AOP is therefore developed based on available information in the databases to identify knowledge gaps in this research field. The conceptual AOP will be further expanded using a combination of laboratory studies and advance *in sillico* predictions of potential EcR ligands and taxonomic appllicablity to inform environmental risk assessment as an ultimate goal.

Summary of the AOP

Stressors

We will add things to here soon

Molecular Initiating Event

Title	Short name	Essentiality
Activation, Ecdysone receptor	Activation, EcR	Strong

Key Events

Title	Short name	Essentiality
Induction, Nuclear receptor E75b gene	Induction, E75b gene	
Suppression, Fushi tarazu factor-1 gene	Suppression, Ftz-f1 gene	
Reduction, Release of circulating ecdysis triggering hormone	Reduction, Release of circulating ETH	Moderate
Reduction, Release of circulating crustacean cardioactive peptide	Reduction, Release of circulating CCAP	
Reduction, Ecdysis motoneuron bursts	Reduction, Ecdysis motoneuron bursts	
Reduction, Excitatory postsynaptic potential	Reduction, Excitatory postsynaptic potential	
Reduction, Abdominal muscle contraction	Reduction, Abdominal muscle contraction	Moderate
Induction, Incomplete ecdysis	Induction, Incomplete ecdysis	Strong

Adverse Outcomes

Title	Short name	Essentiality
Increased, Mortality	Increased, Mortality	

Relationships between Key Events

Upstream Event	Relationship Type	Downstream Event
Activation, Ecdysone receptor	directly leads to	Induction, Nuclear receptor E75b gene
Induction, Nuclear receptor E75b gene	directly leads to	Suppression, Fushi tarazu factor-1 gene
Suppression, Fushi tarazu factor-1 gene	directly leads to	Reduction, Release of circulating ecdysis triggering hormone
Reduction, Release of circulating ecdysis triggering hormone	directly leads to	Reduction, Release of circulating crustacean cardioactive peptide
Reduction, Release of circulating crustacean cardioactive peptide	directly leads to	Reduction, Ecdysis motoneuron bursts
Reduction, Ecdysis motoneuron bursts	directly leads to	Reduction, Excitatory postsynaptic potential
Reduction, Excitatory postsynaptic potential	directly leads to	Reduction, Abdominal muscle contraction

Upstream Event	Relationship Type	Downstream Event
Reduction, Abdominal muscle contraction	directly leads to	Induction, Incomplete ecdysis
Induction, Incomplete ecdysis	directly leads to	Increased, Mortality

Life Stage Applicability

Life Stage	Evidence
Juvenile	Strong
Adult	Moderate

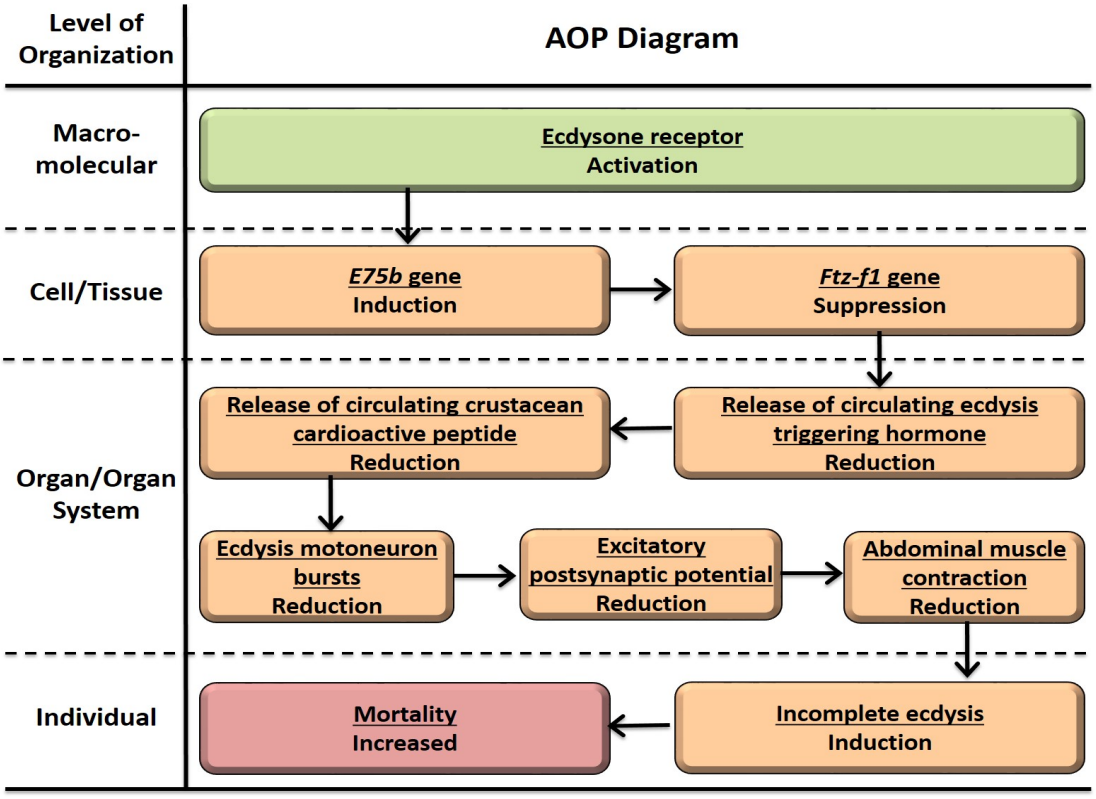
Taxon Applicability

Term	Scientific Term	Evidence
insects	insects	Strong
crustaceans	Daphnia magna	Moderate

Sex Applicability

Sex	Evidence
Unspecific	Moderate

Graphical Representation



Molecular Initating Event

Event ID and Title

103: Activation, Ecdysone receptor
Short Name: Activation, EcR

Key Event Overview

AOPs Including This Key Event

AOP ID and Name	Event Type	Essentiality
4: Ecdysone receptor agonism leading to mortality	MolecularInitiatingEvent	Strong

Stressors

The following are stressors that operate directly through this Event.
Will need to add a loop here once we have chemicals figured out

1. chemical one
2. chemical two

Taxonomic Applicability

There are no Taxonomic Terms associated with this Event

Level of Biological Organization

Molecular

Life Stage Applicability

There are no Life Stages associated with this Event

Sex Applicability

There are no Sexes associated with this Event

Key Events

Event ID and Title

1264: Induction, Nuclear receptor E75b gene
Short Name: Induction, E75b gene

Key Event Overview

AOPs Including This Key Event

AOP ID and Name	Event Type	Essentiality
4: Ecdysone receptor agonism leading to mortality	KeyEvent	

Stressors

The following are stressors that operate directly through this Event.
Will need to add a loop here once we have chemicals figured out

1. chemical one
2. chemical two

Taxonomic Applicability

There are no Taxonomic Terms associated with this Event

Level of Biological Organization

Molecular

Life Stage Applicability

There are no Life Stages associated with this Event

Sex Applicability

There are no Sexes associated with this Event

Event ID and Title

1265: Suppression, Fushi tarazu factor-1 gene
Short Name: Suppression, Ftz-f1 gene

Key Event Overview

AOPs Including This Key Event

AOP ID and Name	Event Type Essentiality
4: Ecdysone receptor agonism leading to mortality	KeyEvent

Stressors

The following are stressors that operate directly through this Event.
Will need to add a loop here once we have chemicals figured out

1. chemical one
2. chemical two

Taxonomic Applicability

There are no Taxonomic Terms associated with this Event

Level of Biological Organization

Molecular

Life Stage Applicability

There are no Life Stages associated with this Event

Sex Applicability

There are no Sexes associated with this Event

Event ID and Title

988: Reduction, Release of circulating ecdysis triggering hormone
Short Name: Reduction, Release of circulating ETH

Key Event Overview

AOPs Including This Key Event

AOP ID and Name	Event Type	Essentiality
4: Ecdysone receptor agonism leading to mortality	KeyEvent	Moderate

Stressors

The following are stressors that operate directly through this Event.
Will need to add a loop here once we have chemicals figured out

1. chemical one
2. chemical two

Taxonomic Applicability

There are no Taxonomic Terms associated with this Event

Level of Biological Organization

Tissue

Life Stage Applicability

There are no Life Stages associated with this Event

Sex Applicability

There are no Sexes associated with this Event

Event ID and Title

1266: Reduction, Release of circulating crustacean cardioactive peptide
Short Name: Reduction, Release of circulating CCAP

Key Event Overview

AOPs Including This Key Event

AOP ID and Name	Event Type Essentiality
4: Ecdysone receptor agonism leading to mortality	KeyEvent

Stressors

The following are stressors that operate directly through this Event.
Will need to add a loop here once we have chemicals figured out

1. chemical one
2. chemical two

Taxonomic Applicability

There are no Taxonomic Terms associated with this Event

Level of Biological Organization

Tissue

Life Stage Applicability

There are no Life Stages associated with this Event

Sex Applicability

There are no Sexes associated with this Event

Event ID and Title

1267: Reduction, Ecdysis motoneuron bursts
Short Name: Reduction, Ecdysis motoneuron bursts

Key Event Overview

AOPs Including This Key Event

AOP ID and Name	Event Type Essentiality
4: Ecdysone receptor agonism leading to mortality	KeyEvent

Stressors

The following are stressors that operate directly through this Event.
Will need to add a loop here once we have chemicals figured out

1. chemical one
2. chemical two

Taxonomic Applicability

There are no Taxonomic Terms associated with this Event

Level of Biological Organization

Tissue

Life Stage Applicability

There are no Life Stages associated with this Event

Sex Applicability

There are no Sexes associated with this Event

Event ID and Title

1268: Reduction, Excitatory postsynaptic potential
Short Name: Reduction, Excitatory postsynaptic potential

Key Event Overview

AOPs Including This Key Event

AOP ID and Name	Event Type Essentiality
4: Ecdysone receptor agonism leading to mortality	KeyEvent

Stressors

The following are stressors that operate directly through this Event.
Will need to add a loop here once we have chemicals figured out

1. chemical one
2. chemical two

Taxonomic Applicability

There are no Taxonomic Terms associated with this Event

Level of Biological Organization

Tissue

Life Stage Applicability

There are no Life Stages associated with this Event

Sex Applicability

There are no Sexes associated with this Event

Event ID and Title

993: Reduction, Abdominal muscle contraction

Short Name: Reduction, Abdominal muscle contraction

Key Event Overview

AOPs Including This Key Event

AOP ID and Name	Event Type	Essentiality
4: Ecdysone receptor agonism leading to mortality	KeyEvent	Moderate

Stressors

The following are stressors that operate directly through this Event.
Will need to add a loop here once we have chemicals figured out

1. chemical one
2. chemical two

Taxonomic Applicability

There are no Taxonomic Terms associated with this Event

Level of Biological Organization

Tissue

Life Stage Applicability

There are no Life Stages associated with this Event

Sex Applicability

There are no Sexes associated with this Event

Event ID and Title

990: Induction, Incomplete ecdysis
Short Name: Induction, Incomplete ecdysis

Key Event Overview

AOPs Including This Key Event

AOP ID and Name	Event Type	Essentiality
4: Ecdysone receptor agonism leading to mortality	KeyEvent	Strong

Stressors

The following are stressors that operate directly through this Event.
Will need to add a loop here once we have chemicals figured out

1. chemical one
2. chemical two

Taxonomic Applicability

There are no Taxonomic Terms associated with this Event

Level of Biological Organization

Individual

Life Stage Applicability

There are no Life Stages associated with this Event

Sex Applicability

There are no Sexes associated with this Event

Adverse Outcome

Event ID and Title

351: Increased, Mortality
Short Name: Increased, Mortality

Key Event Overview

AOPs Including This Key Event

AOP ID and Name	Event Type
16: Acetylcholinesterase inhibition leading to acute mortality	AdverseOutcome
96: Axonal sodium channel modulation leading to acute mortality	AdverseOutcome
104: Altered ion channel activity leading impaired heart function	AdverseOutcome
113: Glutamate-gated chloride channel activation leading to acute mortality	AdverseOutcome
160: Ionotropic gamma-aminobutyric acid receptor activation mediated neurotransmission inhibition leading to mortality	AdverseOutcome
161: Glutamate-gated chloride channel activation leading to neurotransmission inhibition associated mortality	AdverseOutcome
138: Organic anion transporter (OAT1) inhibition leading to renal failure and mortality	AdverseOutcome
177: Cyclooxygenase 1 (COX1) inhibition leading to renal failure and mortality	AdverseOutcome
186: unknown MIE leading to renal failure and mortality	AdverseOutcome
4: Ecdysone receptor agonism leading to mortality	AdverseOutcome

Stressors

The following are stressors that operate directly through this Event.
Will need to add a loop here once we have chemicals figured out

1. chemical one
2. chemical two

Taxonomic Applicability

There are no Taxonomic Terms associated with this Event

Level of Biological Organization

Population

Life Stage Applicability

There are no Life Stages associated with this Event

Sex Applicability

There are no Sexes associated with this Event

Scientific evidence supporting the linkages in the AOP

ID	Upstream Event	Relationship Type	Downstream Event	Evidence	Quantitative Understanding
1121	Activation, Ecdysone receptor	Directly leads to	Induction, Nuclear receptor E75b gene	Strong	Weak
1122	Induction, Nuclear receptor E75b gene	Directly leads to	Suppression, Fushi tarazu factor-1 gene	Strong	Weak
1123	Suppression, Fushi tarazu factor-1 gene	Directly leads to	Reduction, Release of circulating ecdysis triggering hormone	Moderate	Weak
1124	Reduction, Release of circulating ecdysis triggering hormone	Directly leads to	Reduction, Release of circulating crustacean cardioactive peptide	Moderate	Weak
1125	Reduction, Release of circulating crustacean cardioactive peptide	Directly leads to	Reduction, Ecdysis motoneuron bursts	Moderate	Weak
1126	Reduction, Ecdysis motoneuron bursts	Directly leads to	Reduction, Excitatory postsynaptic potential	Moderate	Weak
1127	Reduction, Excitatory postsynaptic potential	Directly leads to	Reduction, Abdominal muscle contraction	Moderate	Weak
1082	Reduction, Abdominal muscle contraction	Directly leads to	Induction, Incomplete ecdysis	Moderate	Weak
1083	Induction, Incomplete ecdysis	Directly leads to	Increased, Mortality	Strong	Strong

Relationship ID and Title:

4: Activation, EcR leads to Induction, E75b gene

Relationship ID and Title:

4: Induction, E75b gene leads to Suppression, Ftz-f1 gene

Relationship ID and Title:

4: Suppression, Ftz-f1 gene leads to Reduction, Release of circulating ETH

Relationship ID and Title:

4: Reduction, Release of circulating ETH leads to Reduction, Release of circulating CCAP

Relationship ID and Title:

4: Reduction, Release of circulating CCAP leads to Reduction, Ecdysis motoneuron bursts

Relationship ID and Title:

4: Reduction, Ecdysis motoneuron bursts leads to Reduction, Excitatory postsynaptic potential

Relationship ID and Title:

4: Reduction, Excitatory postsynaptic potential leads to Reduction, Abdominal muscle contraction

Relationship ID and Title:

4: Reduction, Abdominal muscle contraction leads to Induction, Incomplete ecdysis

Relationship ID and Title:

4: Induction, Incomplete ecdysis leads to Increased, Mortality

Overall Assessment of the AOP

Applicability of the AOP

Life Stage Applicability

Life Stage	Evidence
Juvenile	Strong
Adult	Moderate

Taxon Applicability

Term	Scientific Term	Evidence
insects	insects	Strong
crustaceans	Daphnia magna	Moderate

Sex Applicability

Sex	Evidence
Unspecific	Moderate

References