Adverse Outcome Pathway for Effects of Anticoagulant Rodenticides on Predatory Birds

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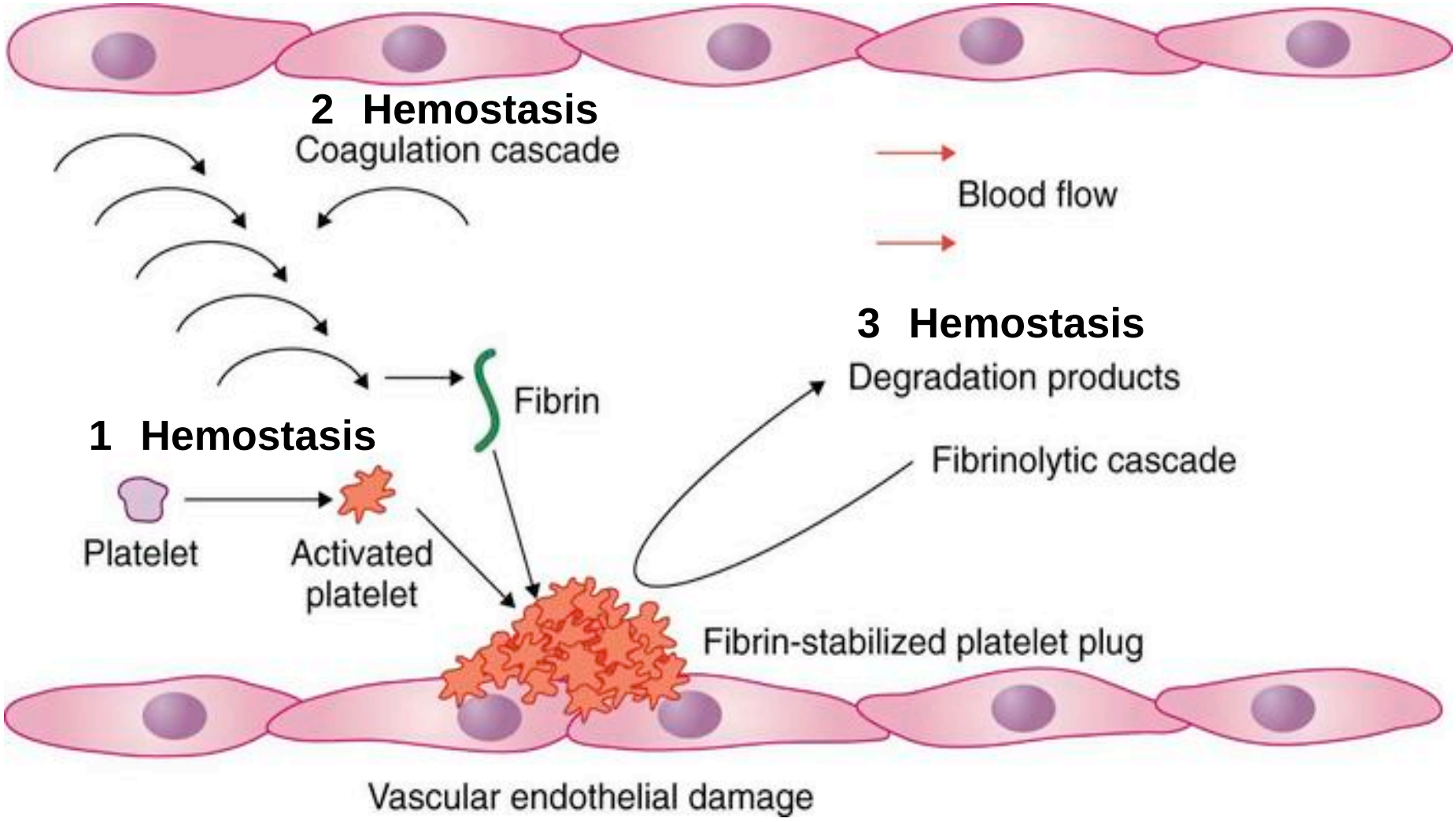

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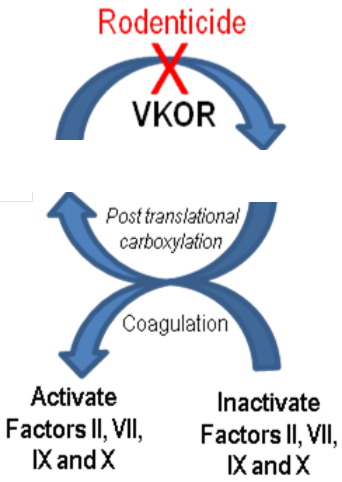
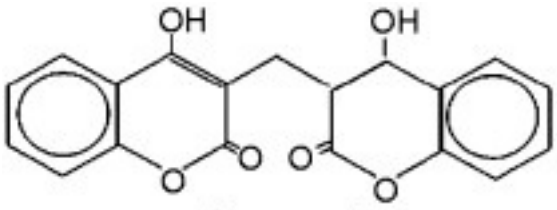
Adapted from Cleveland Clinic Center for Continuing Education

Anticoagulant Rodenticides

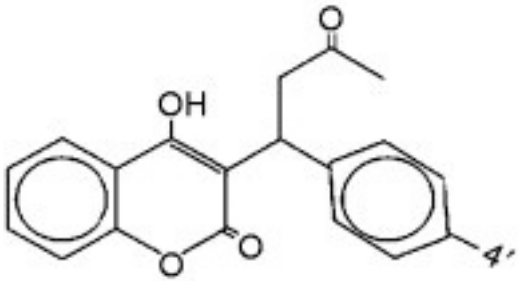
Block Vitamin K cycle

Inhibits formation active clotting Factors II, VII, IX, and X, resulting in hemorrhage





Dicumarol



Warfarin

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1st Generation Anticoagulant Rodenticides – FGARs

Warfarin (1948)

Diphacinone (1960) intermediate generation

Chlorophacinone (1971) intermediate generation

Multiple feeding to cause death (short half-life)

Genetic changes in rats (Scotland, Europe, Japan) – “Resistance”

2nd Generation Anticoagulant Rodenticides - SGARs

Brodifacoum (1979), Bromadiolone, Difethialone, Difenacoum

Single feeding can cause death

More toxic, longer half-life (potentially PBT)

Greater hazard to Non-target Species

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Widespread Use

Residential, Urban, Agriculture, Island Restoration

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Primary Exposure

Humans (AAPCC: >12,000 calls/yr)

Companion animals (APCC: 8,000 calls/yr)

Exposure in Predatory Birds and Mammals

High detection rates in liver of wildlife (principally SGARs)

Canada	70% of 164 owls	Albert et al. 2010
France	73% of 30 raptors	Lambert et al. 2007
France	12% of 122 mustelids	Fournier-Chambrillon et al. 2004
Scotland	47% of 773 raptors	Hughes et al. 2013
Britain	37% of 351 raptors	Walker et al. 2008
Britain	26% of 717 barn owls	Newton et al.1999
Britain	31% of 100 polecats	Shore et al. 2003
New Zealand	Various species	Eason et al. 1995, 2002
United States	79% of 58 fishers	Gabriel et al. 2012
United States	90% of 39 bobcat	Riley et al. 2007
United States	49% of 265 raptors	Stone et al. 2003
United States	86% of 161 raptors	Murray 2011

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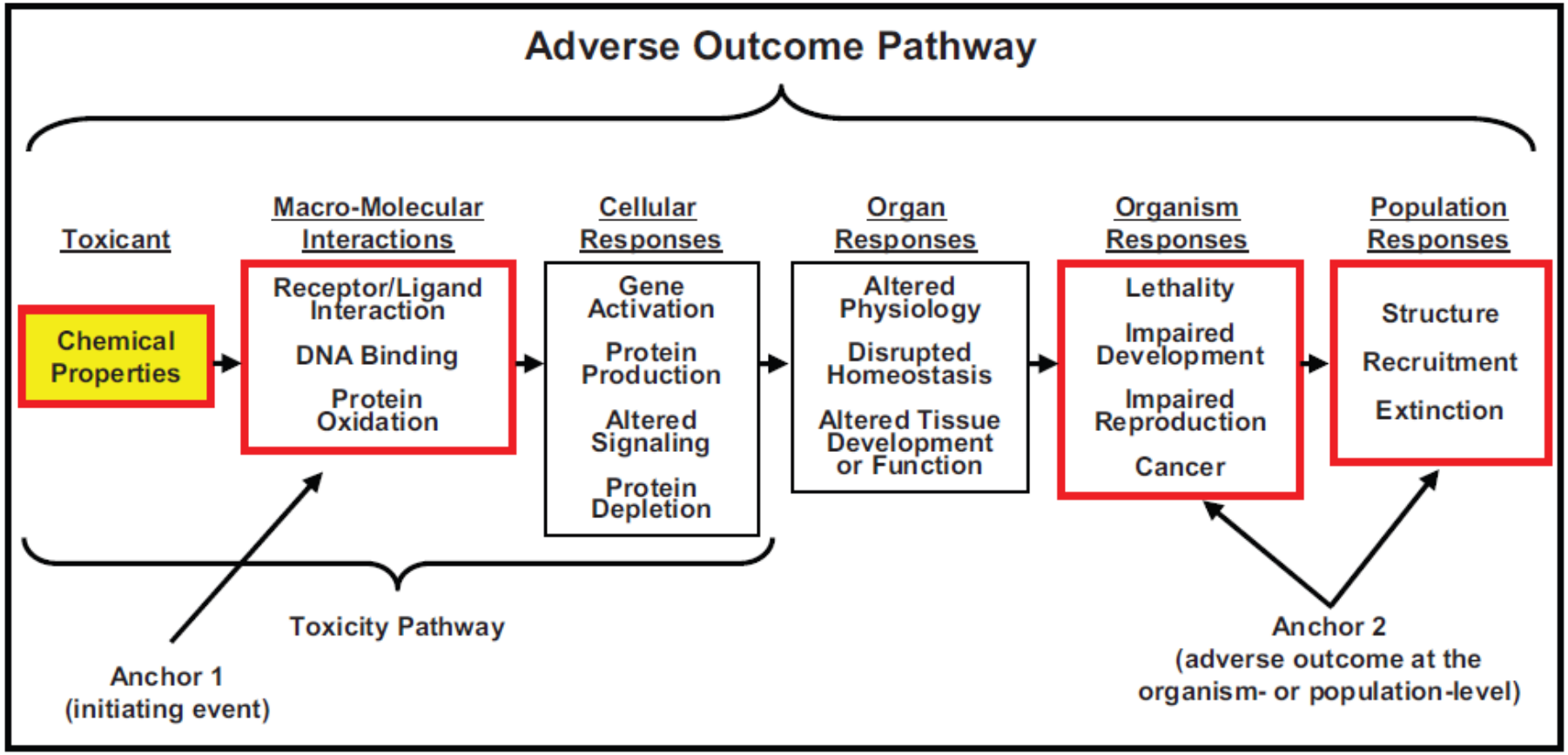

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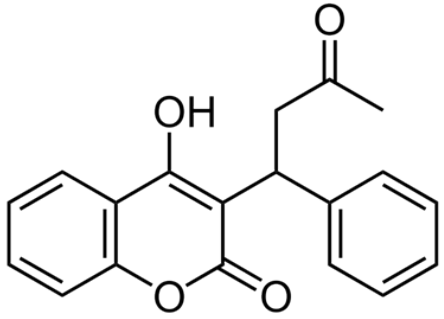
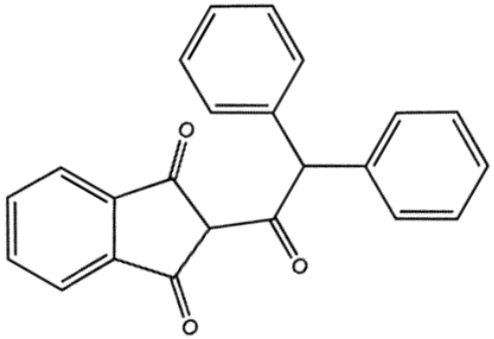
Ankley et al. 2010. Environmental Toxicology & Chemistry

Toxicant

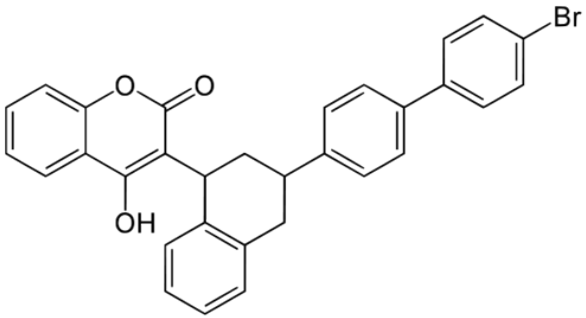
Warfarin
hydroxycoumarin
Log Kow 2.6



Diphacinone
indandione
Log Kow 4.27



Brodifacoum
hydroxycoumarin
Log Kow 8.5



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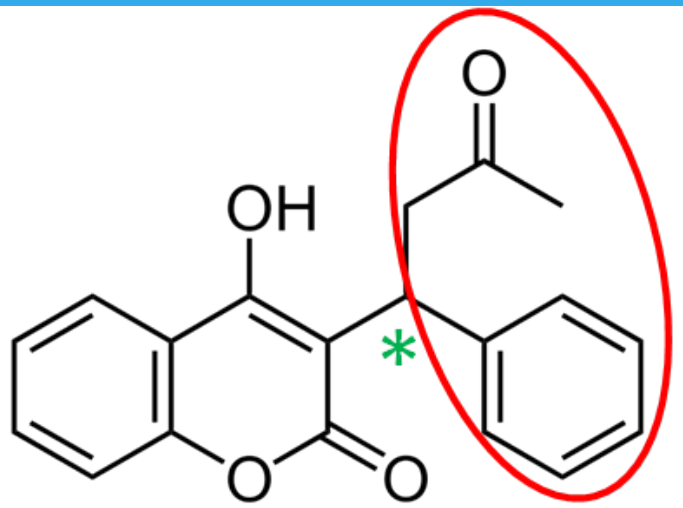
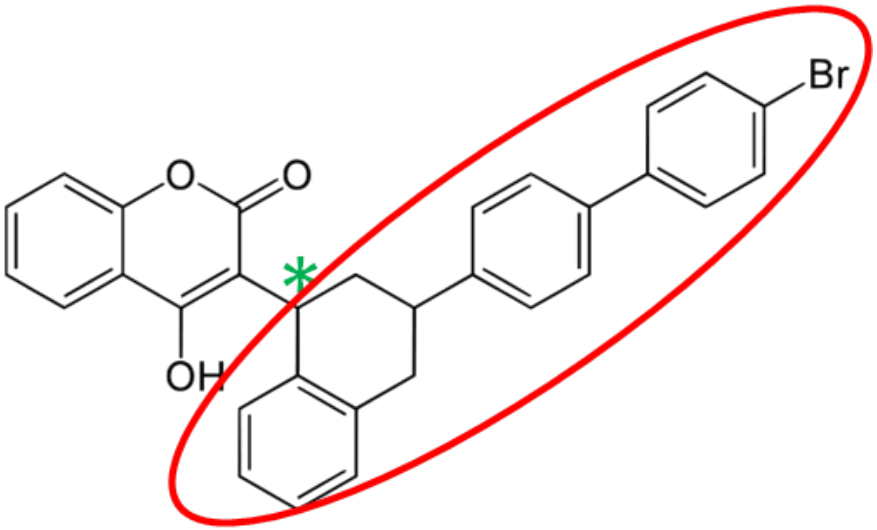
Structure Activity Relationship Models

Warfarin



Brodifacoum



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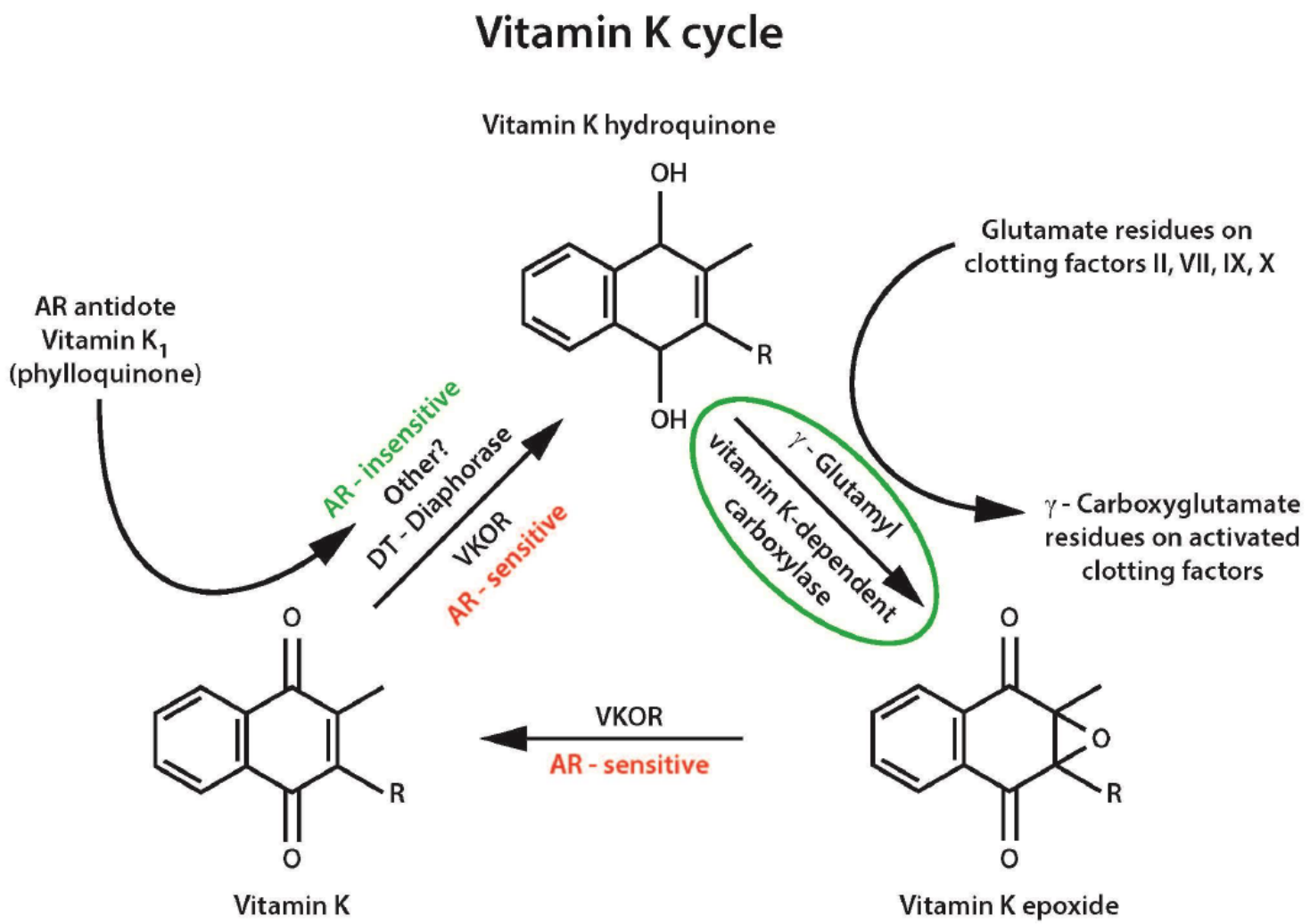
Macromolecular Interactions



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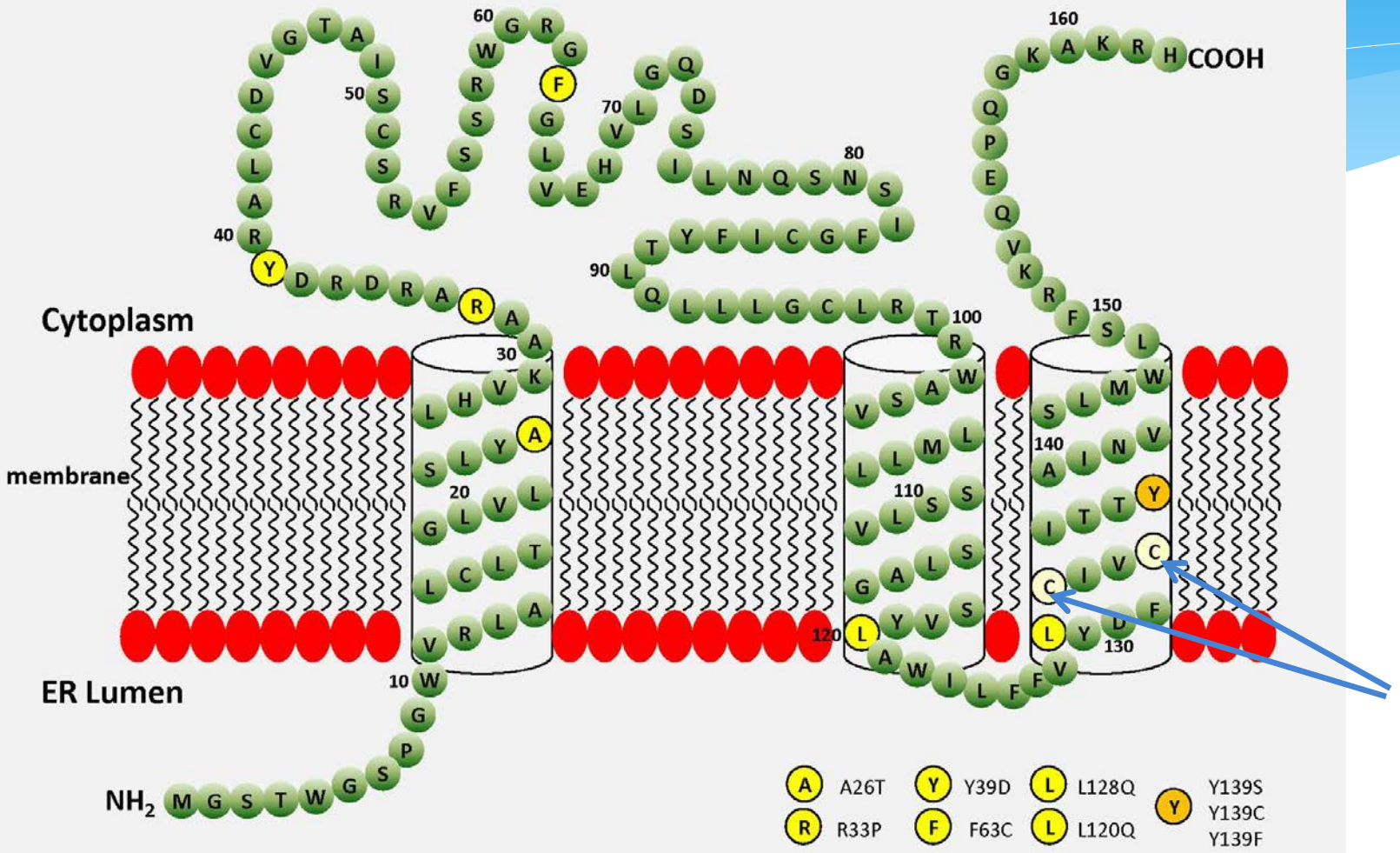
Macromolecular Interactions



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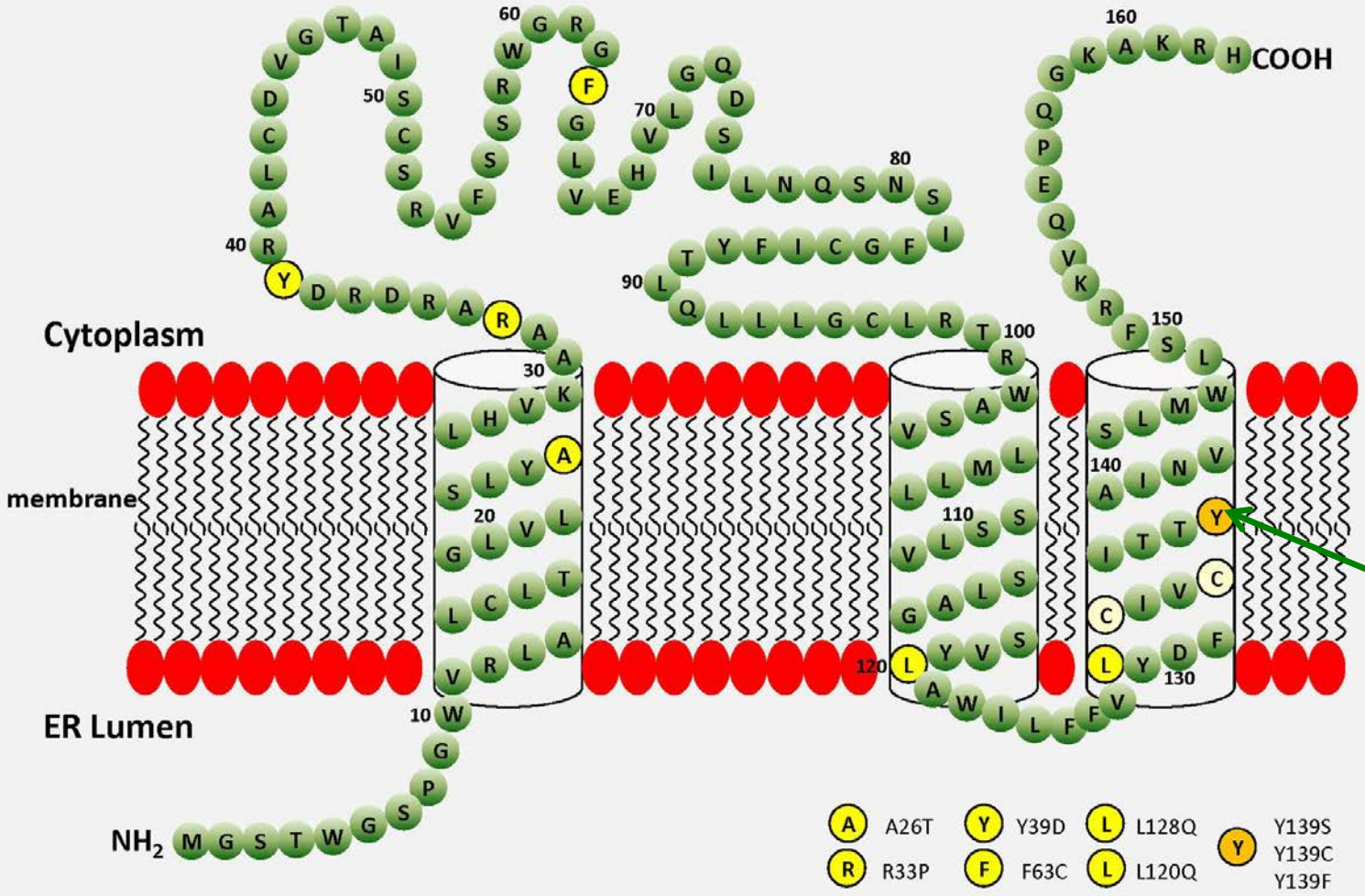
Macromolecular Interactions



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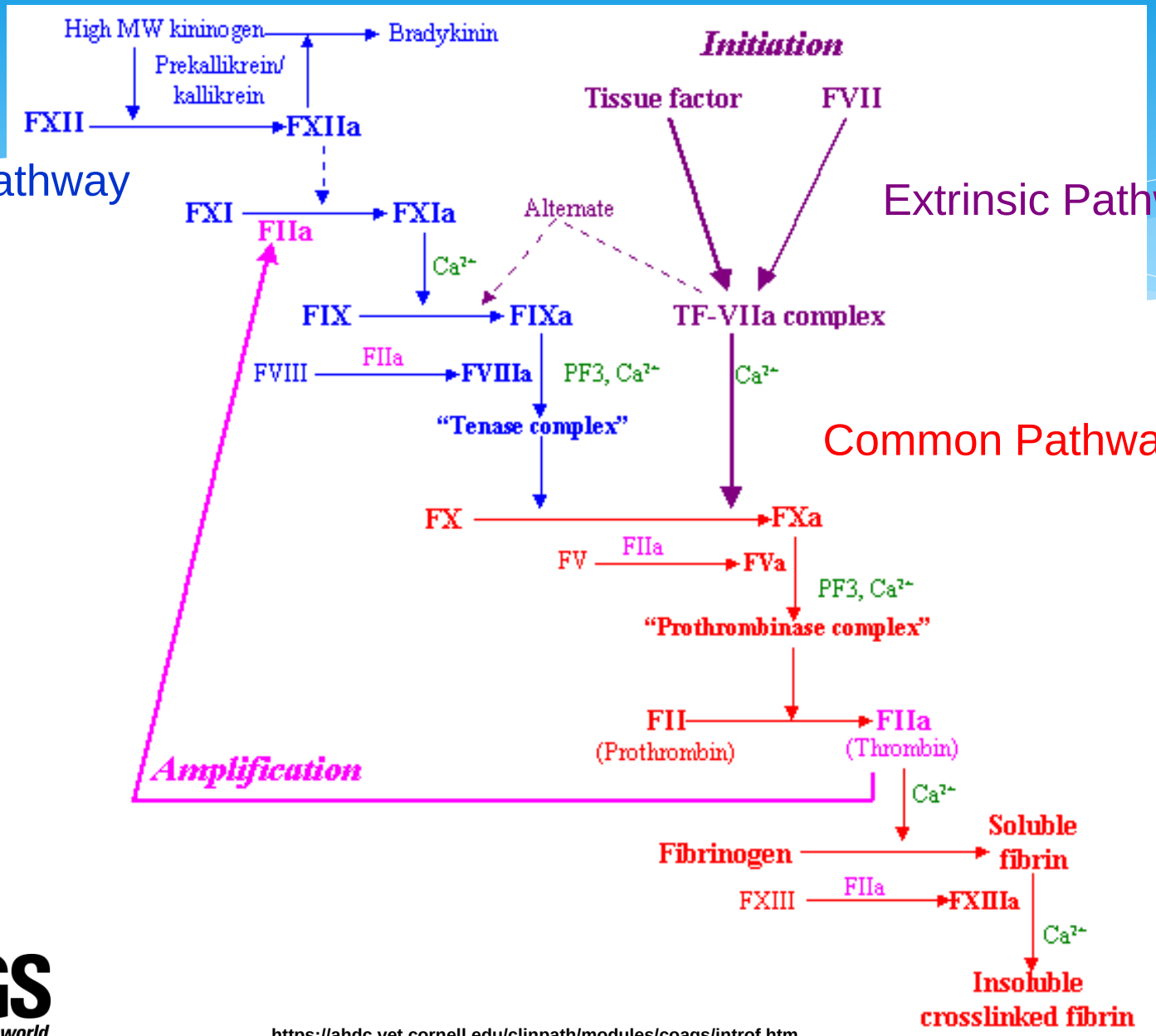
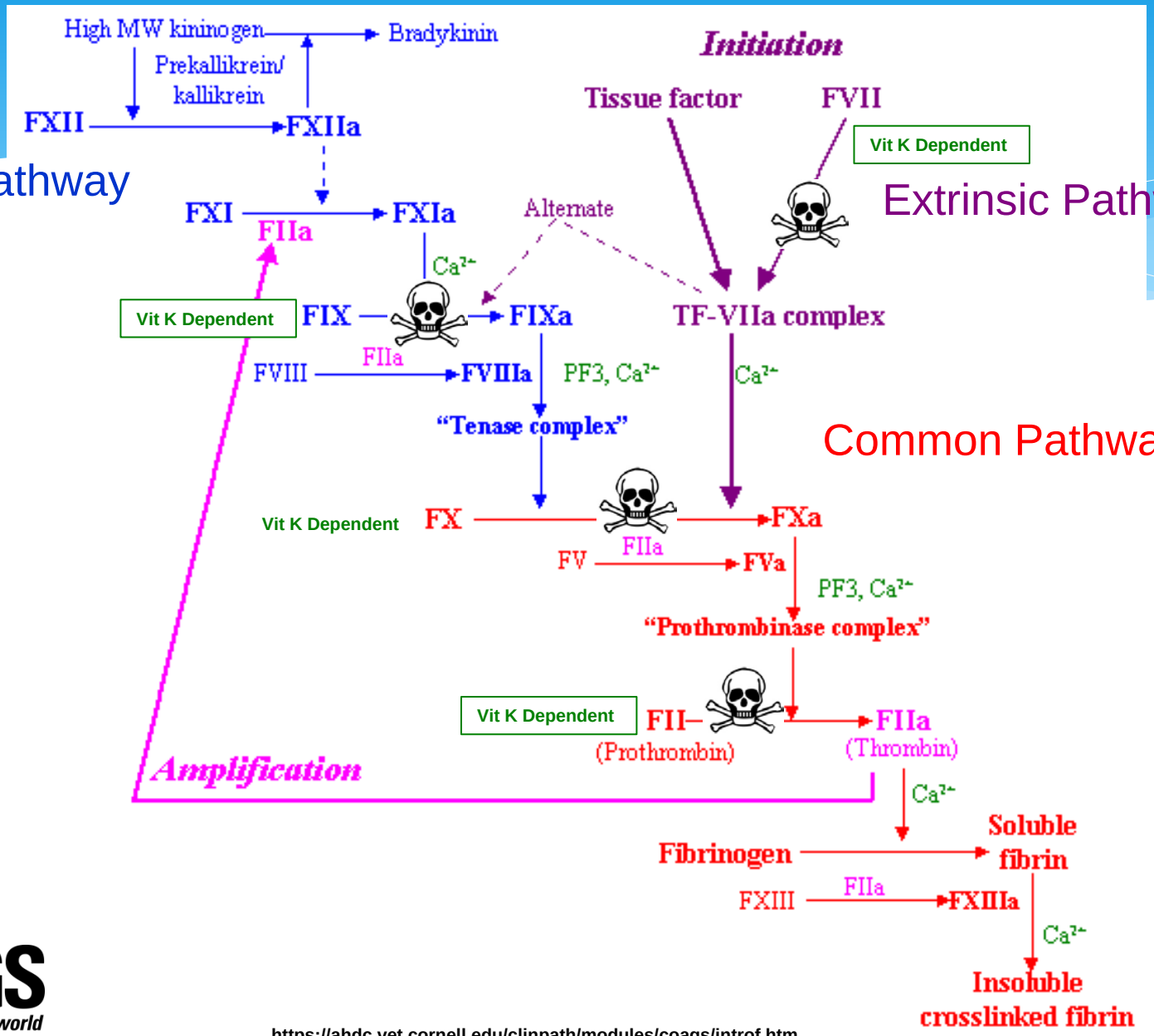
Cascade Model



https://ahdc.vet.cornell.edu/clinpath/modules/coags/introf.htm

Cascade Model



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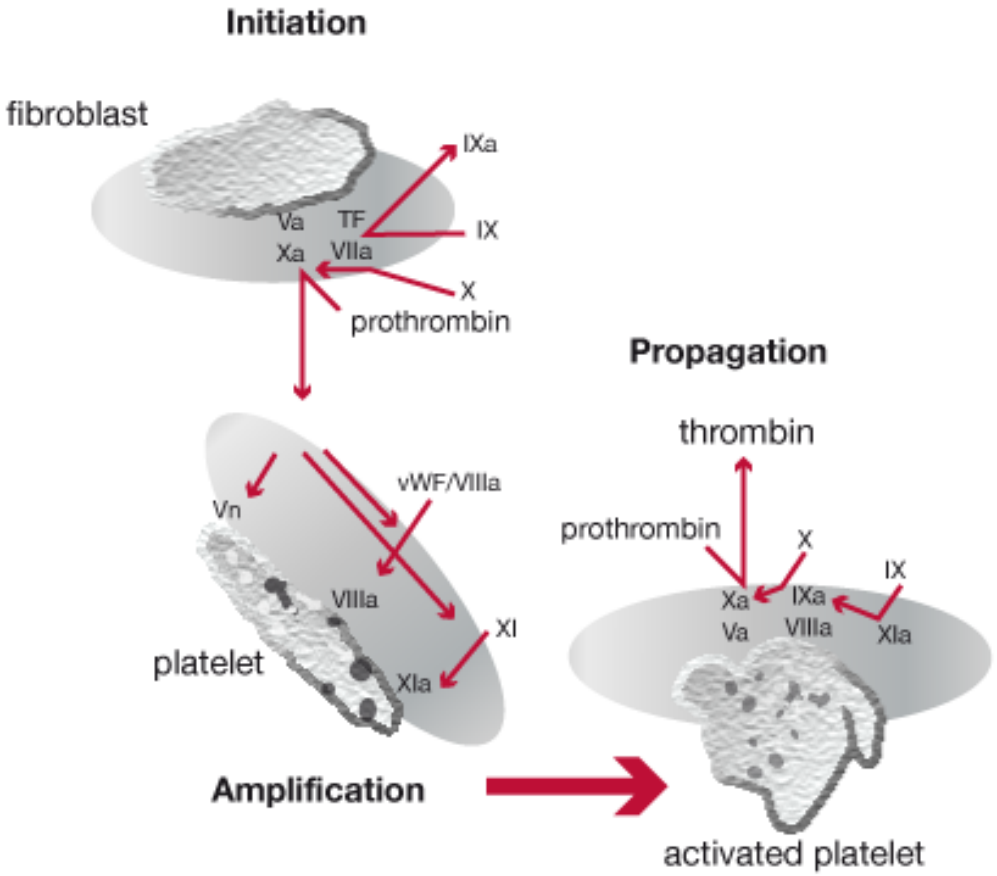
Macromolecular to the Cellular Response
Cell-based Model of Hemostasis



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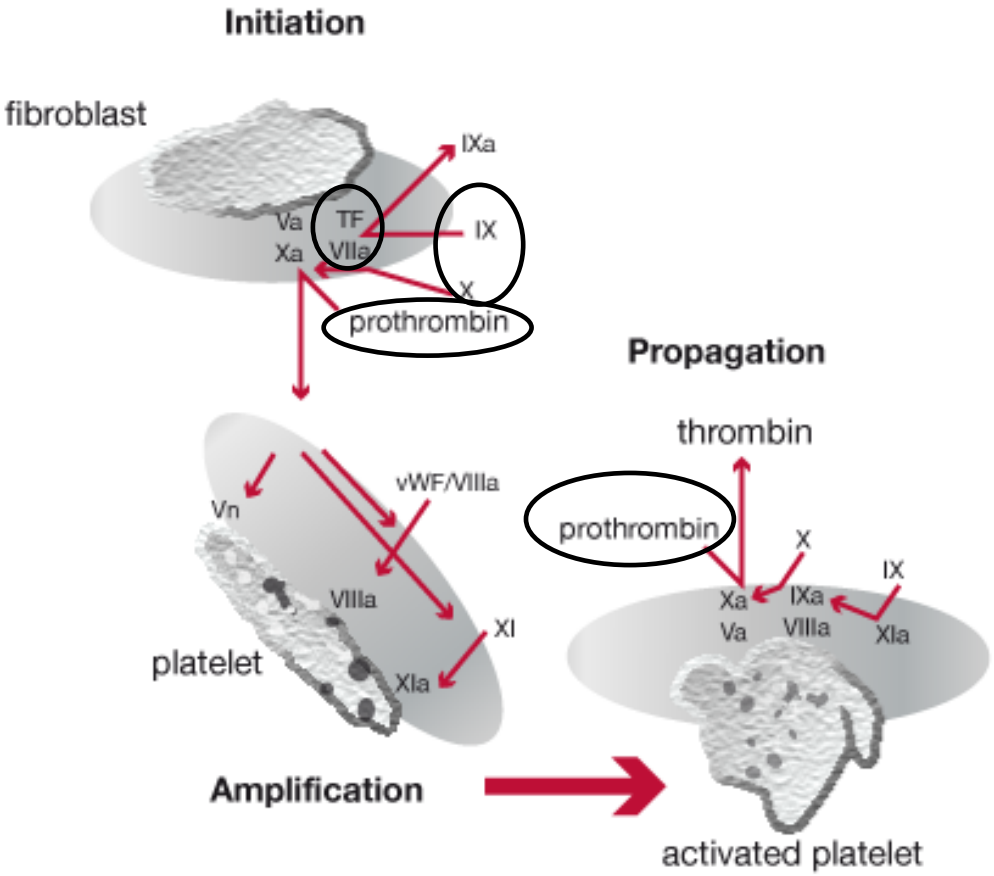
Hoffman and Monroe. 2001. Thrombosis and Haemostasis

Macromolecular to the Cellular Response
Cell-based Model of Hemostasis



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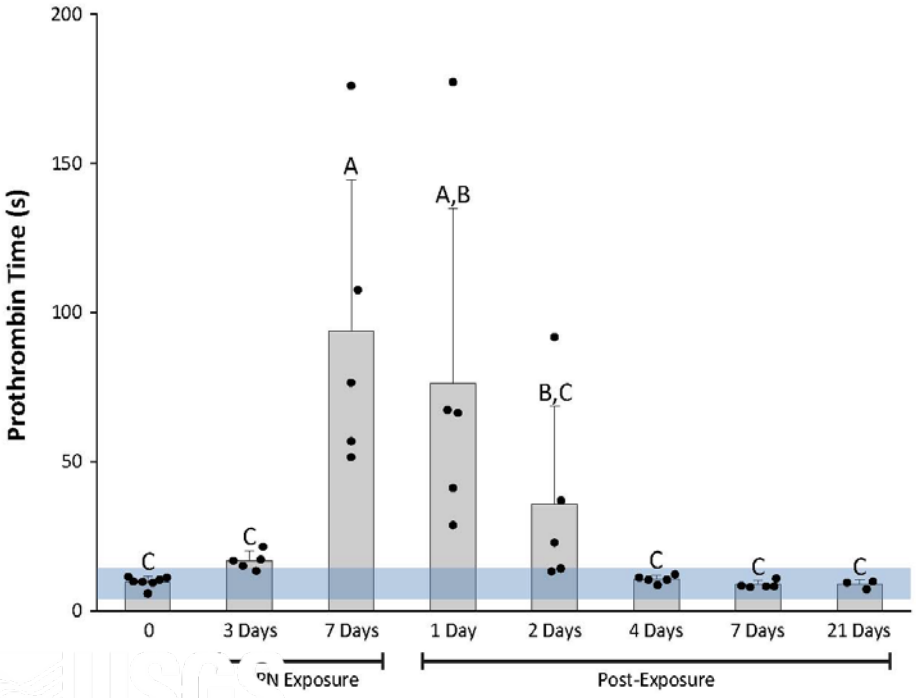
Hoffman and Monroe. 2001. Thrombosis and Haemostasis

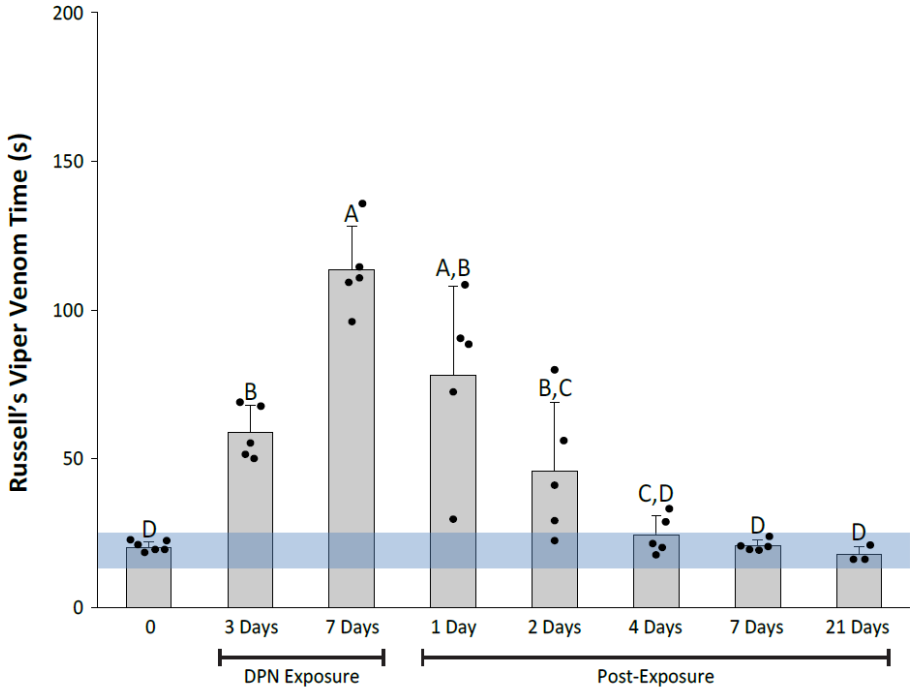
Lag for Onset of Coagulopathy

Clearance of "functional" clotting factors in humans

Clotting Factor	II	VII	IX	X
Half-Life	48-120 hr	2-6 hr	18-40 hr	30-70 hr

Appearance of "des-carboxy dysfunctional" factors





Other Cellular Responses

Vitamin K cycle-related

-reduced bone density

- anti-inflammatory and immune signaling

-inhibits cell proliferation

Uncouple oxidative phosphorylation (mitochondrial toxicity)

Peroxisome proliferator-activated receptor

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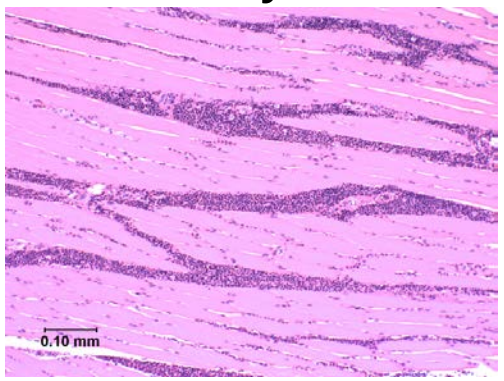
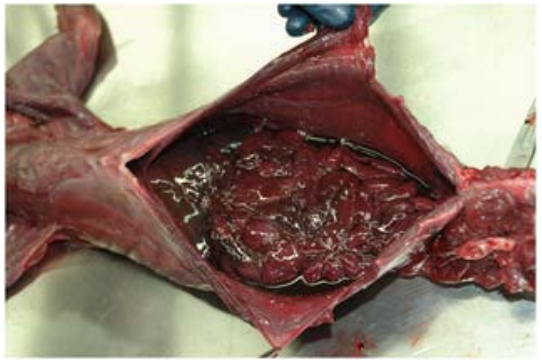
Multiple Organ Response

Hemorrhage due to coagulopathy:

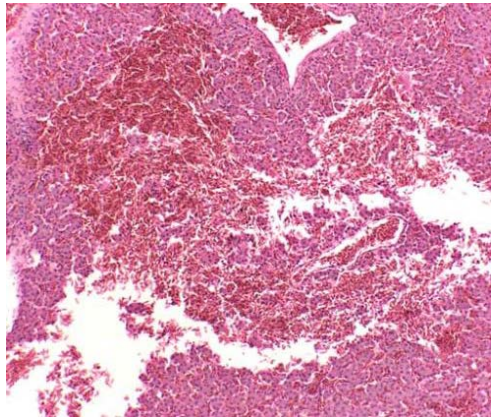
Skin Musculoskeletal Respiratory Renal

Gastrointestinal Reproductive Central Nervous System





Gabriel et al. 2012. PLOS ONE

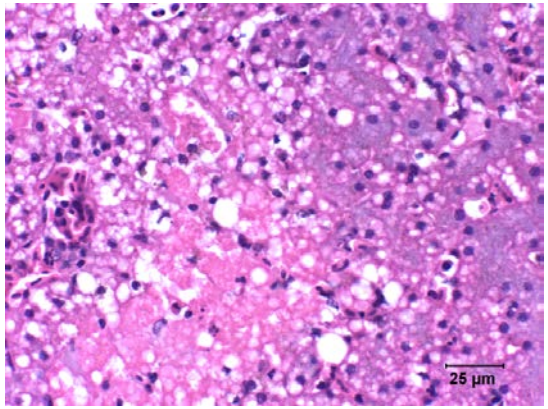


Blood Loss and Anemia

Reduced RBC count and hematocrit resulting in pallor

- Metabolic acidosis
- Increased cardiac output
- Hypovolemic shock
- Severe hypoperfusion
- Localized ischemia, hypoxia
- Organ dysfunction
- Necrosis

Plausible Linkage



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Organism Response

Lethargy (“weakness, fatigue”)

- ↓ Body condition, reduced fitness
- ↑ Blood loss from minor trauma
- Susceptibility to disease (notoedric mange)
- Alter predator-prey dynamics?

Hypothetical Linkage

Reproductive toxicants

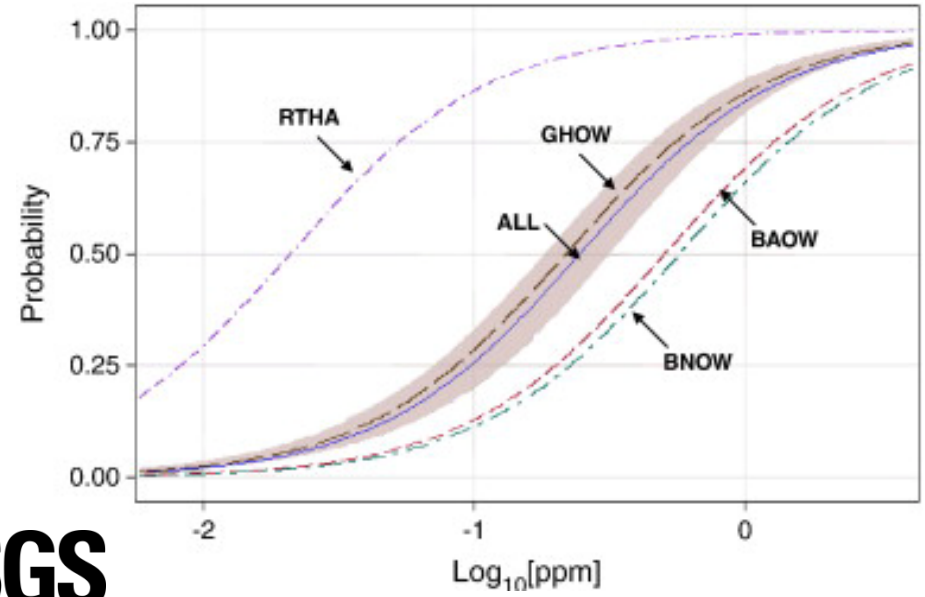
Recovery or Death

http://www.urbancarnivores.com/notoedric-mange-a-disease-of/

Population Response

Incidence of confirmed poisoning of total exposures (~10%)

Canada	6 of 114 owls	Albert et al. 2010
France	3 of 16 mustelids	Fournier-Chambrillon et al. 2004
Scotland	15 of 362 raptors	Hughes et al. 2013
Britain	9 of 187 barn owls	Newton et al. 1999
USA	4 of 46 fishers	Gabriel et al. 2012
	9 of 139 raptors	Murray 2011



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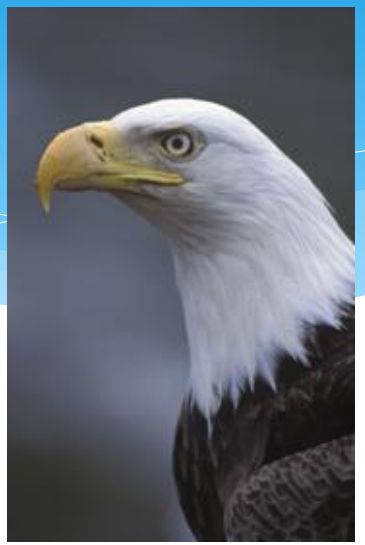
Thomas, Mineau, Shore et al. 2011. Environment International

Species of Special Conservation Status

Weka	New Zealand
Red kite	France
San Joaquin kit fox	US
Bald eagle	US
Barn owl	Canada



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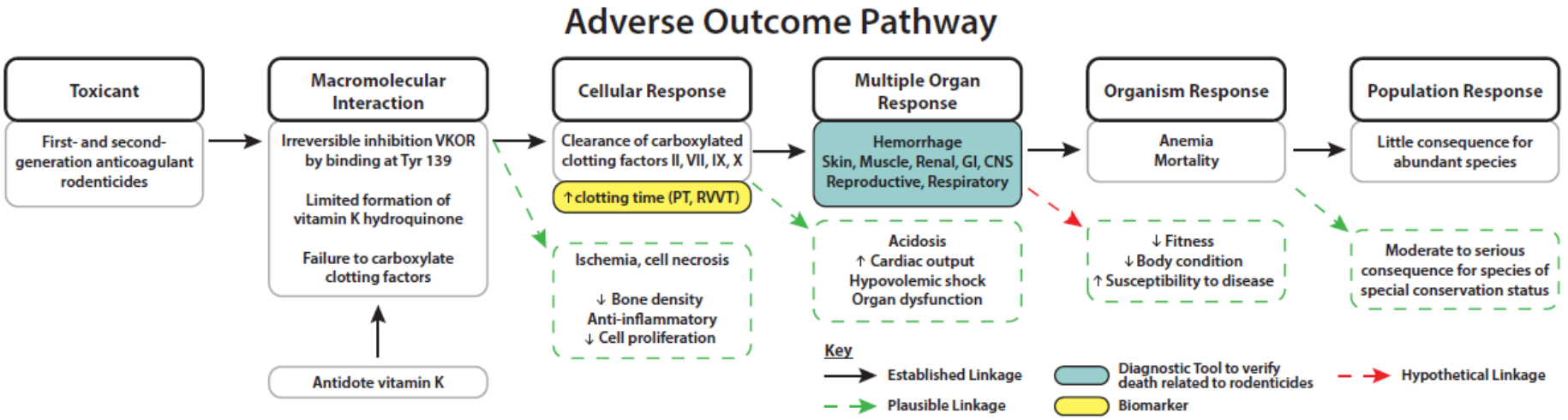
Adverse Outcome Pathway



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Rattner et al. 2014. Environmental Science & Technology

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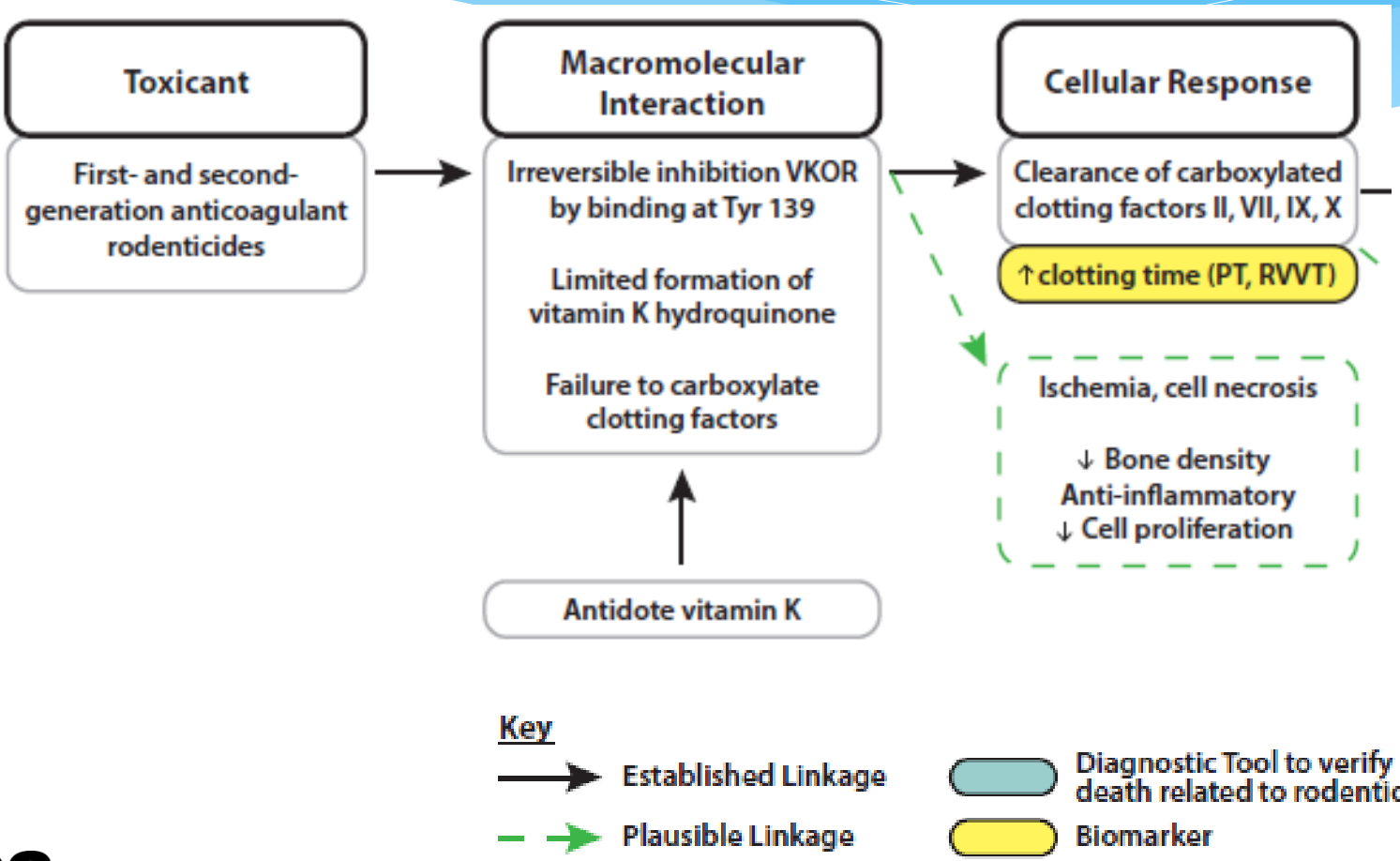

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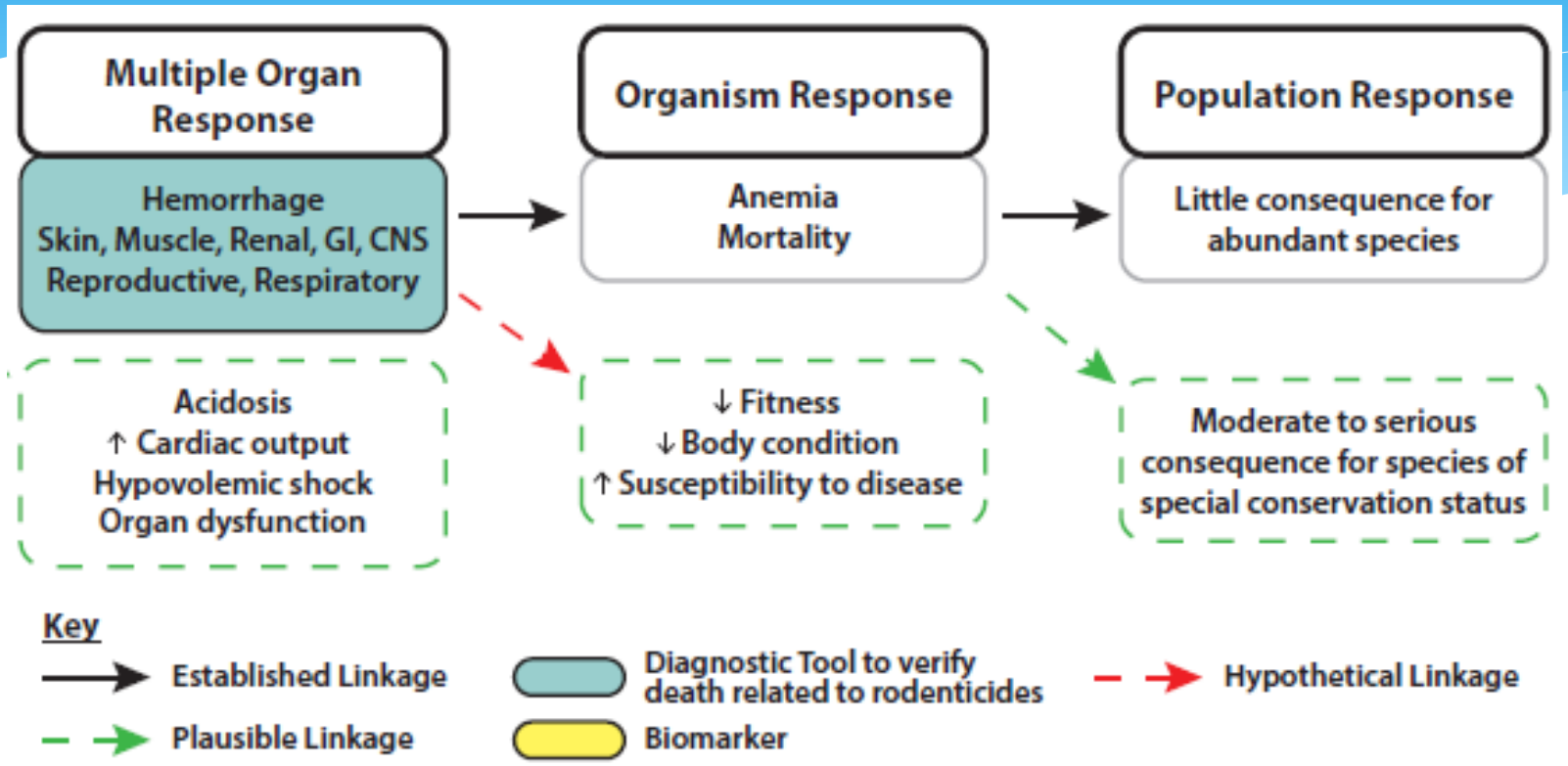

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Data Gaps and Research Needs

Interspecific differences in sensitivity (raptors > granivores)

- -VKOR activity
- -Are there sensitive sub-populations or conserved across species
- -Metabolism and elimination

Relative potency of ARs for VKOR (additive tox models for mixtures)

Role of vitamin K status

Significance of sublethal effects at individual- and population-level

Quantitative estimates non-target predator mortality

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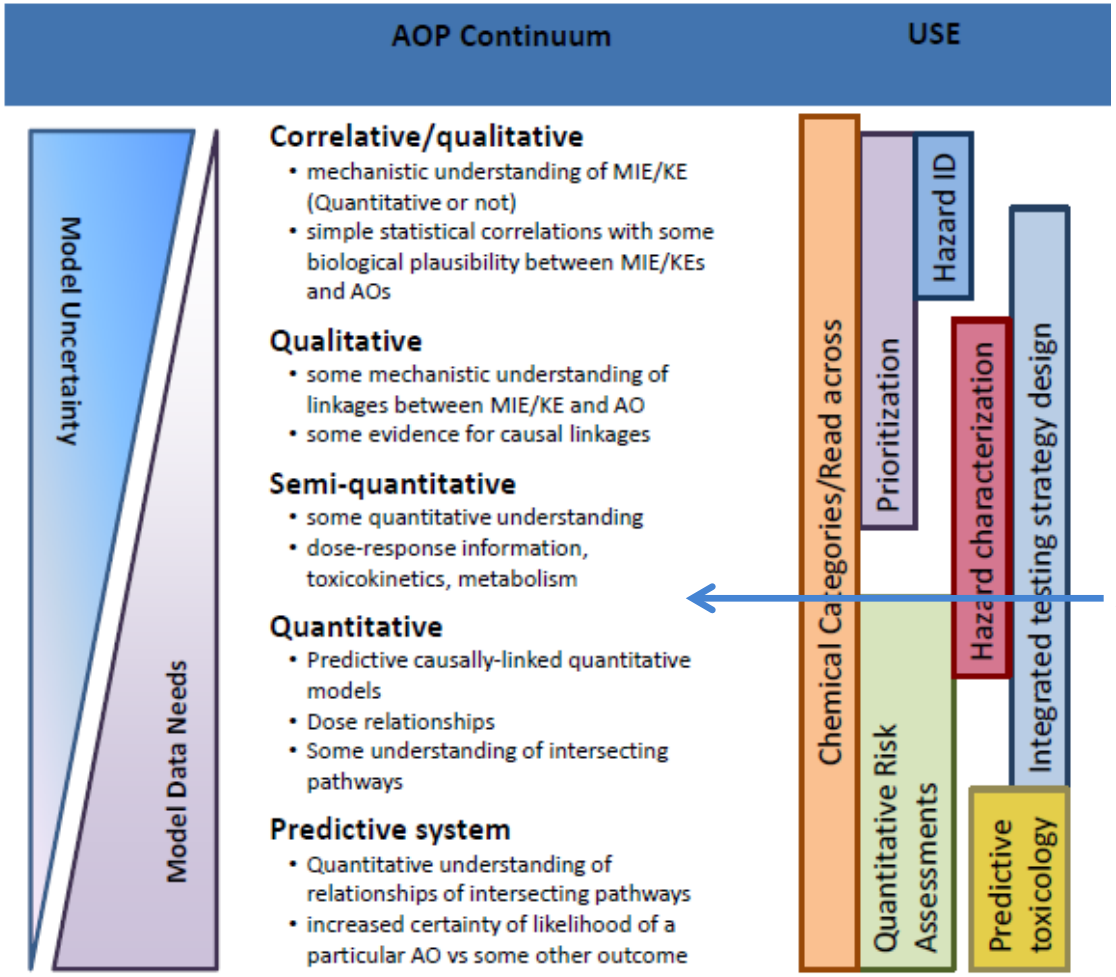
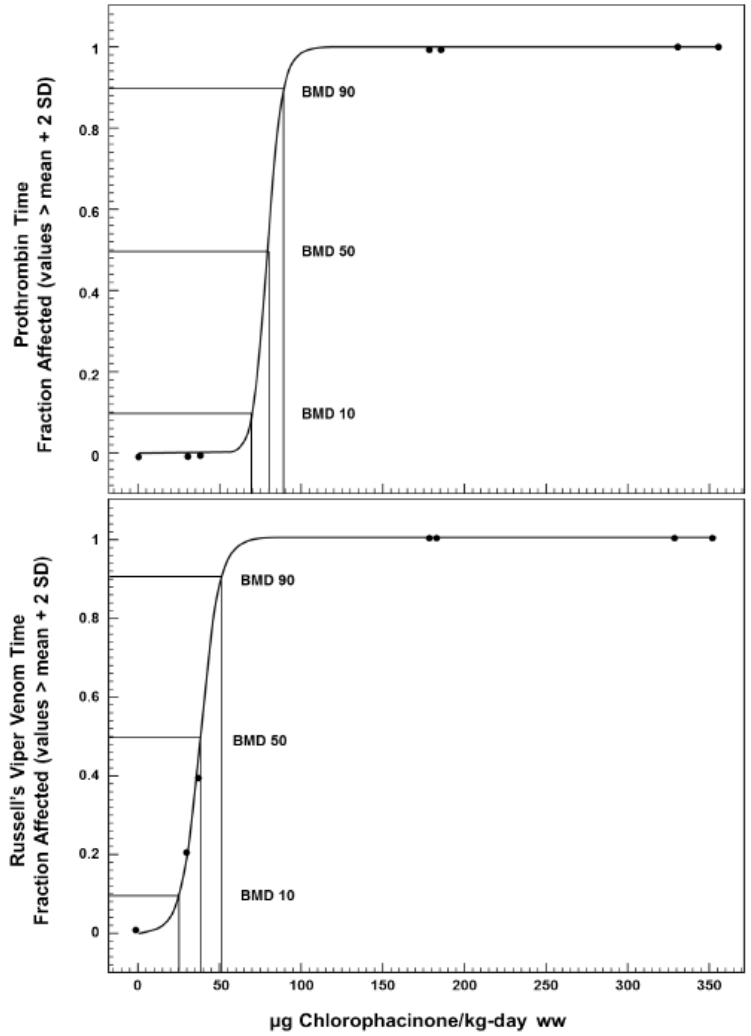
Regulatory Application

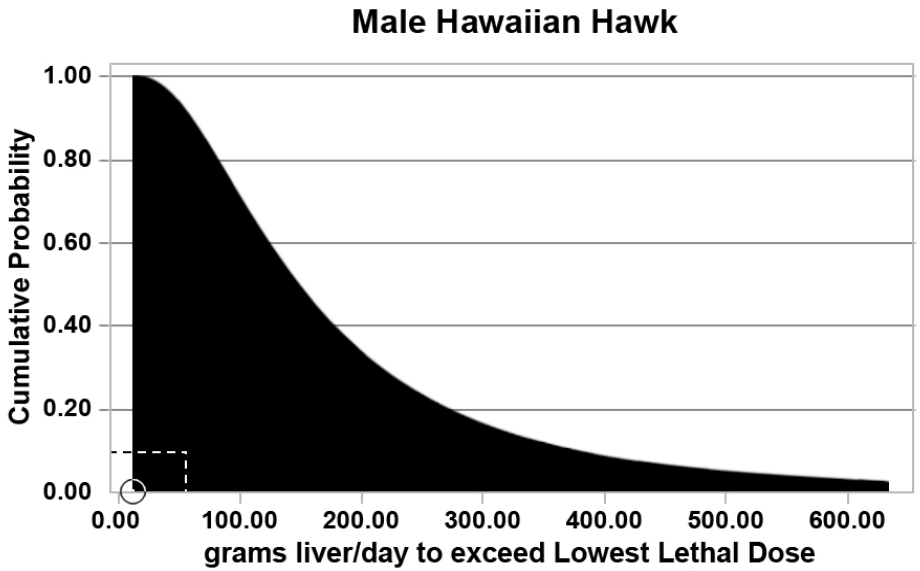


Anticoagulant Rodenticide AOP for “non-target predatory wildlife”

Perkins et al. 2014. Advancing AOPs for Integrated Toxicology and Regulatory Applications

Toxicity Reference Values
Cumulative Probability Survival Curves





Regulatory Application of the AR-AOP?

The train already left the station –

major regulatory decisions already made in U.S. EPA, EC and EU in the past 5 years without AOP framework

AR-AOP could provide biological plausibility for a decision (EIA)

Good communication tool for regulatory agencies and public

Increase confidence in a risk assessment by using Weight of Evidence Approach in an AOP Framework

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Conclusions

Mechanism of action at molecular level well-known

Relative potency of ARs only partially understood

Limited demographic studies in areas of high AR use

Development of mechanistic dynamic models in silico

Look at other toxicants (Pb) that may have same AO (anemia) through a different MIE

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Questions?

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