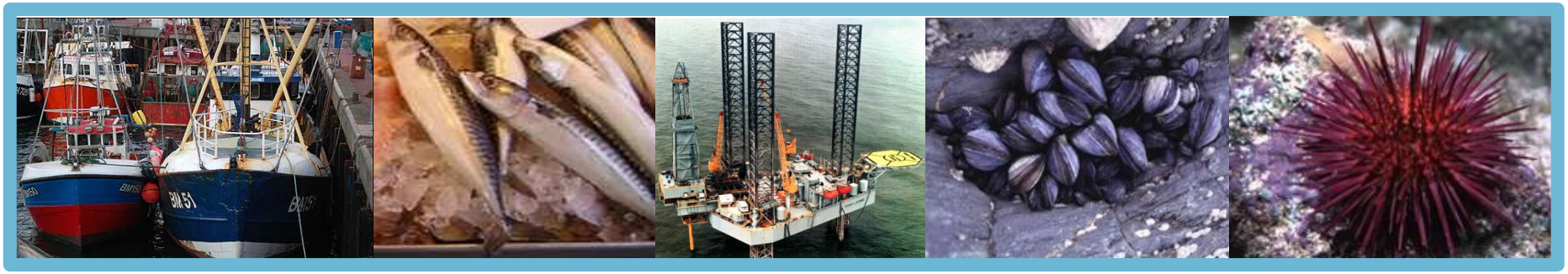
Environmental Safety Assessment of Chemicals in the Marine Environment: Challenges & Opportunities.



Professor Tom Hutchinson FRSB, FLS, FHEA
University of Plymouth
(tom.hutchinson@plymouth.ac.uk)

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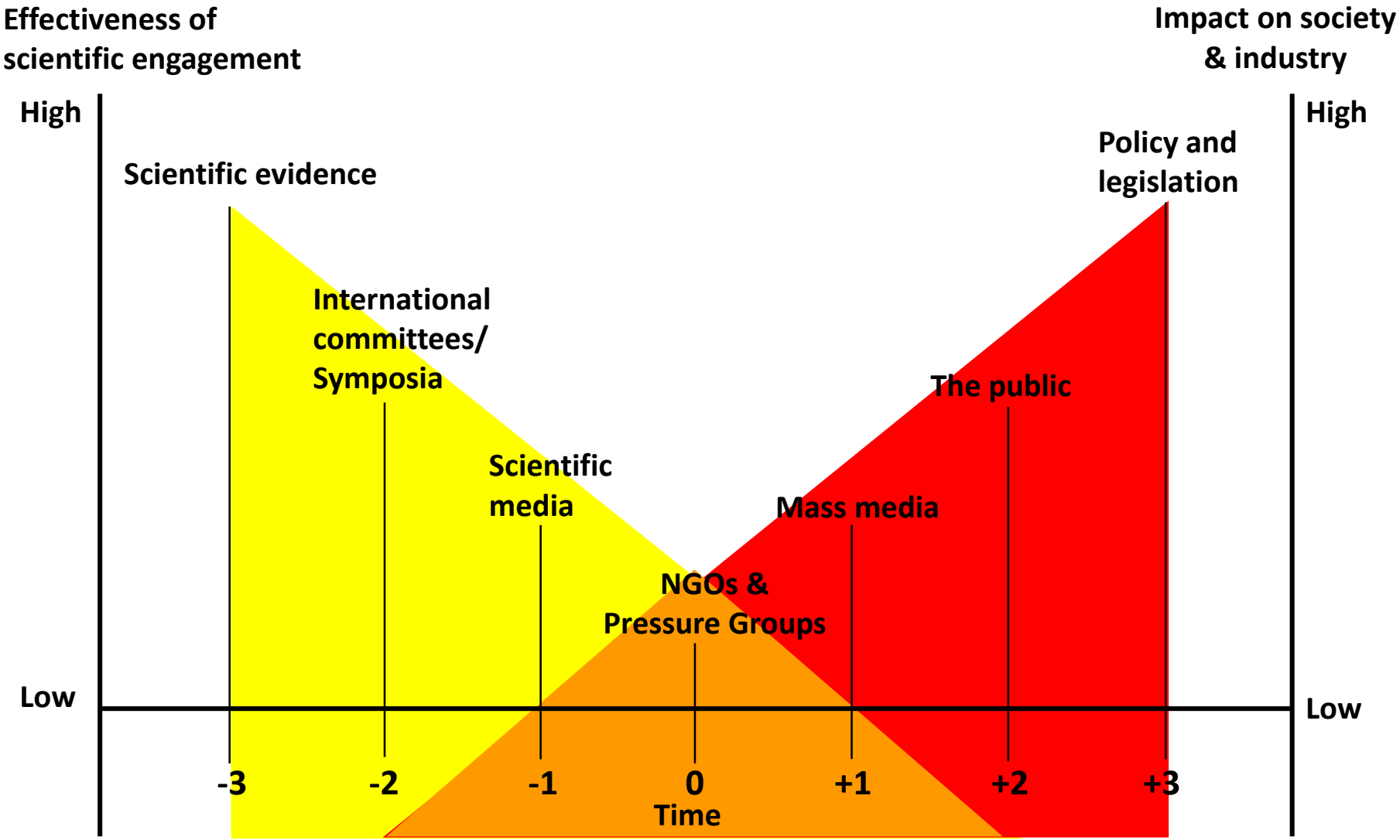
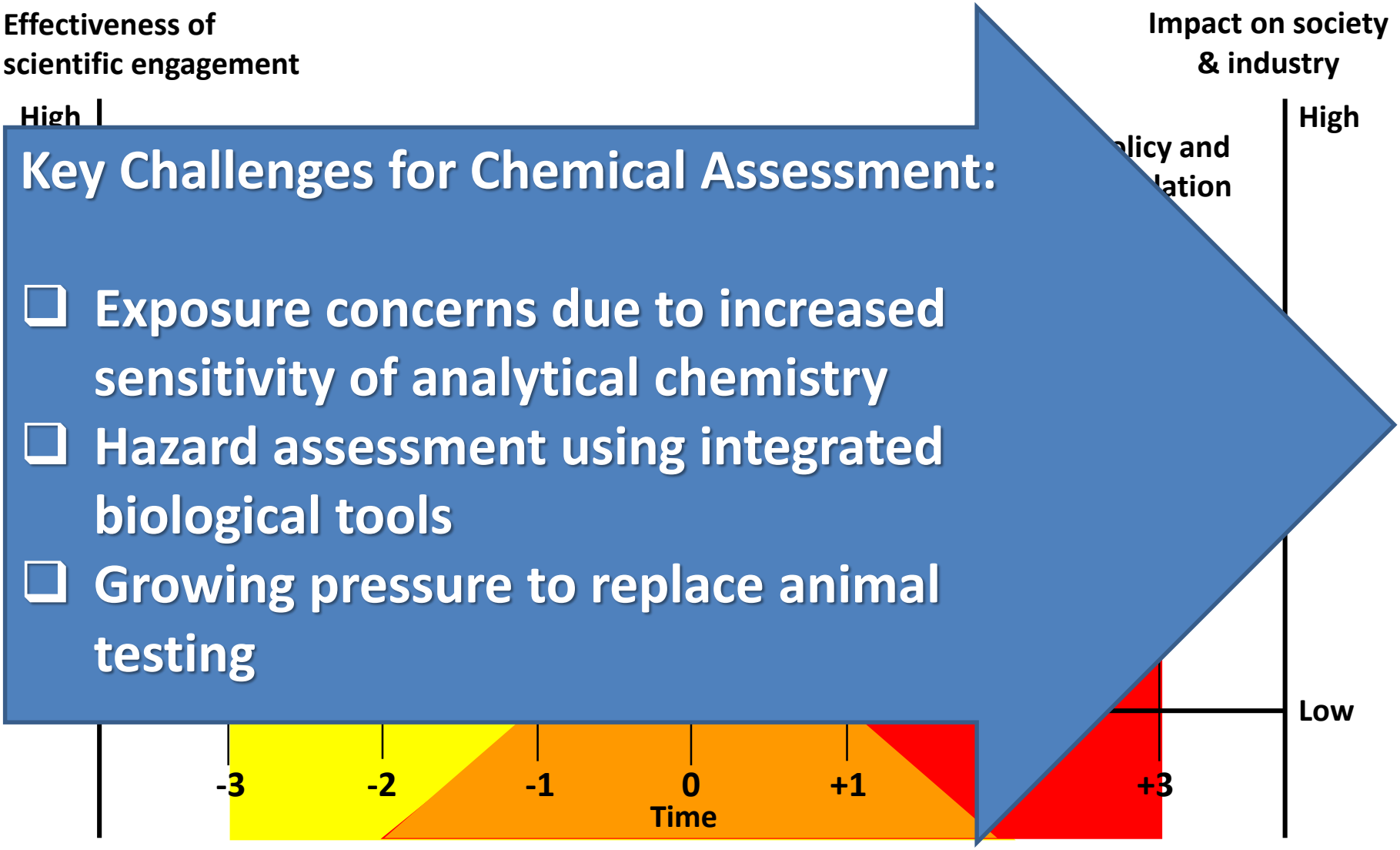
Strategic Issues Management



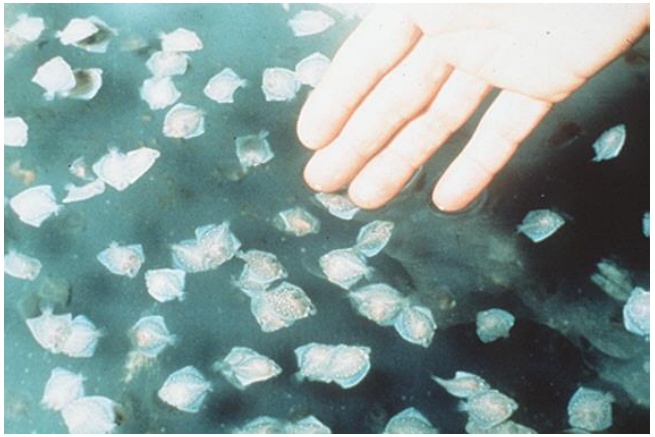
Strategic Issues Management



Key Challenges for Chemical Assessment:

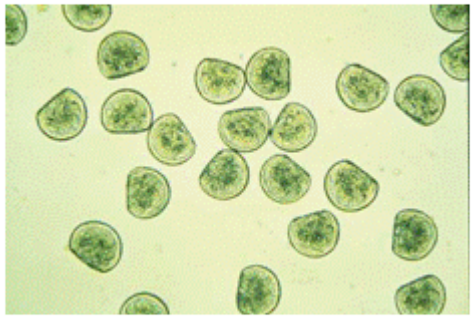
- ❑ Exposure concerns due to increased sensitivity of analytical chemistry
- ❑ Hazard assessment using integrated biological tools
- ❑ Growing pressure to replace animal testing

Challenge 1
Animal Testing



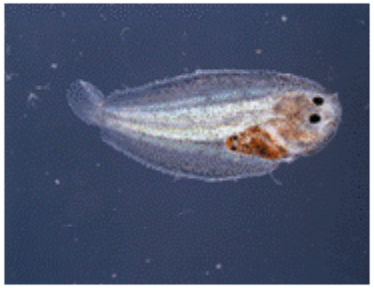
Growing pressure to replace, reduce or refine fish testing in environmental safety assessment

Approaches to Marine Testing



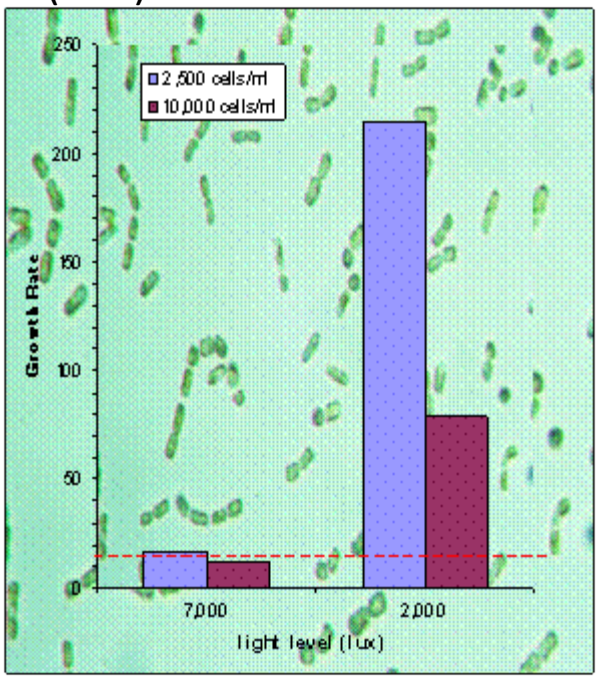
Mollusc larvae

Acute fish tests (96 h)



Fish larvae

Acute microalgal tests (72h)



Diatoms (e.g. *Skeletonema* sp.)

Acute invertebrate tests (24 – 48 h)

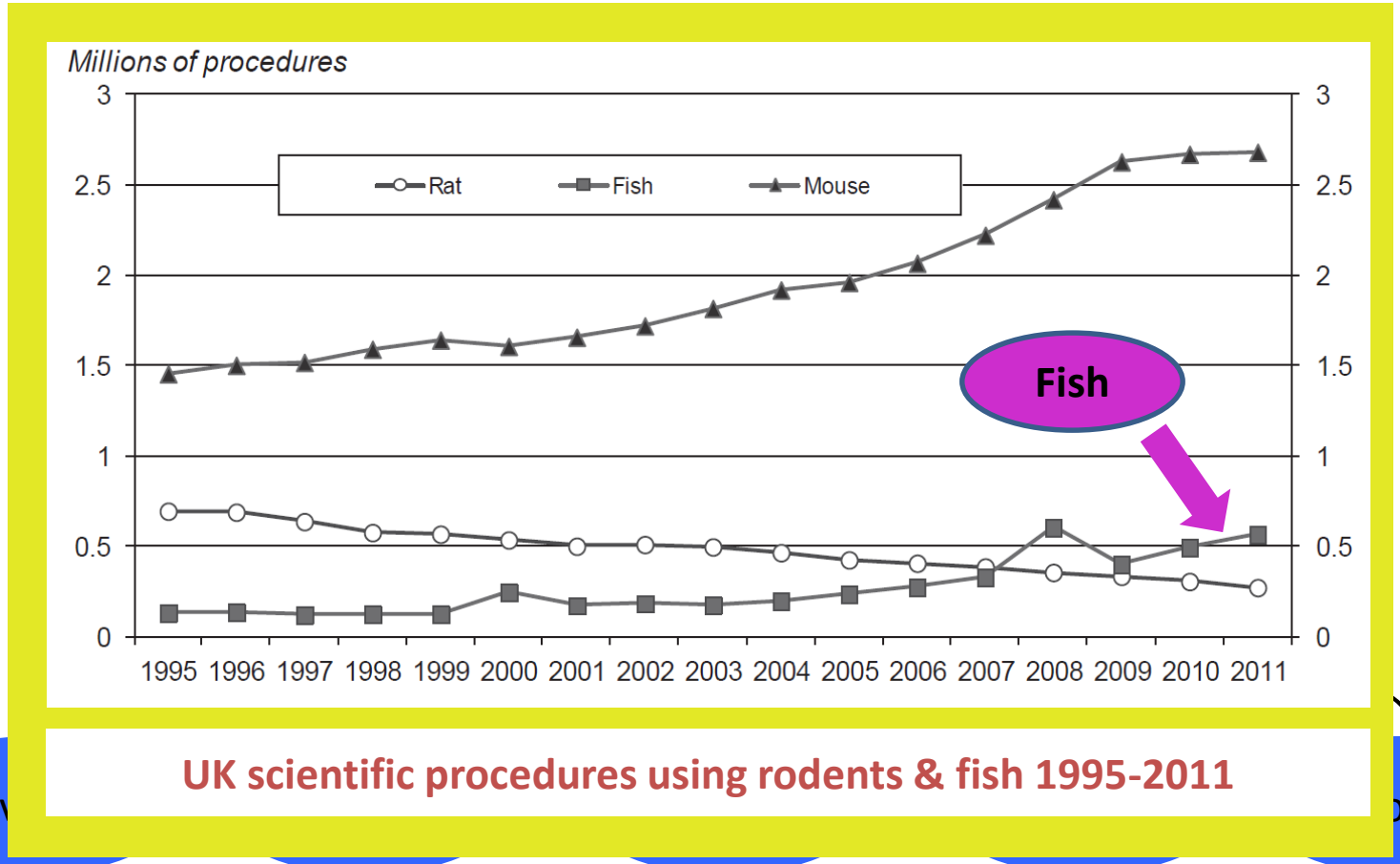
Crustaceans

Mussels

Echinoderms

The Animal Testing Challenge …

- Increasing demand for (eco) toxicity data …



UK scientific procedures using rodents & fish 1995-2011

- Ethics & costs of animal testing – millions $$$

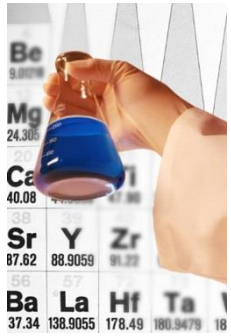
Refs: UK Home Office (2012) report HC345 & Toxcast http://www.epa.gov/comptox/toxcast

Challenge 2
Analytical Chemistry

Increasing sensitivity of analytical chemistry used in environmental safety assessment

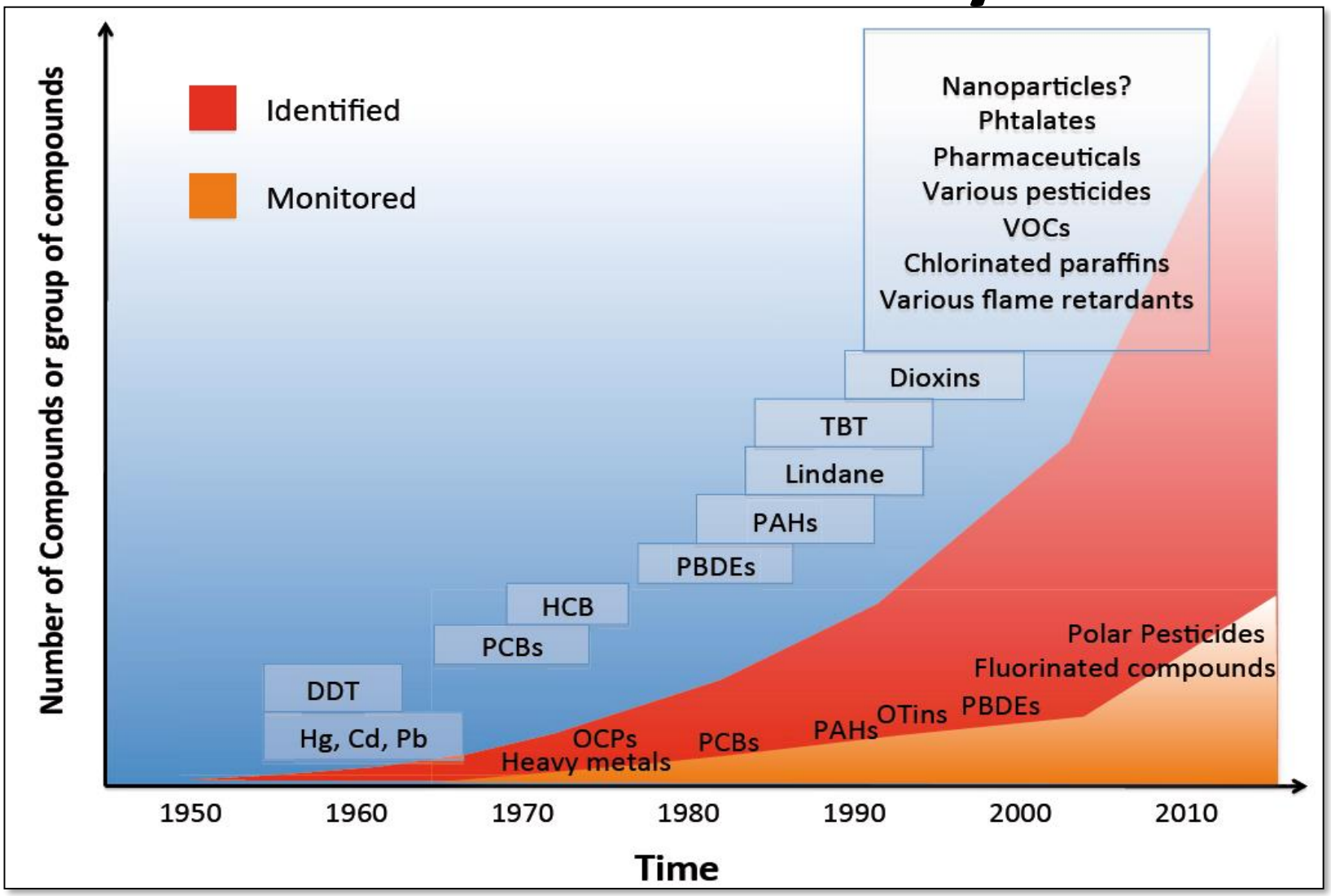
Chemical Contaminants

Analysts Can Find Anything, Anywhere If They Take a Large Enough Sample and Look Hard Enough



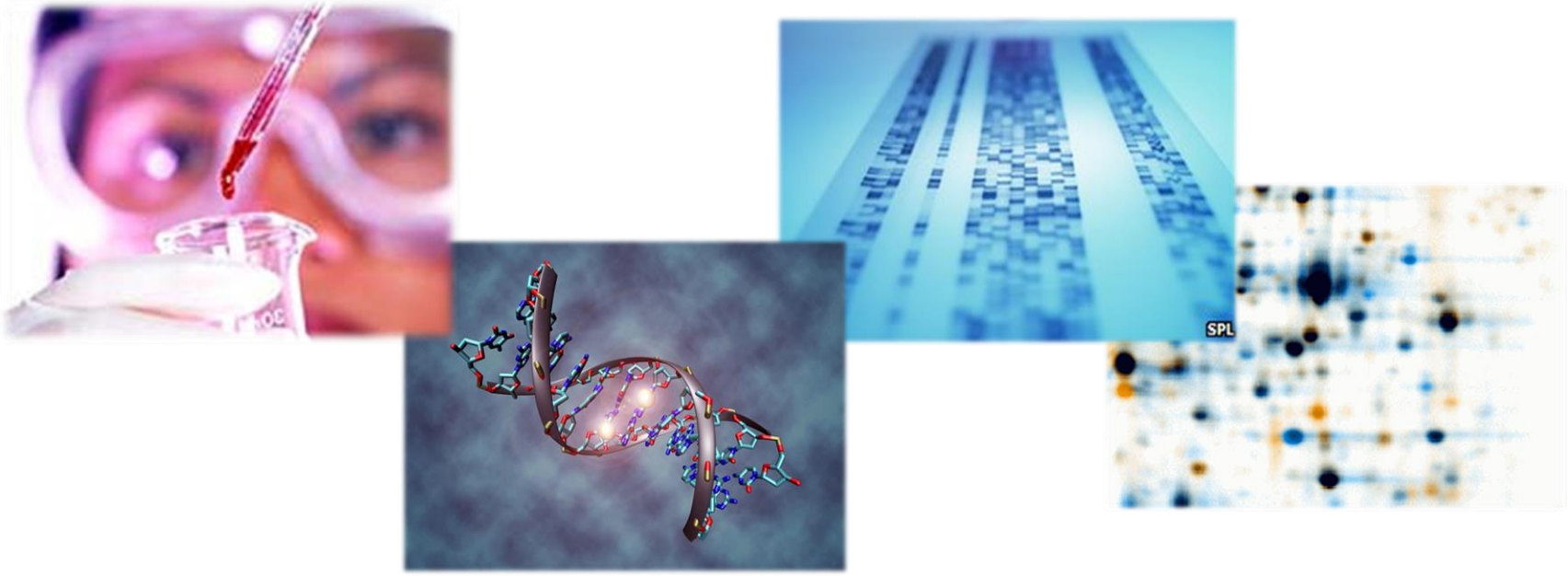
Decade	Detection Limit	Ratio	Description
1900s	0.1%	1 in 10^3	Parts per thousand
1930s	1 milligramme / litre	1 in 10^6	Parts per million
1960s	1 microgramme / litre	1 in 10^9	Parts per billion
1980s	1 nanogramme / litre	1 in 10^{12}	Parts per trillion
1990s	1 picogramme / litre	1 in 10^{15}	Parts per quadrillion
2000s	1 femtogramme / litre	1 in 10^{18}	Parts per quintillion

Environmental Chemistry Trends



Timelag between the discovery and routine monitoring of chemicals (European Science Foundation (2011) Marine Pollution).

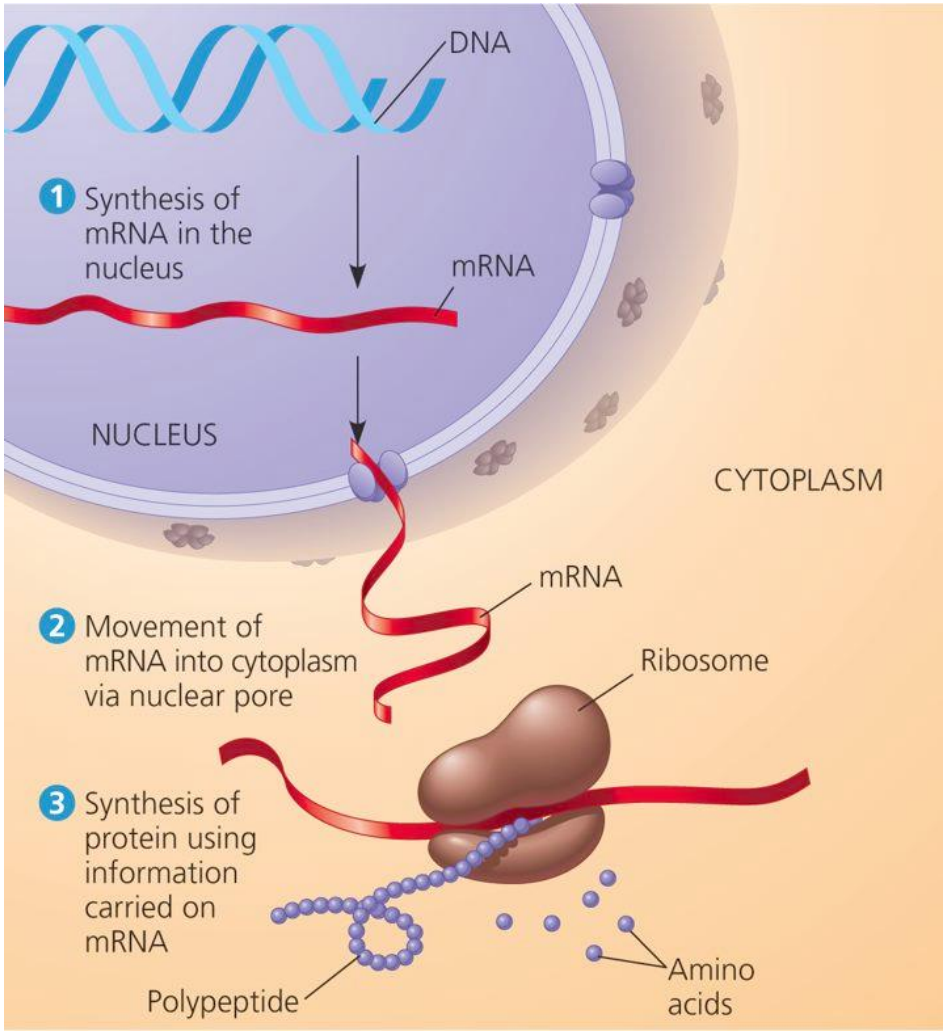
Challenge 3
Making Sense of Molecular Toxicology



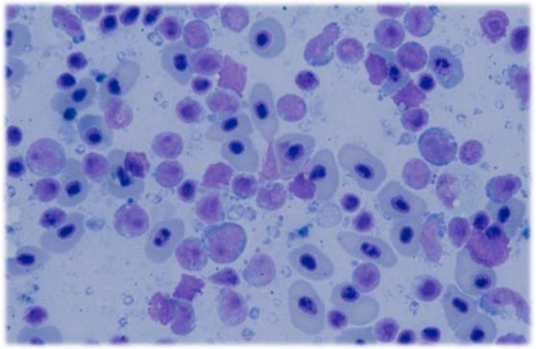
Increasing power of biological measurements in field and laboratory studies

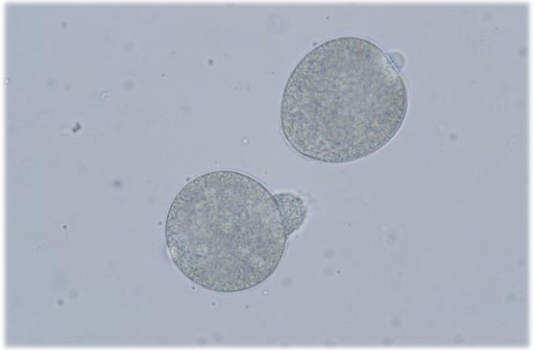
Animal Physiology & Molecular Biology

(DNA → RNA → Protein → Function)



Fish blood cells





Oyster eggs & sperm

Reference: Campbell Biology" 9th edition (editors Reece *et al*., 2011)

Predictive Ecotoxicology

Chemical exposure

Absorption

Distribution

Metabolism

Excretion

Target sites

a) physico-chemical properties & mammalian MOA information

Field monitoring

Species selection

Lab studies

b) guidance on design of *in vivo* tests

Population impacts

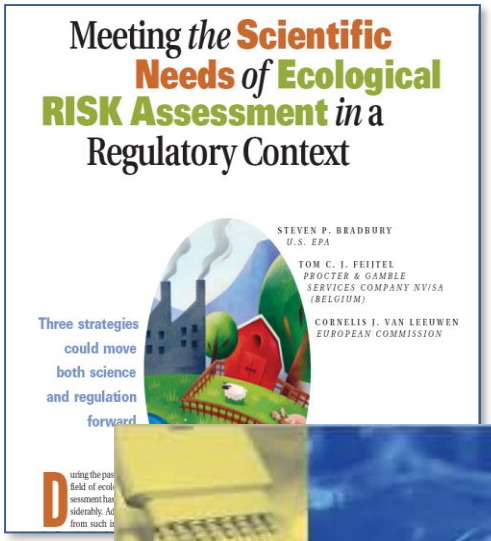
Environmental Risk Assessment

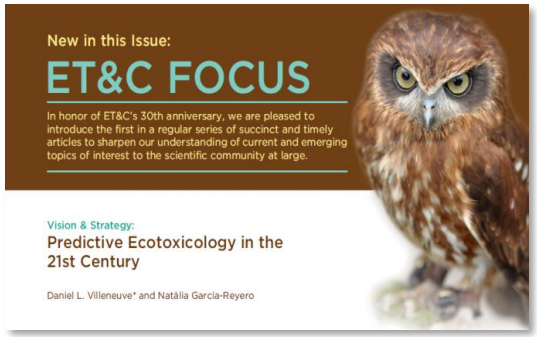
c) safety assessment

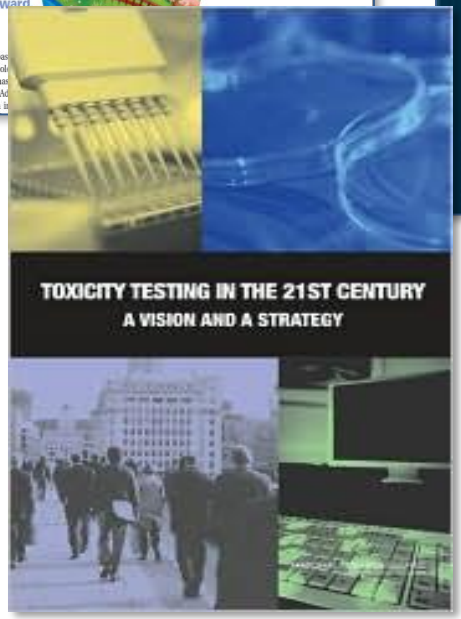
Opportunities

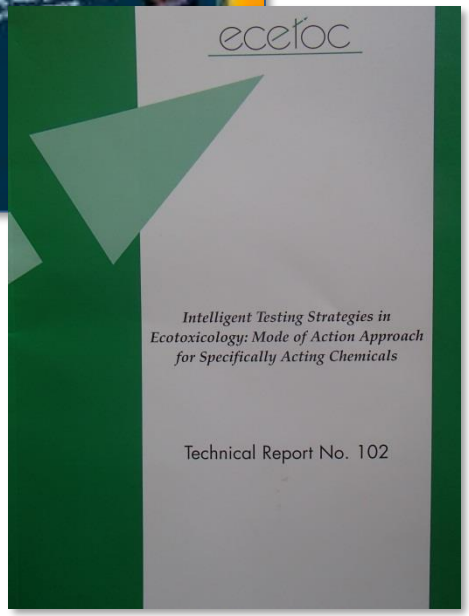
Economics, ethics & environmental safety assessment

Toxicity Testing in the 21st Century







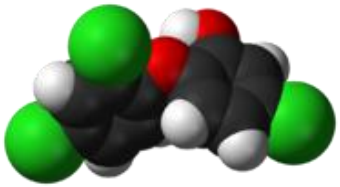


- **Landmark NRC (2007) report focused on human health but also relevant to ecological risks**
- **Less reliance on whole animal testing**
- **Increased integration & use of mechanistic data**
- **Predictive, rather than empirical**

Ref: National Research Council (2007) Toxicity Testing in the 21st Century

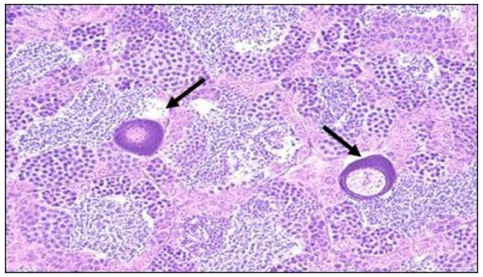
OECD Adverse Outcome Pathways (AOP) Approach

1. Toxicant description



2. Macromolecular target site

3. Cellular response



4. Organ response

5. Organism response

6. Population response

Ref: OECD (2012) http://www.oecd.org/chemicalsafety/testingofchemicals/49963554.pdf

OECD Definition

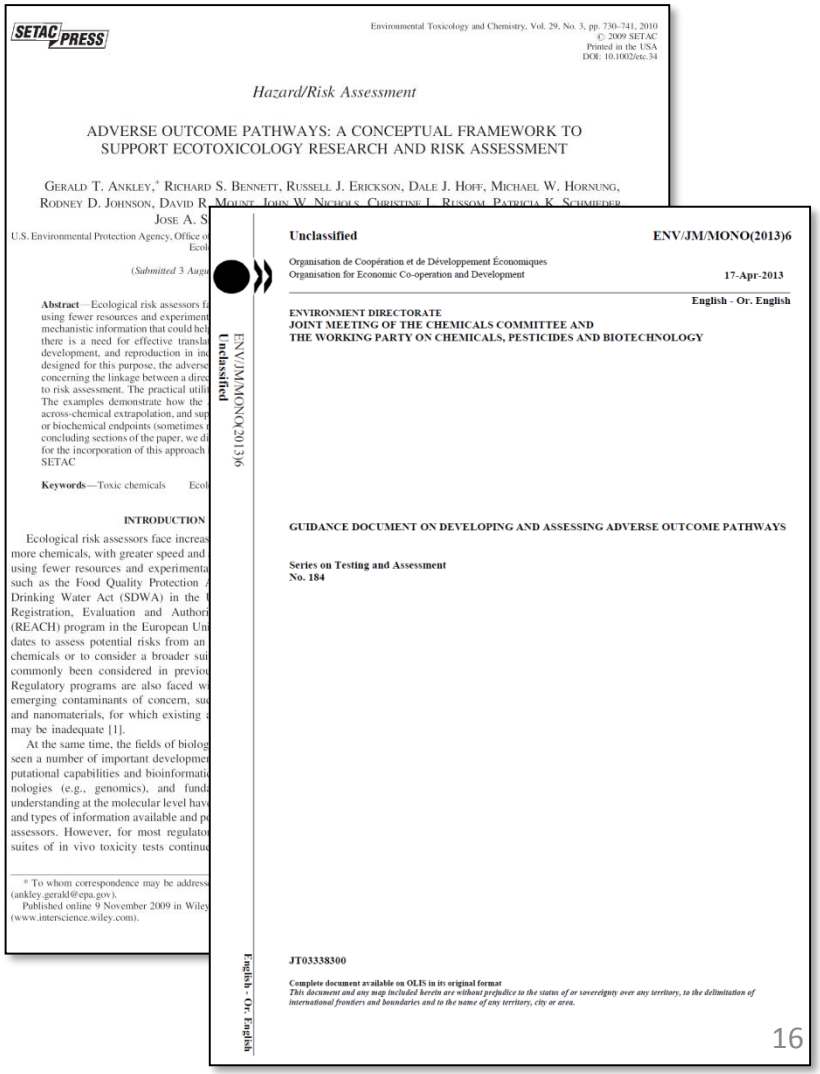
ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

OECD

- Adverse Outcome Pathway:

"An Adverse Outcome Pathway (AOP) is a conceptual framework that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome, at a level of biological organization relevant to risk assessment."

Ankley *et al*. (2010)
Environ Tox Chem 29: 730-741



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DOI: 10.1002/etc.34

Hazard/Risk Assessment

ADVERSE OUTCOME PATHWAYS: A CONCEPTUAL FRAMEWORK TO SUPPORT ECOTOXICOLOGY RESEARCH AND RISK ASSESSMENT

Gerald T. Ankley,* Richard S. Bennett, Russell J. Erickson, Dale J. Hoff, Michael W. Hornung, Rodney D. Johnson, David R. Mount, John W. Nichols, Christine L. Russom, Patricia K. Schmieder, Jose A. S...

U.S. Environmental Protection Agency, Office o... Ecol...

(Submitted 3 Aug...

Abstract—Ecological risk assessors f... using fewer resources and experiment... mechanistic information that could hel... there is a need for effective transla... development, and reproduction in in... designed for this purpose, the adverse... concerning the linkage between a direc... to risk assessment. The practical utili... The examples demonstrate how the... across-chemical extrapolation, and sup... or biochemical endpoints (sometimes... concluding sections of the paper, we di... for the incorporation of this approach ... SETAC

Keywords—Toxic chemicals Ecol...

INTRODUCTION

Ecological risk assessors face increas... more chemicals, with greater speed and ... using fewer resources and experimenta... such as the Food Quality Protection ... Drinking Water Act (SDWA) in the ... Registration, Evaluation and Author... (REACH) program in the European Un... dates to assess potential risks from an ... chemicals or to consider a broader sui... commonly been considered in previou... Regulatory programs are also faced w... emerging contaminants of concern, su... and nanomaterials, for which existing ... may be inadequate [1].

At the same time, the fields of biolog... seen a number of important developme... putational capabilities and bioinformati... nologies (e.g., genomics), and funda... understanding at the molecular level hav... and types of information available and p... assessors. However, for most regulato... suites of in vivo toxicity tests continu...

* To whom correspondence may be address... (ankley.gerald@epa.gov).
Published online 9 November 2009 in Wiley... (www.interscience.wiley.com).

Unclassified ENV/JM/MONO(2013)6

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development 17-Apr-2013

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

GUIDANCE DOCUMENT ON DEVELOPING AND ASSESSING ADVERSE OUTCOME PATHWAYS

Series on Testing and Assessment
No. 184

JT03338300

Complete document available on OLIS in its original format
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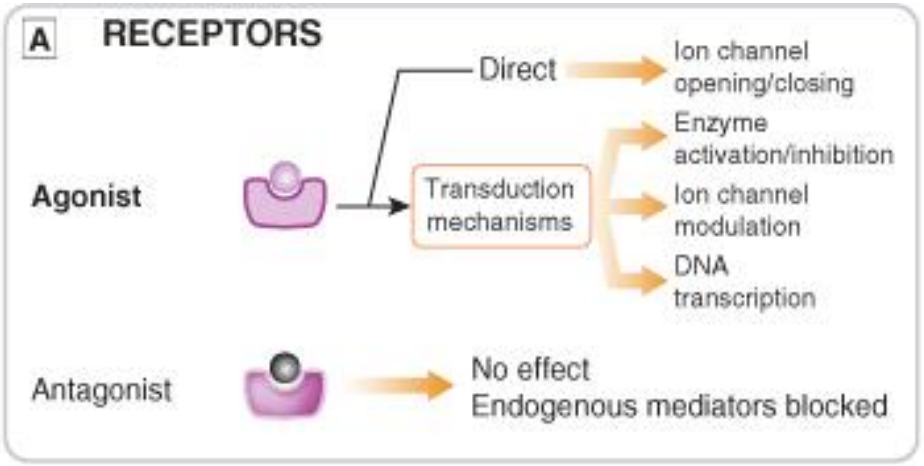
ENV/JM/MONO(2013)6 Unclassified English - Or. English

Modes-of-action in ecotoxicology

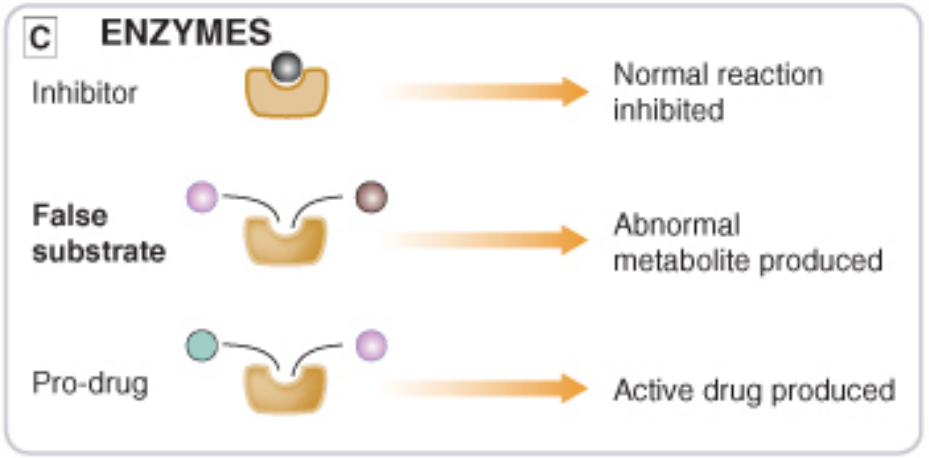
	Verhaar et al (1992)	ECETOC (2007)	Chemical examples
1	MOA1 - Narcotics	-	Linear alkyl benzene sulphonate
2	MOA2 - Polar narcotic chemicals	-	Phenol
3	MOA3 - Reactive chemicals	-	Epichlorohydrin
4	MOA4 - Specifically acting	MOA4a – Enzyme	Chlorpyrifos Fadrozole
5		MOA4b - Ion channel blocker	Cypermethrin
6		MOA4c – Receptor	Atenolol Ethinylestradiol
7		MOA4d - Transporter protein	Fluoxetine Omeprazole

Refs: Verhaar *et al.* (1992) Chemosphere 25: 471-491;
ECETOC (2007) Technical report 102, 145 pp

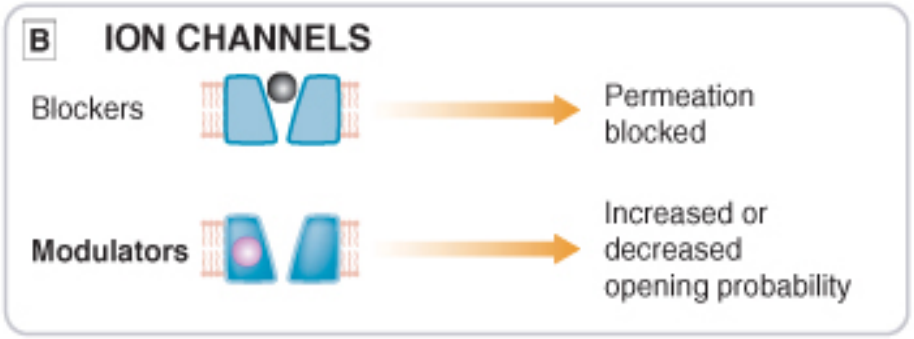
Mode of Toxic Action: Key Protein Targets



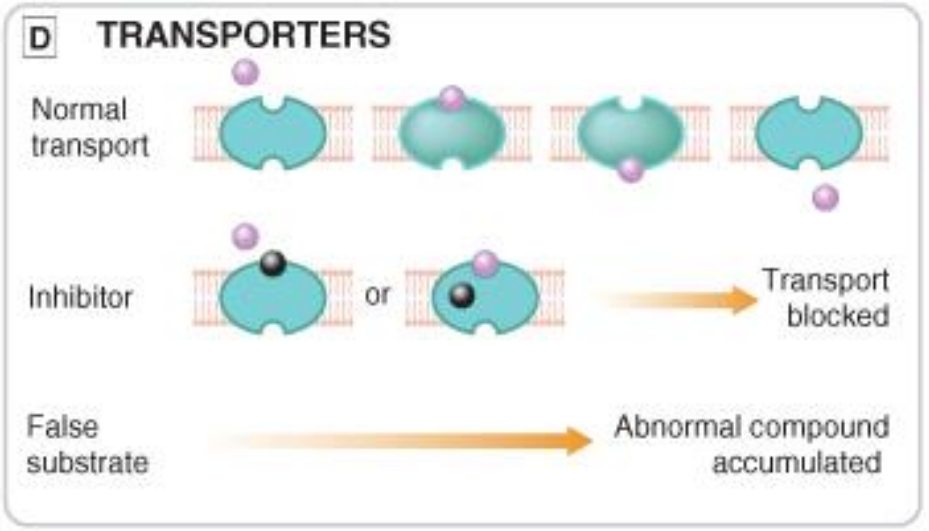
(eg beta blockers, ethinylestradiol)



(eg aspirin, fadrozole)



(eg brevetoxin, cypermethrin)

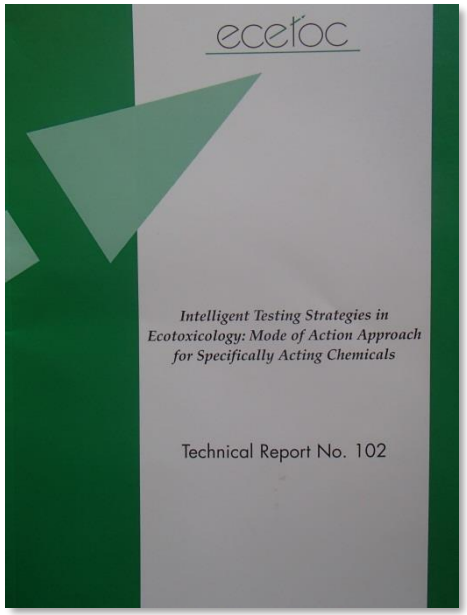


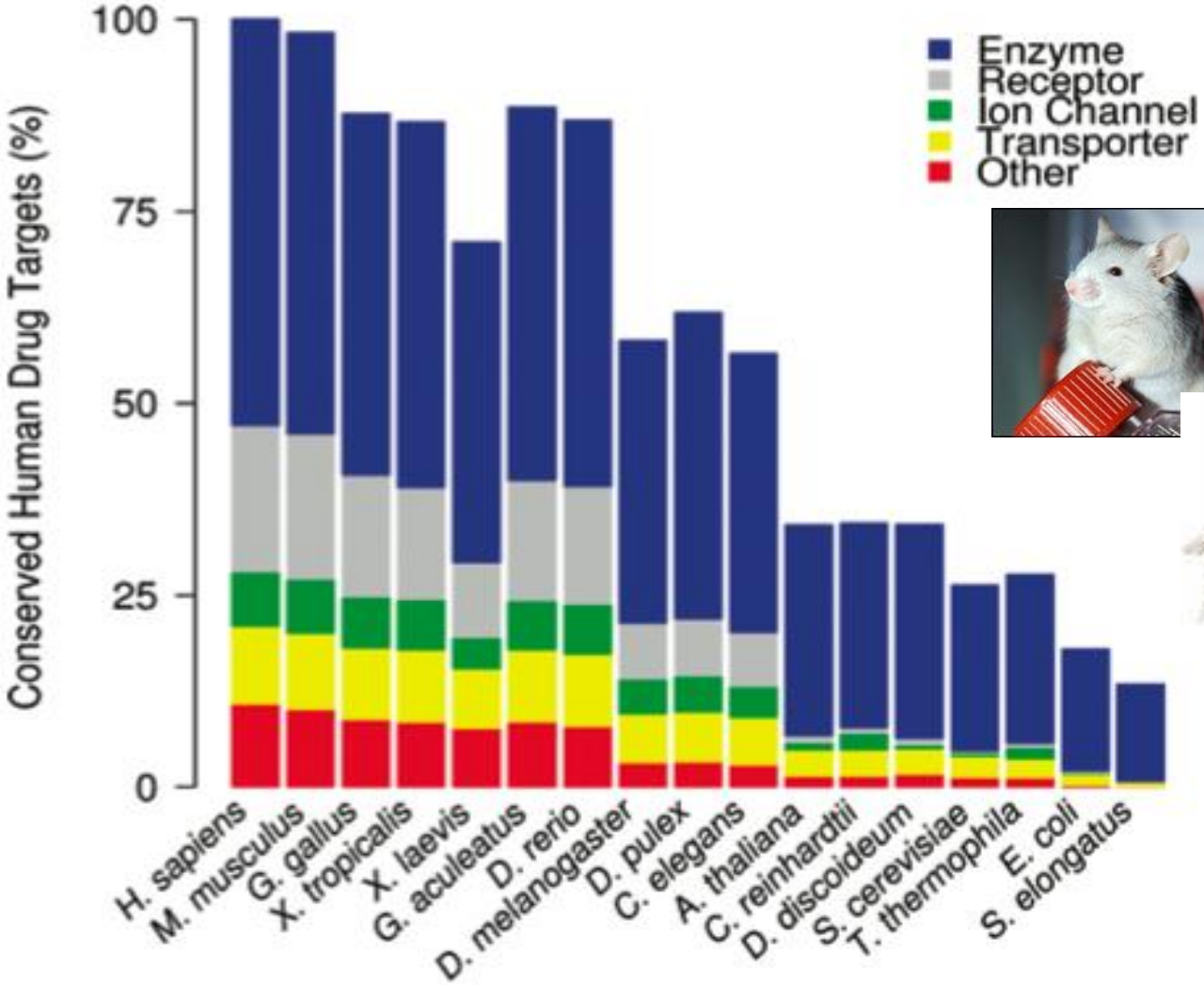
(eg tricyclic antidepressants)

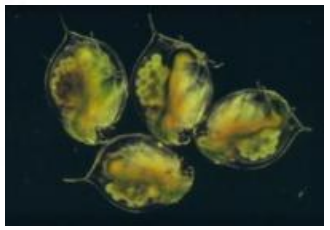
Agonist/normal substrate
Abnormal product
Antagonist/inhibitor
Pro-drug

Ref: Rang et al (2003) & ECETOC (2007)

Drug Target Conservation: Bioinformatics Approach







Ref:
Gunnarsson *et al.* (2008)
Env Sci Technol
42: 5807-5813

Medical endocrine disrupters

Cholesterol

- side-chain cleavage
- 17α-hydroxylase
- $C_{17}C_{20}$ lyase
- 17β-hydroxy dehydrogenase

Testosterone

Aromatase

Oestradiol

5α reductase

Dihydrotestosterone

Tamoxifen

Fulvestrant

Estrogen Receptor (ER)

Androgen Receptor (AR)

Ref: Purchase & Randall (1998) Pure Appl Chem 70: 1671-1784

Environmental endocrine disrupters

RXR

Tributyltin

Cholesterol

- side-chain cleavage
- 17α-hydroxylase
- $C_{17}C_{20}$ lyase ← *Ketoconazole*
- 17β-hydroxy dehydrogenase

Aromatase

Oestradiol ← Testosterone

5α reductase ← *Finasteride*

Tamoxifen → Dihydrotestosterone

Flutamide →

ER

AR

Competitive Agonists

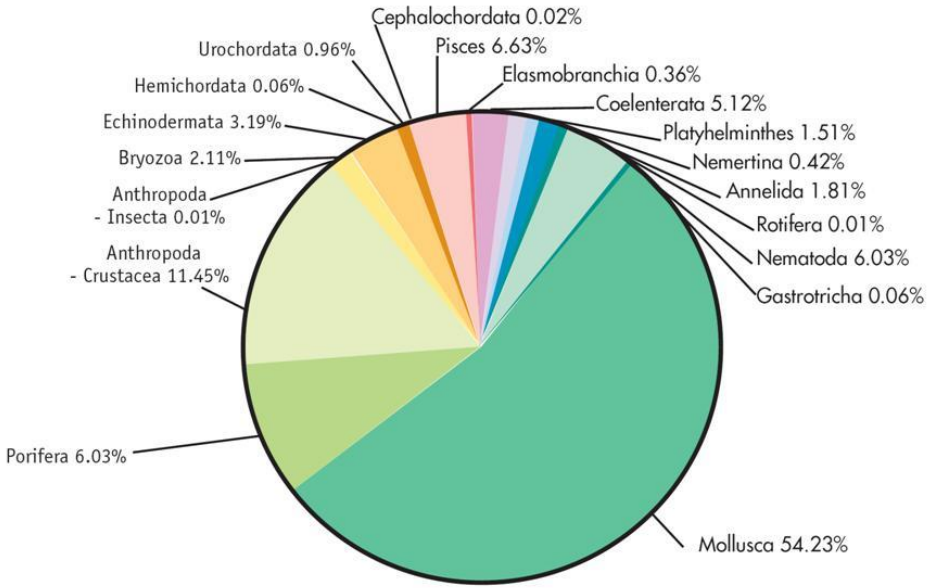
Bisphenol A
Diethylstilbestrol
Ethinylestradiol
Genistein
Nonylphenol

Competitive Agonists

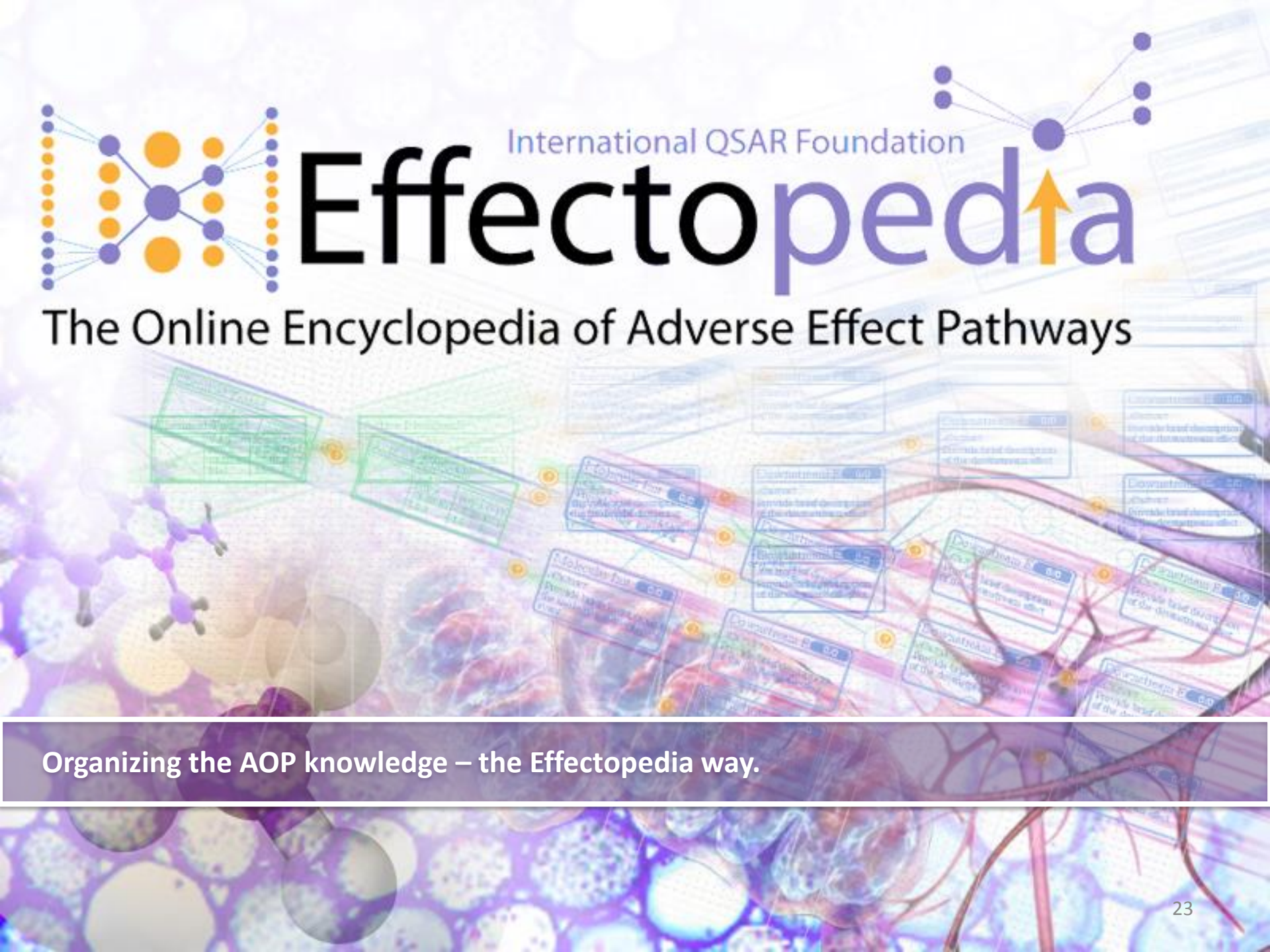
DDT & metabolites
Procymidone
Vinclozolin

Marine Biodiversity >> Freshwater

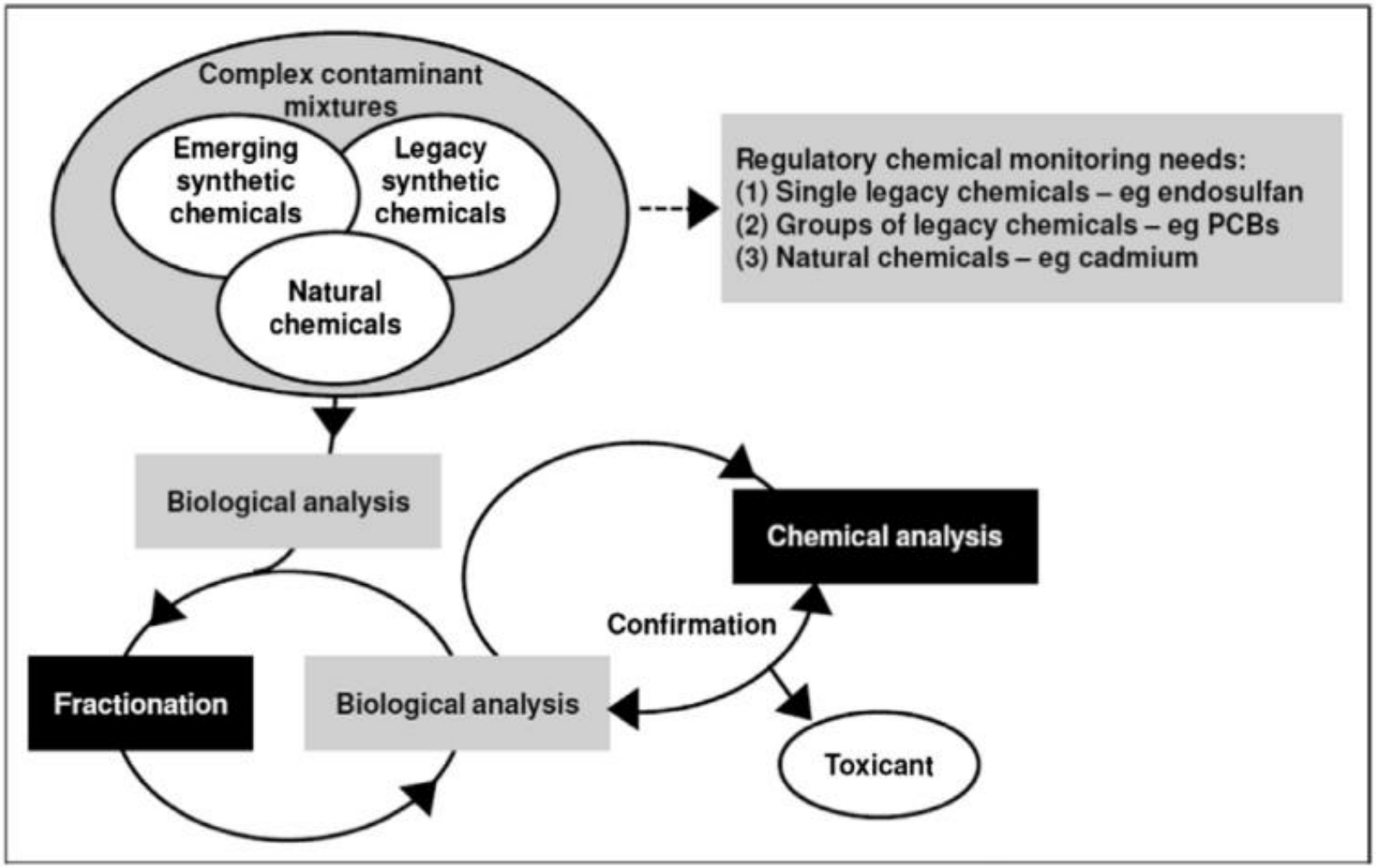
- Problem of ‘base set’ of algae, crustacean & fish testing: <u>82% marine species not represented (18 phyla marine only)</u>



Source: ECETOC (2001) Technical Report number 82

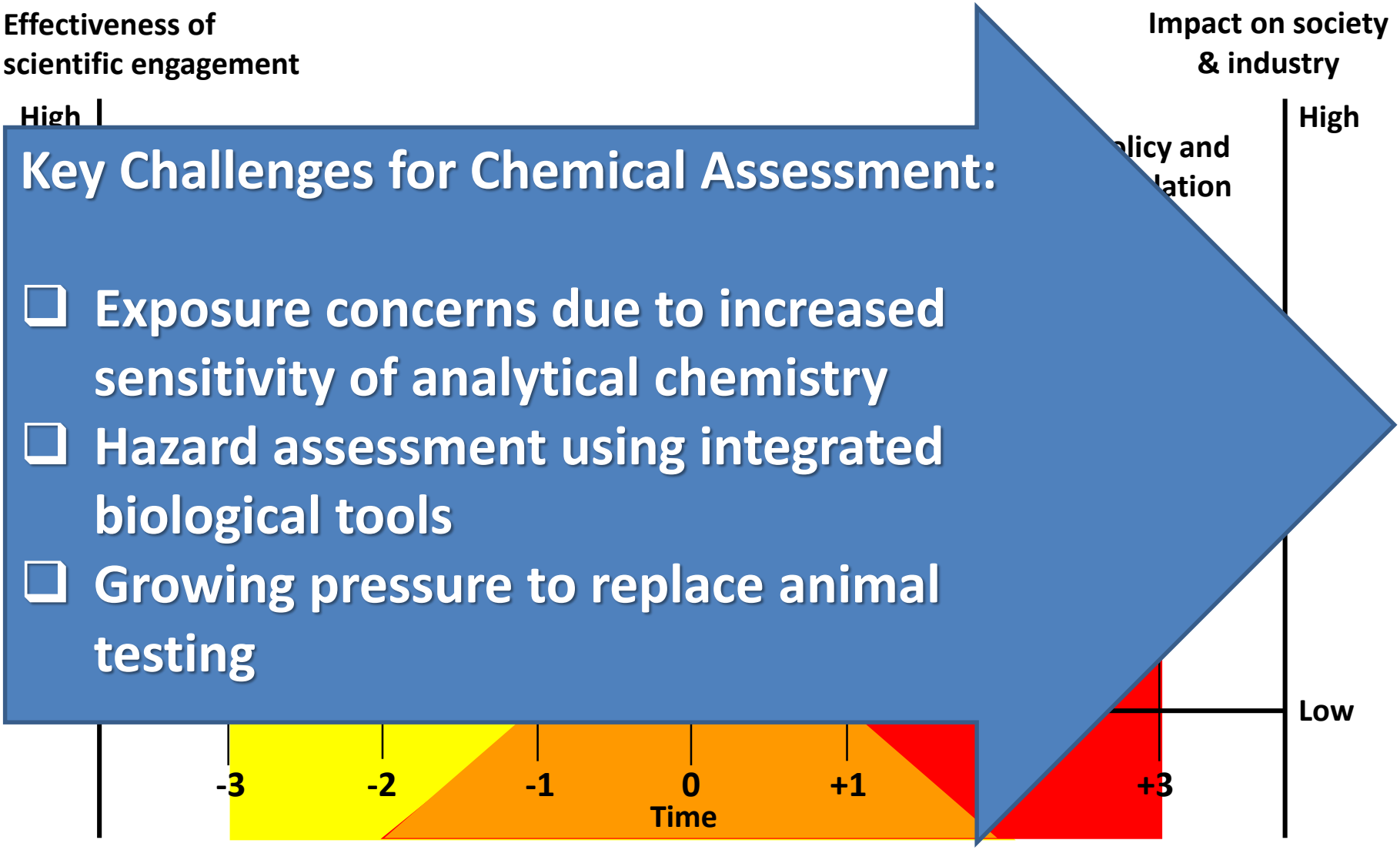

International QSAR Foundation
Effectopedia
The Online Encyclopedia of Adverse Effect Pathways
Organizing the AOP knowledge – the Effectopedia way.

Integrated Approach



Hutchinson *et al.* (2013) Mar Poll Bull 74: 517-525

Conclusions



Key Challenges for Chemical Assessment:

- ❑ Exposure concerns due to increased sensitivity of analytical chemistry
- ❑ Hazard assessment using integrated biological tools
- ❑ Growing pressure to replace animal testing

Thank you for listening …

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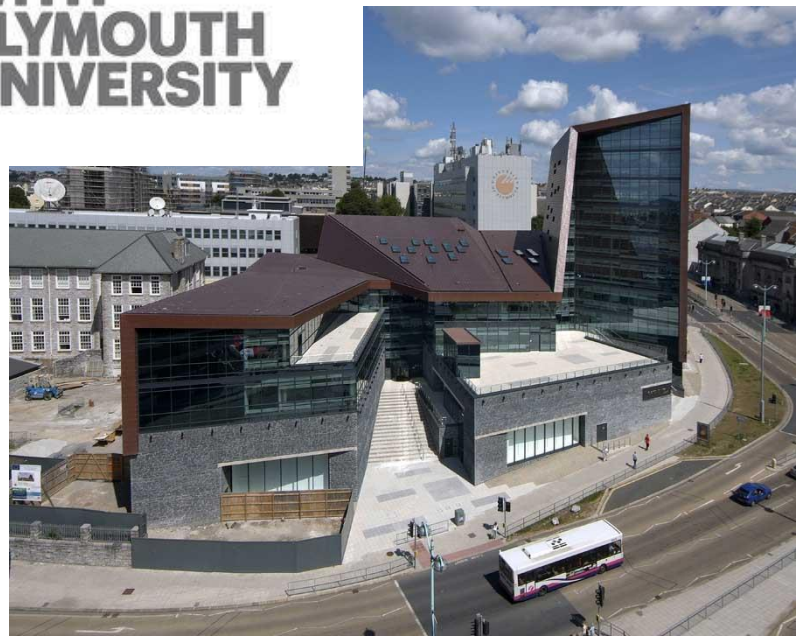
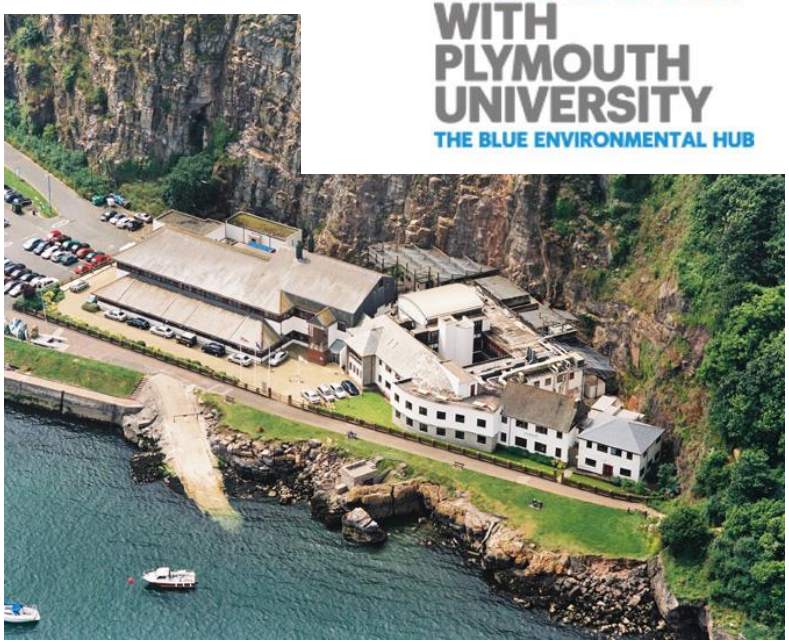


BRIXHAM LABORATORY WITH PLYMOUTH UNIVERSITY
THE BLUE ENVIRONMENTAL HUB



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University of Plymouth,
Tel 07939 673129 or email tom.hutchinson@plymouth.ac.uk