

Toxicological Interaction by Mixture Exposure

—

Concepts, Models, and Terminology for Mixture Toxicity Analysis

Rolf Altenburger

*Helmholtz Centre for Environmental Research - UFZ,
Dept. Bioanalytical Ecotoxicology,
Leipzig, Germany*

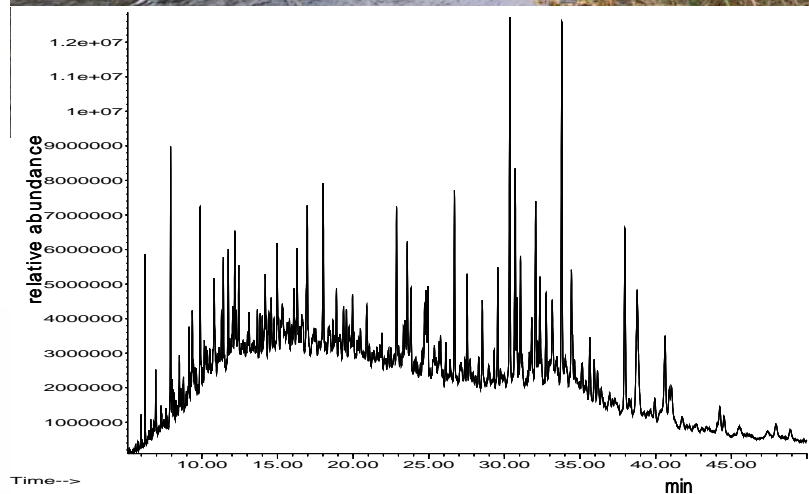
Outline

- **Co-occurrence of chemicals in the environmental is reality**
- **Multiple exposure is probable**
- **Combined effects happen**
- **Assessment of mixture toxicity requires explicit concepts**
- **Additive combined effects are predictable**
- **Synergism is not predictable**
- **Risk assessment may account for mixtures**

Acknowledgment to collaborators

Co-occurrence of chemicals in the environment is reality

An example depicting the GC-MS Scan of an organic extract from a riverine sediment shows:
Analytics typically finds multiple mixtures of chemicals in environmental samples



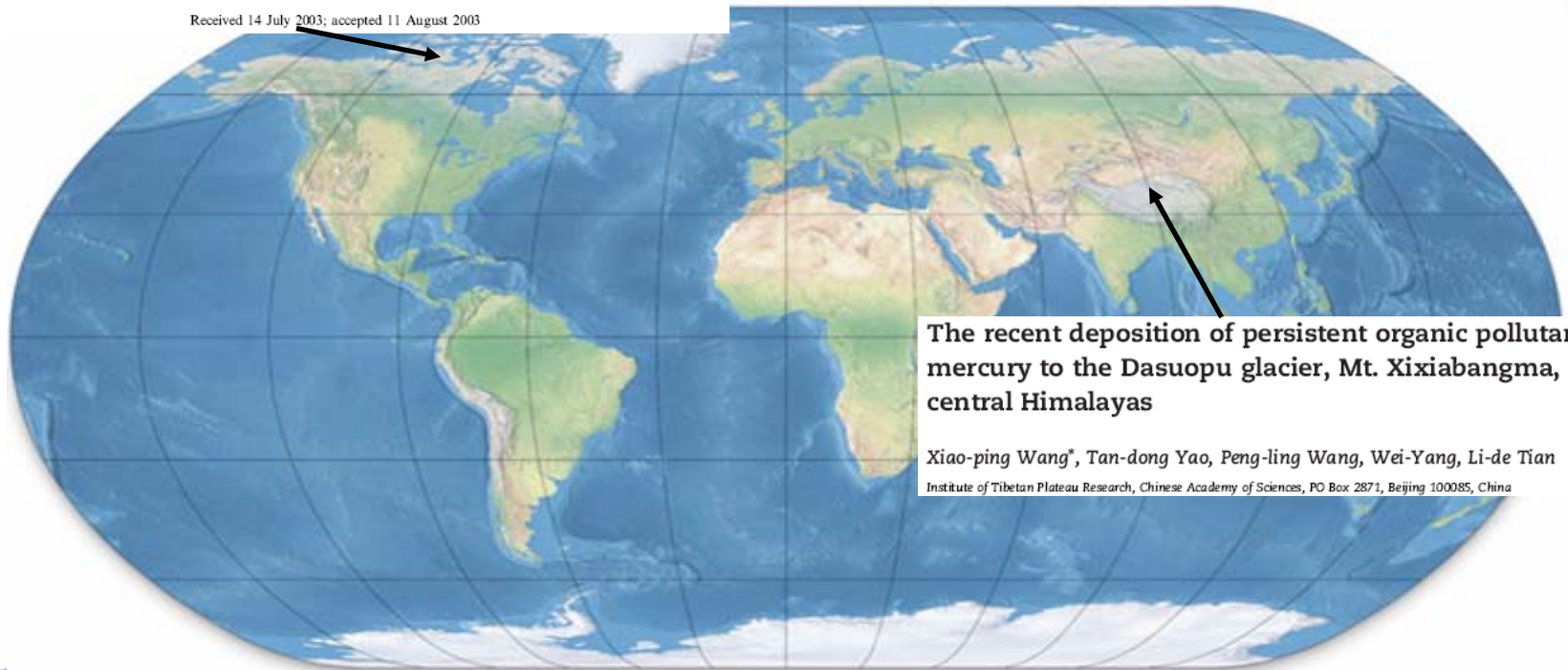
Mixtures of POPs

Investigating the occurrence of persistent organic pollutants (POPs) in the arctic: their atmospheric behaviour and interaction with the seasonal snow pack

Crispin J. Halsall*

Environmental Science Department, Lancaster University, Lancaster LA1 4YQ, UK

Received 14 July 2003; accepted 11 August 2003



The recent deposition of persistent organic pollutants and mercury to the Dasuopu glacier, Mt. Xixiabangma, central Himalayas

Xiao-ping Wang*, Tan-dong Yao, Peng-ling Wang, Wei-Yang, Li-de Tian
Institute of Tibetan Plateau Research, Chinese Academy of Sciences, PO Box 2871, Beijing 100085, China

Multiple exposure is probable

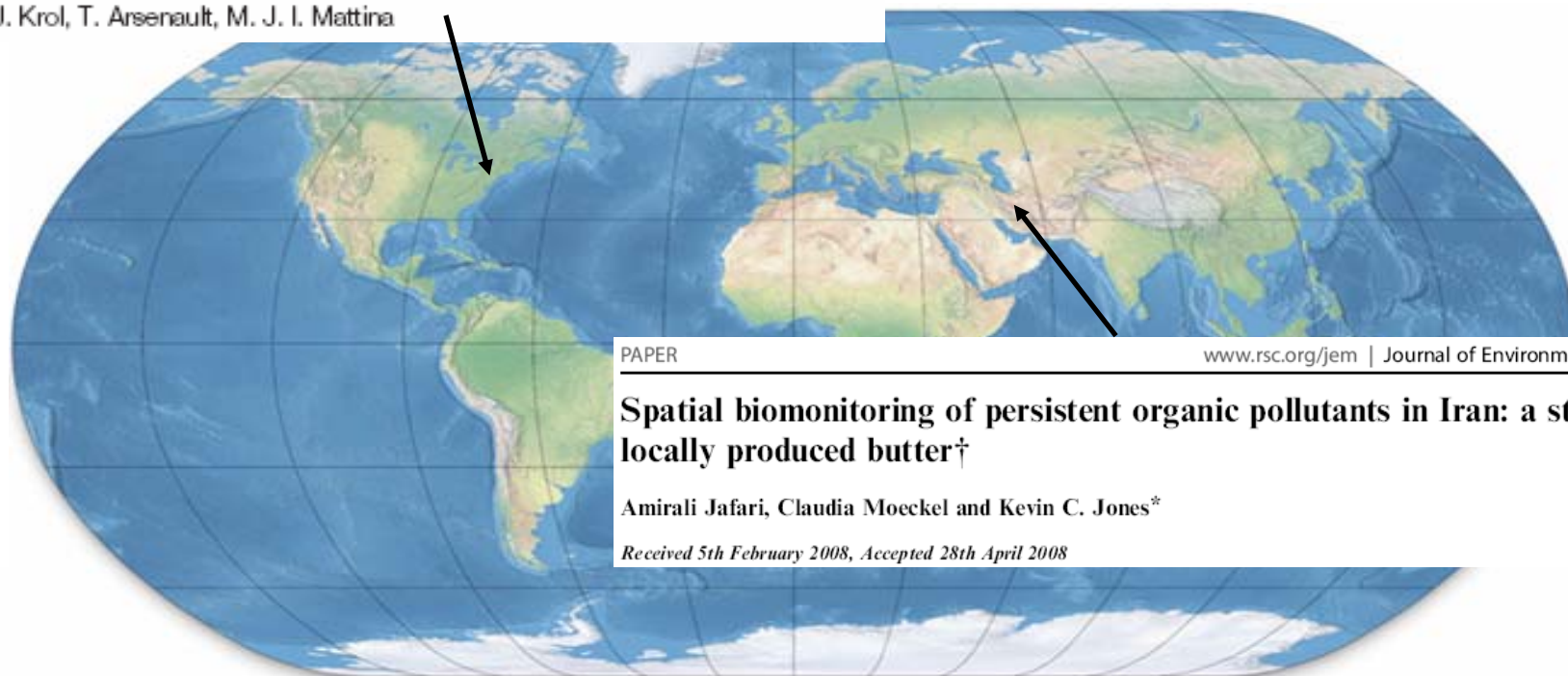
Bioavailability?

Bull. Environ. Contam. Toxicol. (2002) 69:452–458
© 2002 Springer-Verlag New York Inc.
DOI: 10.1007/s00128-002-0083-9

Journal of
**Environmental
Contamination
and Toxicology**

Persistent Organochlorine Pesticide Contamination of Birds Collected in Connecticut During the Year 2000

W. J. Krol, T. Arsenault, M. J. I. Mattina



PAPER

www.rsc.org/jem | Journal of Environmental Monitoring

Spatial biomonitoring of persistent organic pollutants in Iran: a study using locally produced butter†

Amirali Jafari, Claudia Moeckel and Kevin C. Jones*

Received 5th February 2008, Accepted 28th April 2008

Multiple exposure is probable

Bioavailability?

WHO-coordinated surveys of human milk for POPs:

e.g. Environ Res 99 (2005) 285



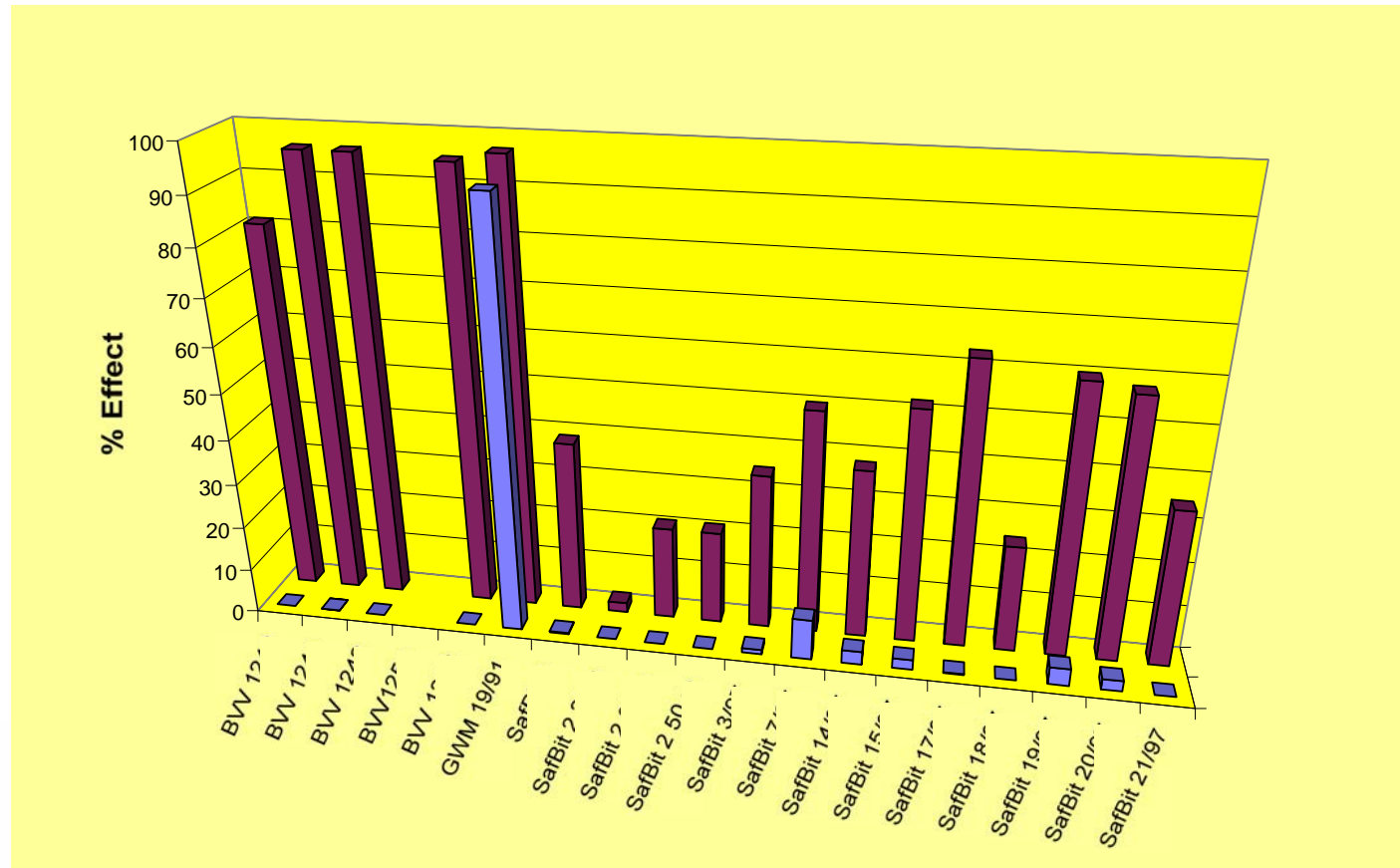
Persistent organic pollutants in human milk in women from urban and rural areas in northern China[☆]

Su-Ju Sun^{a,b,c}, Jian-Hong Zhao^{a,c,d}, Minoru Koga^e, Yu-Xia Ma^b, Dian-Wu Liu^b, Masafumi Nakamura^f, Huai-Jun Liu^d, Hyogo Horiguchi^{a,c}, George C. Clark^g, Fujio Kayama^{a,c,*}

Combined effects from mixture exposure?

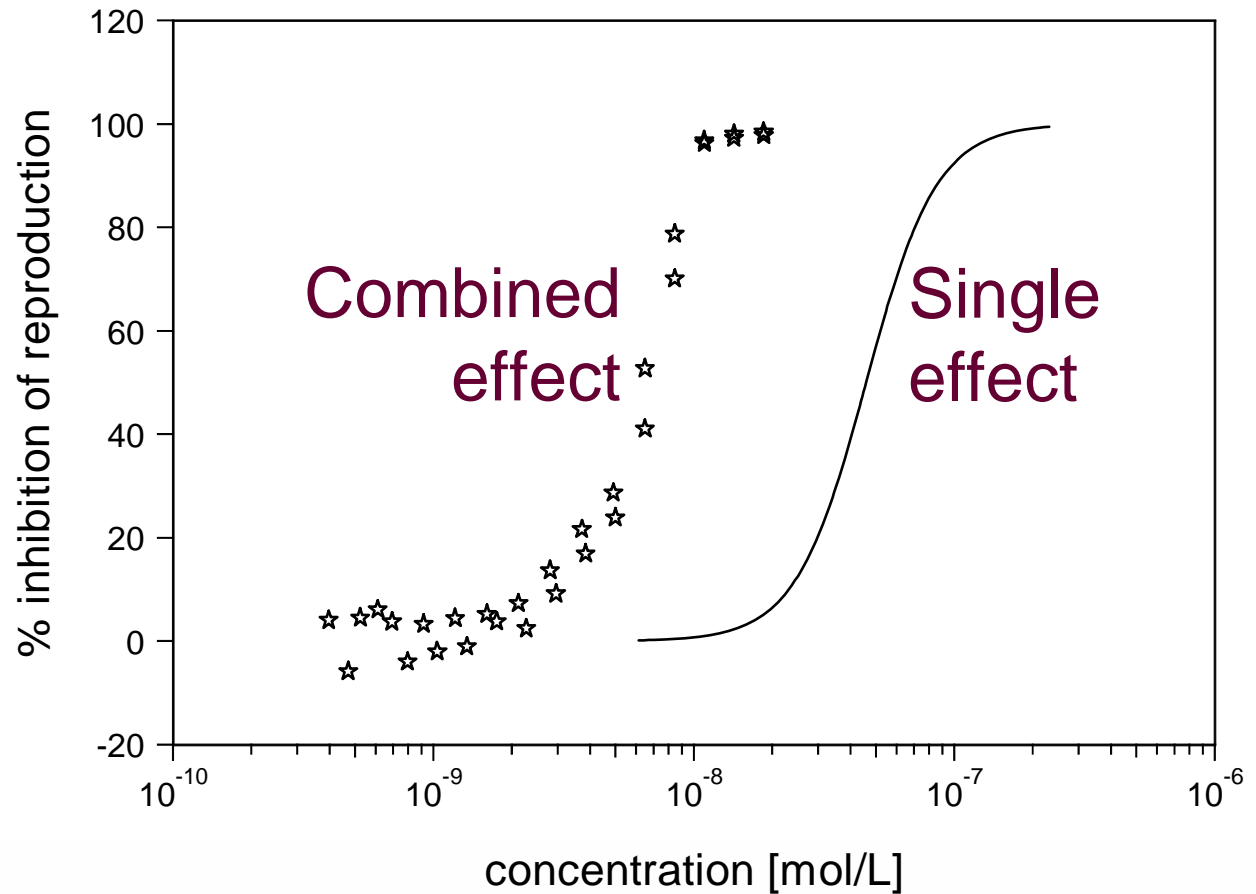
Combined effects happen

E.G.: Expected effects by chlorobenzene
& **observed effects** from a multiple contaminated aquifer



Combined effects happen

Expected
concentration-
response versus
Observed
responses for
...
in the presence of
other
nitrobenzene-type
compounds



Altenburger et al. ETC 2005

And for POPs?

Gregorszczuk et al. 2008. Steroid secretion following exposure of ovarian follicular cells to three different natural mixtures of persistent organic pollutants (POPs). *Repro. Tox.* 25:58-66.

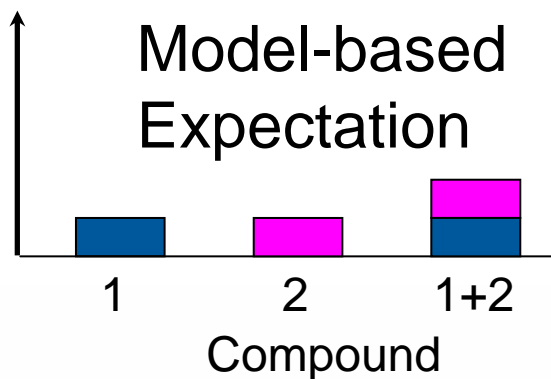
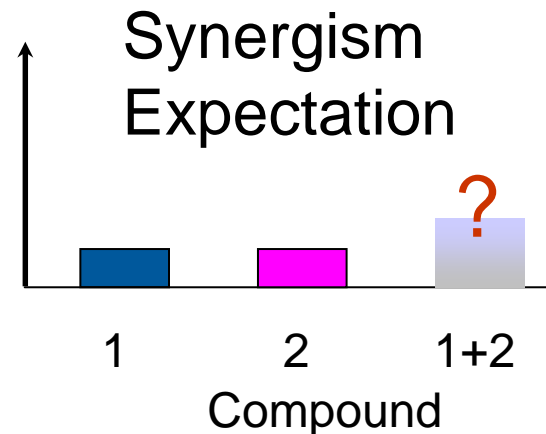
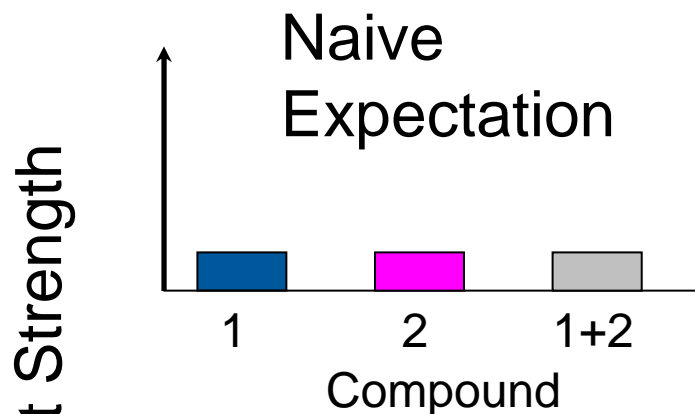
Chu et al. 2008. Toxicological effects of in utero and lactational exposure of rats to a mixture of environmental conataminants detected in Canadian arctic populations. *J Toxicol Environ Health A* 71:93-108

Desaulniers et al. 2005. Effects of postnatal exposure to a mixture of polychlorinated biphenyls, p,p'-dichlororphenyldichloroethene in prepubertal and adult female Sprague-Dawley rats. *Int J Toxicol* 24:111-127.

=> Yes, in principle

Combined effects:
Can they be predicted and assessed ?

Assessment of mixture toxicity requires explicit concepts

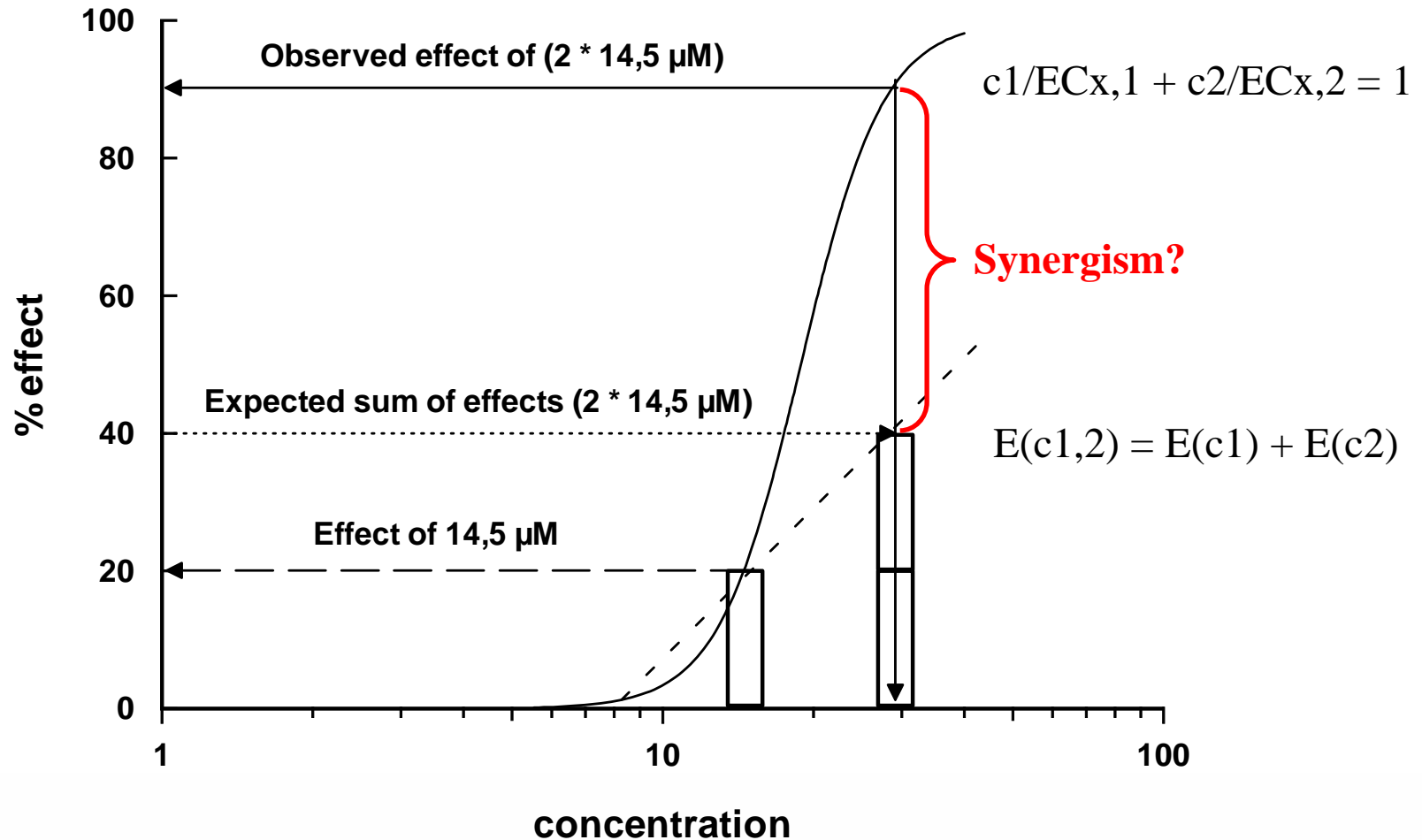


$$E_{S1} ; E_{S2} ; \dots ; E_{Si}$$



$$E_{S1,2,\dots,i}$$

Assessment of mixture toxicity requires explicit concepts



Altenburger, Nendza, Schuurmann ETC 2003 22:1900

XXIV.

Aus dem Pharmakologischen Institut der Universität Tartu-Dorpat.

Über Kombinationswirkungen.

I. Mitteilung: Hilfsmittel der Fragestellung.

Von

S. Loewe und H. Muischnek.

(Mit 3 Abbildungen.)

(Eingegangen am 17. V. 1926.)

Bei der experimentellen Behandlung wie bei der Darstellung von Problemen aus dem Bereich der Kombinationswirkungen der Pharmaka stehen die Bezeichnungen »Synergismus«, »Antagonismus«, »Addierung« und »Potenzierung« im Mittelpunkt der Terminologie. Diesen Wendungen entsprechen nicht immer einheitlich gebrauchte Begriffe. Da in einer Anzahl hier folgender Mitteilungen über das Ergebnis experimenteller Beschäftigung mit pharmakologischen Kombinationswirkungen berichtet werden soll, ist es vielleicht gestattet, einige Erwägungen vorzuschicken, welche zum mindesten der vereinfachten Darstellung unserer Versuchsergebnisse dienlich sein werden, darüber hinaus aber möglicherweise auch für Versuchsordnung, Fragestellung und Befundsberichte anderer Bearbeiter von Nutzen sind.

*Naunyn-
Schmiedebergs
Arch Exp Pathol
Pharmakol 114:
313, 1926*

Assessment of mixture toxicity requires explicit concepts

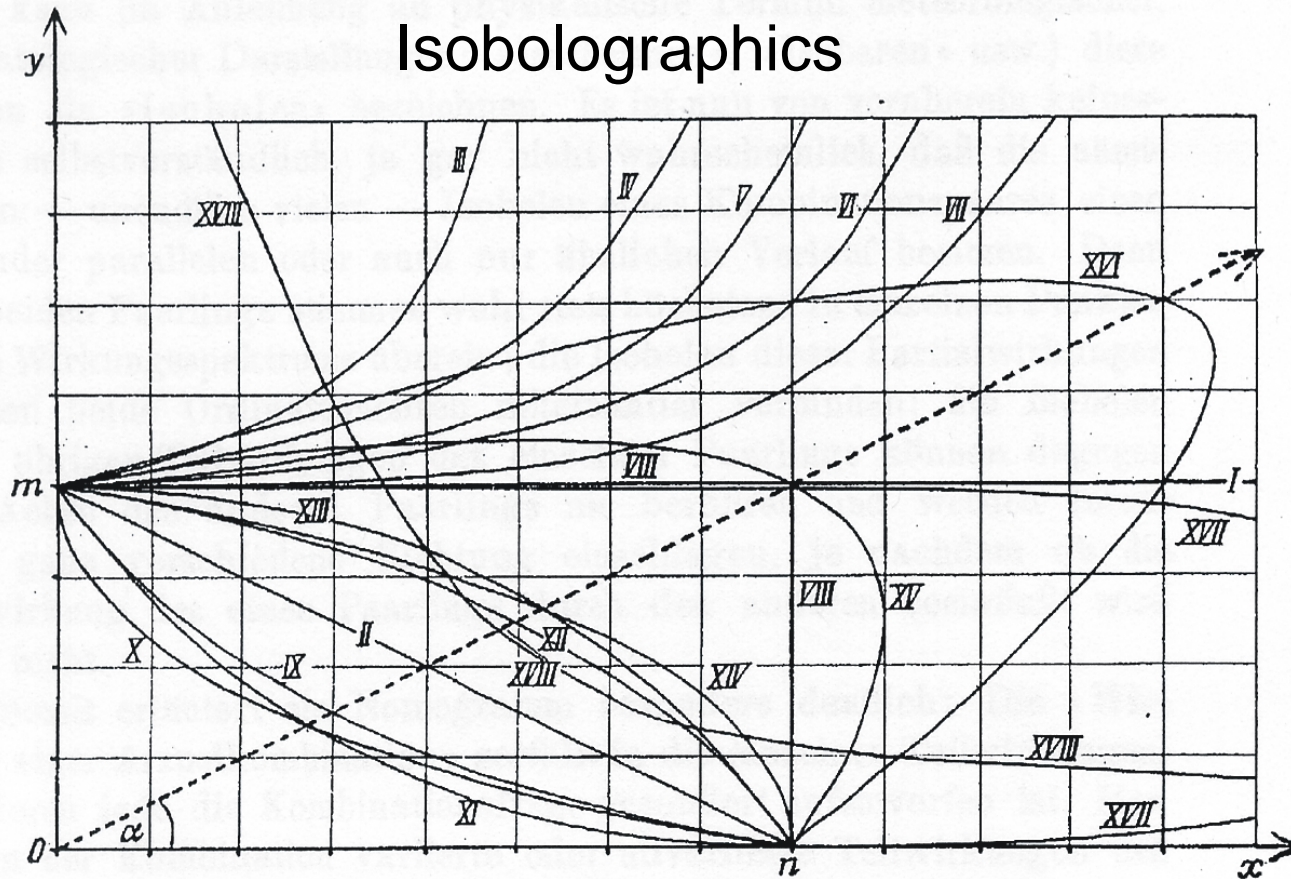


Abb. 1.

Modell of Concentration Addition

$$1 = \frac{c_1}{EC_{x,1}} + \frac{c_2}{EC_{x,2}}$$

THE TOXICITY OF POISONS APPLIED JOINTLY¹

By C. I. BLISS (1939)

Mexico, D.F.

(With 14 Text-figures)

*Ann Appl
Biol 26: 585
1939*

CONTENTS

	PAGE
Introduction	585
Types of joint action	586
Independent joint action	587
Similar joint action	595
Synergistic action	599
Summary	613
References	615

Modell of Independent Action/Response Addition

$$E(c_{1,2}) = E(c_1) + E(c_2) - E(c_1)E(c_2)$$

Journal of the Royal Statistical Society

SERIES B (METHODOLOGICAL)

Vol. XIV, No. 2, 1952

QUANTAL RESPONSES TO MIXTURES OF POISONS

By R. L. PLACKETT

Department of Applied Mathematics, University of Liverpool

and P. S. HEWLETT

Pest Infestation Laboratory, Slough

[Read before the RESEARCH SECTION OF THE ROYAL STATISTICAL SOCIETY, March 19th, 1952,
Professor M. S. BARTLETT in the Chair.]

SUMMARY

VARIOUS models for the joint action of poisons are examined. An attempt is made

Distinction between mode of action
and effect type may be helpful

Assessment of mixture toxicity requires explicit concepts

J. theor. Biol. (1985) 114, 413-431

The Expected Effect of a Combination of Agents: the General Solution

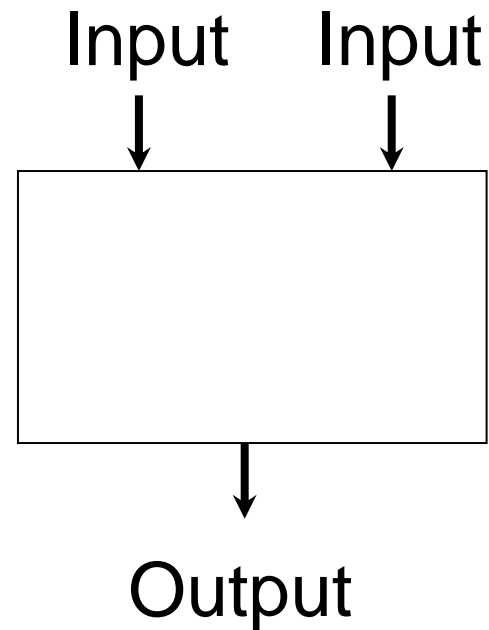
MORRIS C. BERENBAUM

*Department of Experimental Pathology, St Mary's Hospital Medical
School, London W2, England*

(Received 30 July 1984, and in revised form 6 December 1984)

Interactions between agents (drugs, carcinogens, physiological stimuli, environmental pollutants, etc.) in producing their effects are of fundamental interest and practical importance in virtually every branch of biology and medicine. A combination of agents is said to show interaction when the

Quantitative prediction
of combined effects
is possible

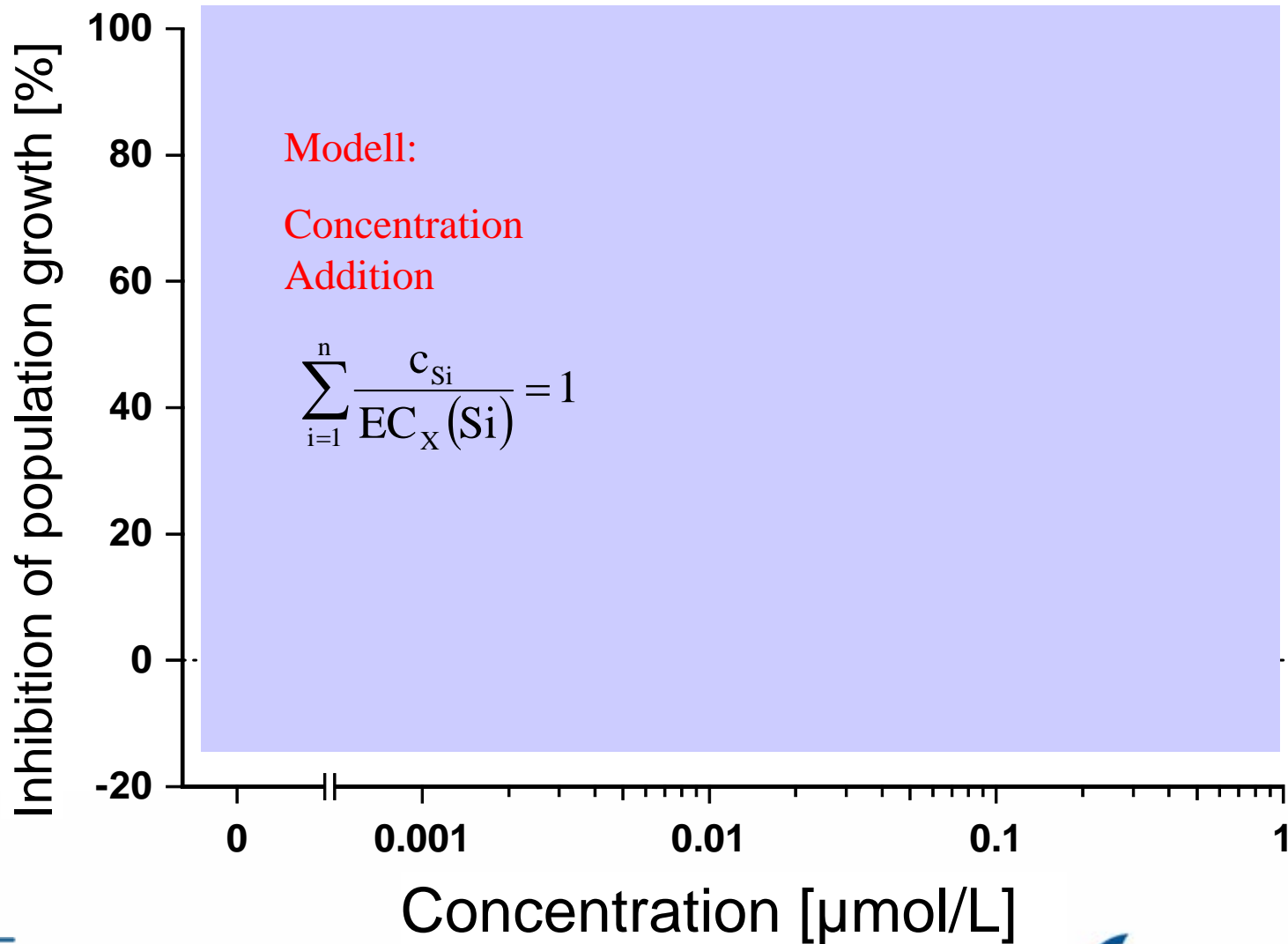


versus

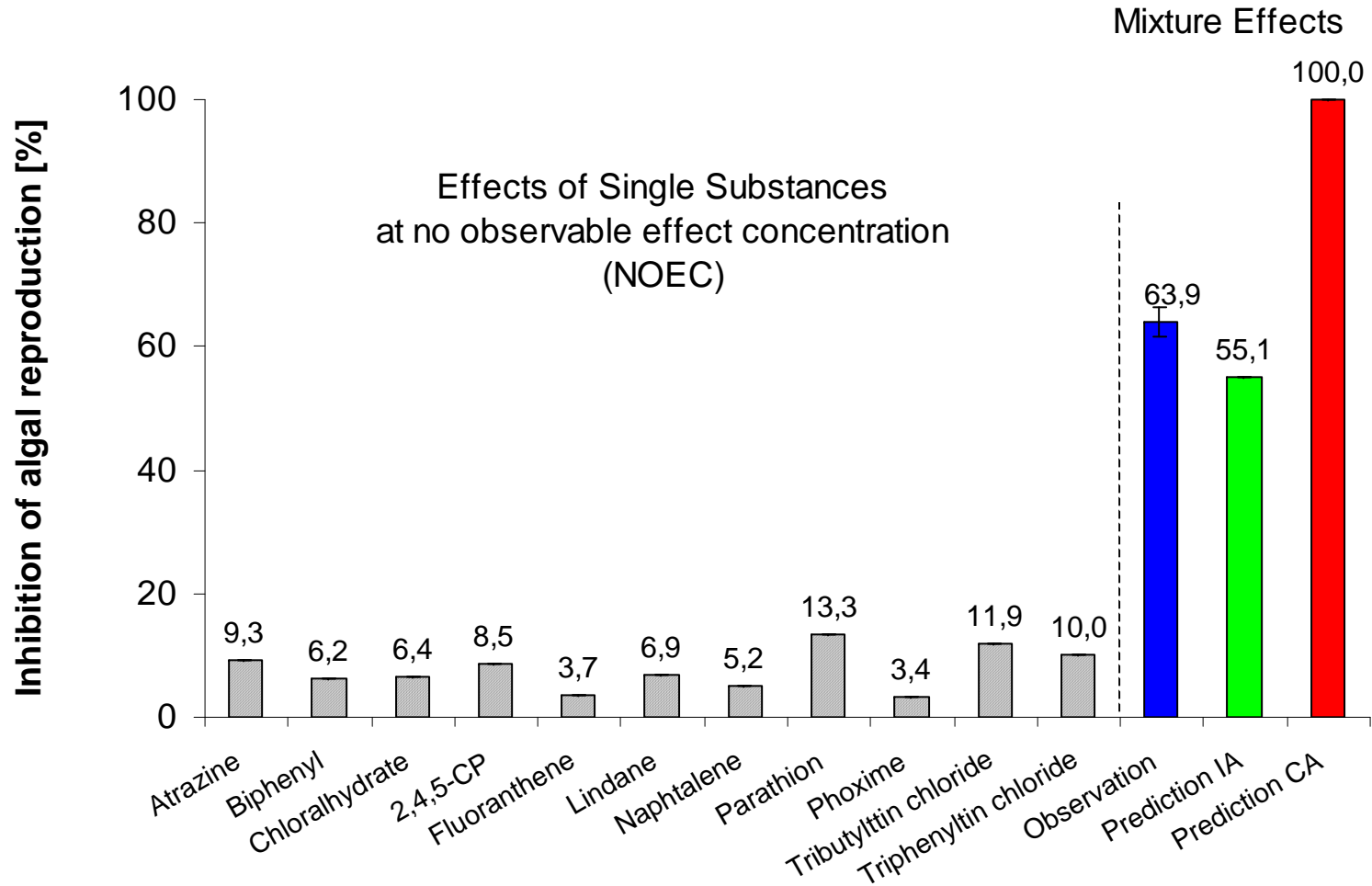


OLTZ
RE FOR
ONMENTAL
ARCH - UFZ

Additive combined effects are predictable



Additive combined effects are predictable

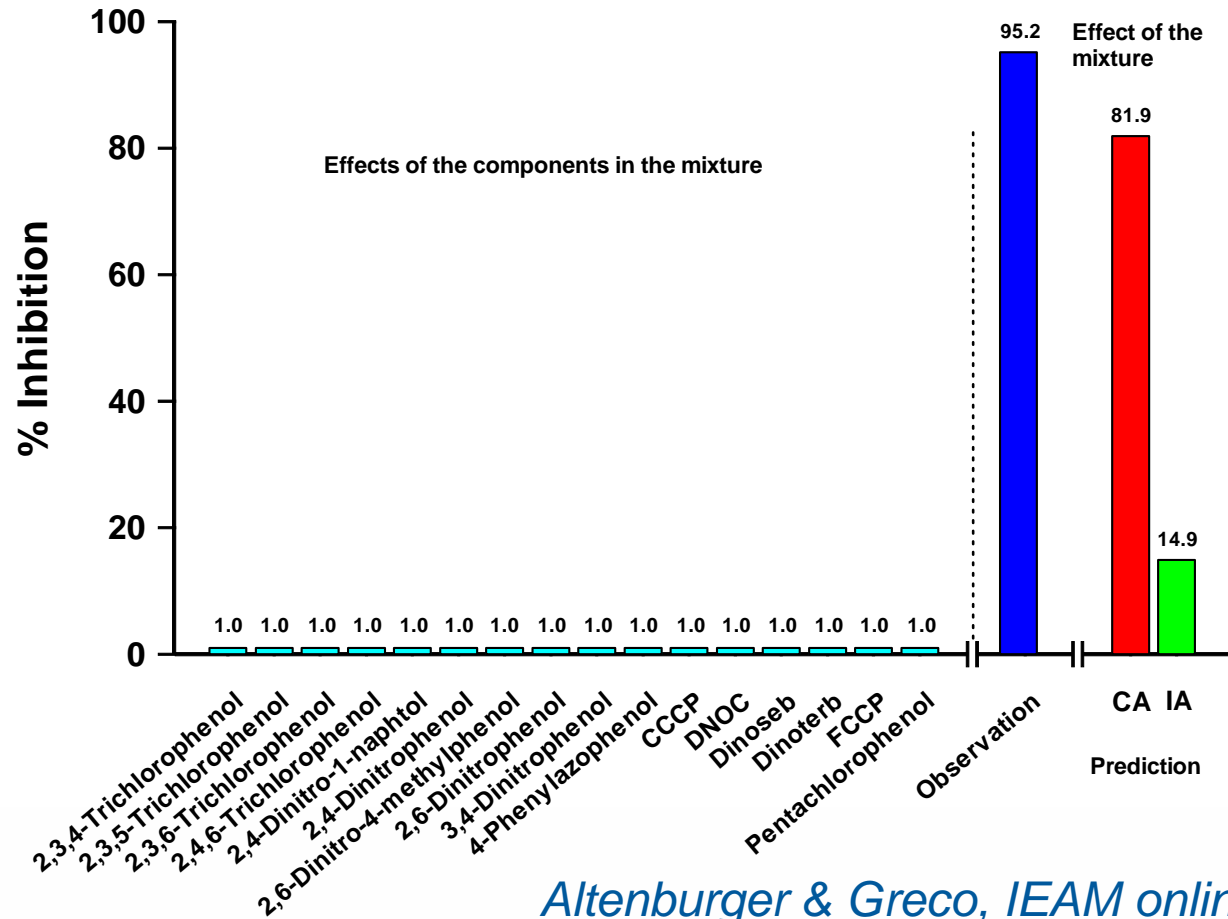


Walter et al. 2002

Additive combined effects are predictable

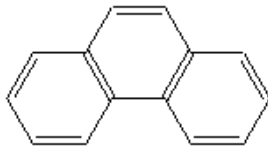
Something
from
nothing

Silva et al.
ES&T 36:1751

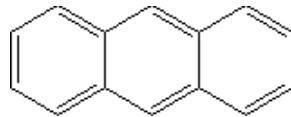


Additive combined effects are predictable

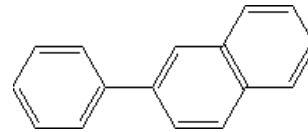
Analysis of potentially biologically active substances: Sediment contaminants



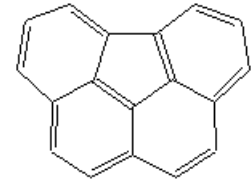
Phenanthrene



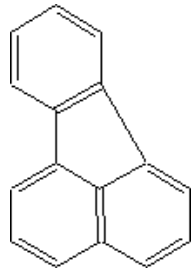
Anthracene



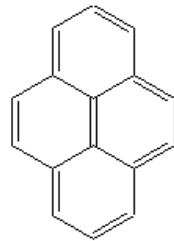
2-Phenyl-naphthalene



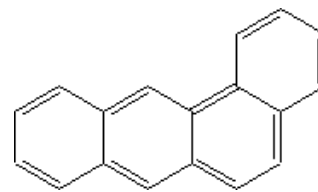
Benzo[*ghi*]fluoranthene



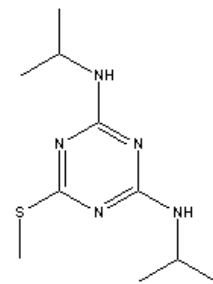
Fluoranthene



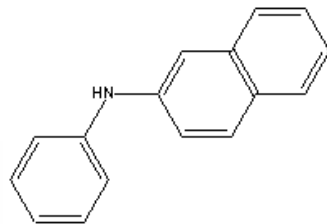
Pyrene



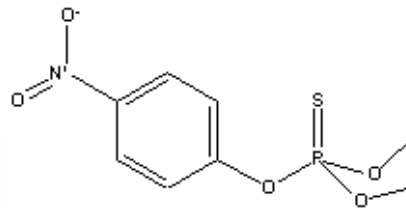
Benzo[*a*]anthracene



Prometryn



N-Phenyl-β-naphthylamine

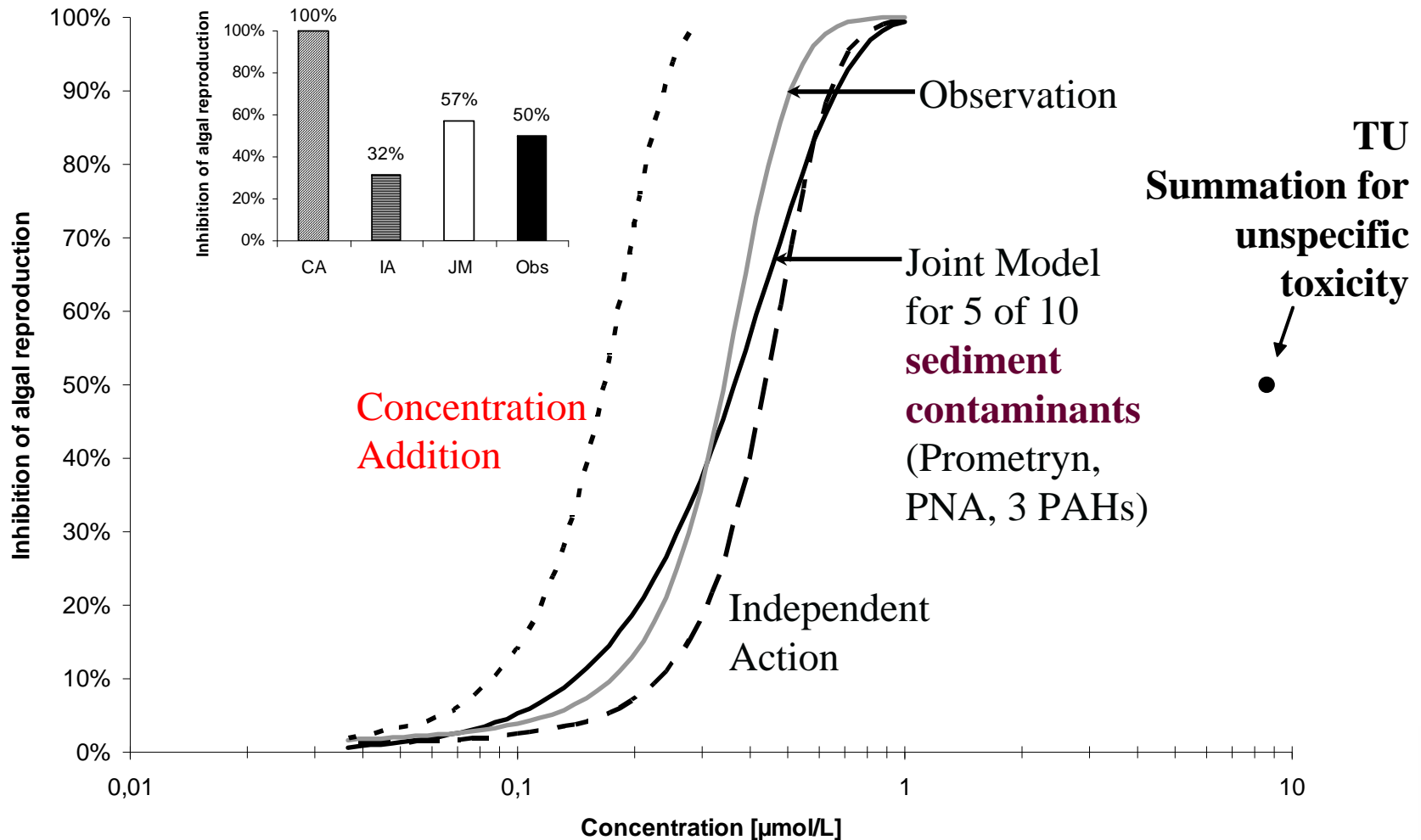


Methyl parathion

=> Mixture of specifically & unspecifically acting substances:

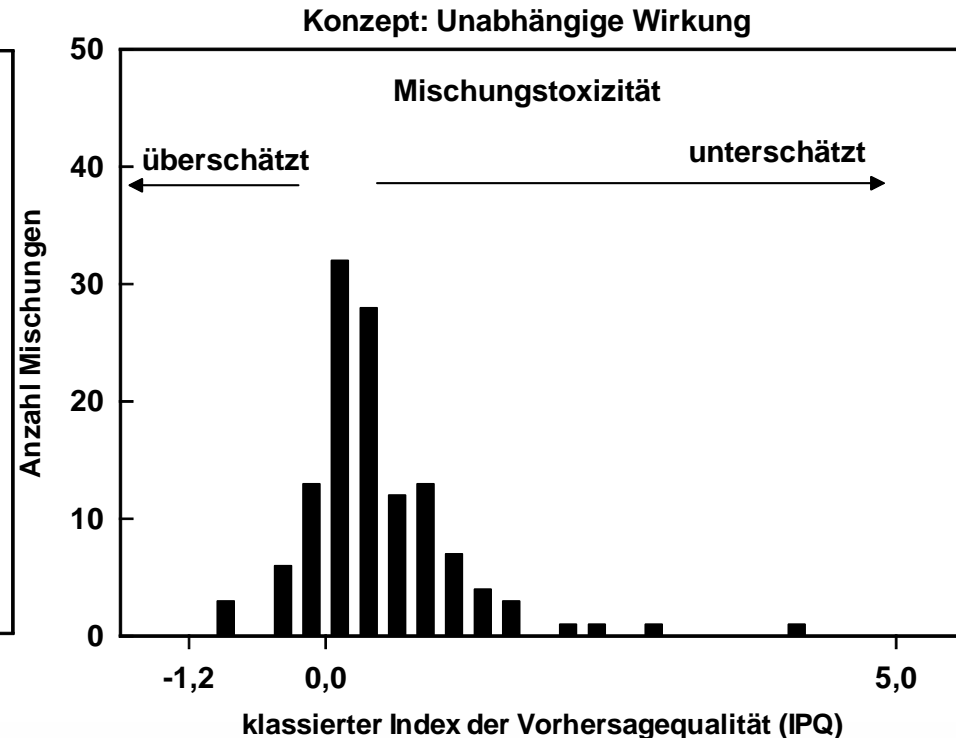
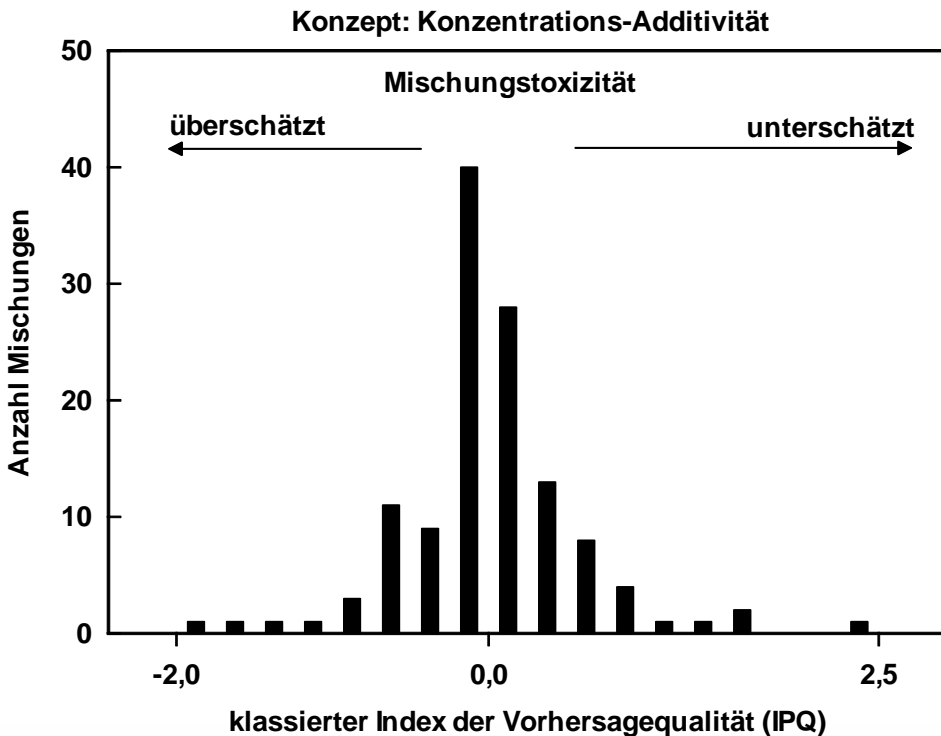
Do they all contribute equally to a combined effect?

Additive combined effects are predictable



Synergism is not predictable (quantitatively)

Pattern of combined effects (EC50) for 137 binary mixtures of pesticides and surfactants



=> but synergism seems to be rare

Based on

- Exposure (e.g. EU drinking water directive parameter 77);
- Effects (e.g. waste water regulation, TEF)
- Hazards and Risks (e.g. HI, ...)

Risk assessment may account for mixtures

augmentation

additivity

antagonism

coalism

additivism

antergism

enhancement

independence

depotential

potentiation

indifference

desensitisation

sensitisation

non-interaction

infraadditivity

superadditivity

summation

negative synergism

supraadditivism

zero-interaction

non-interaction

synergism



potentiation

synergy

subadditivity

zero-interaction

no addition

Thank you for your attention !

