

CONSENSUS ON CONCEPTS AND TERMINOLOGY FOR COMBINED-ACTION ASSESSMENT: THE SAARISELKÄ AGREEMENT

Greco W¹, Unkelbach H-D², Pösch G³, Sühnel J⁴, Kundi M⁵, Bödeker W⁶

¹Department of Biomathematics, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263-0001, USA

²Fachhochschule Wiesbaden, Fachbereich, MND, Von-Lade-Strasse 1, D-6222 Geisenheim, Germany

³Institute of Pharmacology and Toxicology, University of Graz, Univ. pl. 2, A-8010 Graz, Austria

⁴Institute of Molecular Biotechnology, Beutenbergstr. 11, D-O-6900 Jena, Germany

⁵Institute of Environmental Hygiene, University of Vienna, Kinderspitalgasse 15, Vienna 1095, Austria

⁶Institute for Cell Biology, Biochemistry and Biotechnology, University of Bremen, D-2800 Bremen 33, Germany

Abstract

A consensus was reached among the six authors regarding terminology and concepts for two-agent combined-actions. For the case in which both agents are effective individually, Loewe additivity is defined by the equation, $\frac{C_1}{EC_{x,1}} + \frac{C_2}{EC_{x,2}}$, in which C_1 and C_2 are the concentrations (or doses or intensities) of two agents

(chemical or physical or abstract) in a mixture which elicits $X\%$ effect, and $EC_{x,1}$, $EC_{x,2}$ are the concentrations of each agent alone which would elicit $X\%$ effect. Bliss independence is defined by the equation, $fa_{12} = fa_1 + fa_2 - fa_1 fa_2$, in which fa_1 , fa_2 and fa_{12} are the fractions of total possible effect affected by agent 1, 2 and the combination. For the cases in which the observed effects are more or less than predicted by these models, we propose the terms, Loewe synergism, Loewe antagonism, Bliss synergism and Bliss antagonism, respectively. When only one agent in a pair is effective alone, we propose inertism for the lack of influence of the second agent, synergism (without a leading adjective) for an increased effect caused by the second agent, and antagonism for the opposite case. When neither drug is effective alone, an effective combination is termed coalism. The relative merits of rival response surface models and model-fitting methodology is still unresolved. This "Saariselkä agreement" may form the nucleus for future standards in the field of combined-action assessment.

(*Archives of Complex Environmental Studies* 4(3): 65-69, 1992)

Key words: Loewe additivity – Bliss independence – Loewe synergism – Loewe antagonism – Bliss synergism – Bliss antagonism – Inertism – Synergism – Antagonism – Coalism

Introduction

A group of six scientists with strong interests in the assessment of the joint effects of combinations of agents, met together for the Fifth International Conference on the Combined Effects of Environmental Factors, ICCEF'92, in Saariselkä, Finnish

Lapland, September 6-10, 1992. The six scientists, from the fields of Pharmacology, Toxicology and Biometry, made presentations at the conference which underscored the controversies, disagreements and paradoxes endemic to the field of agent interactions. The group comprised a good representative sample of advocates of diametrically opposing