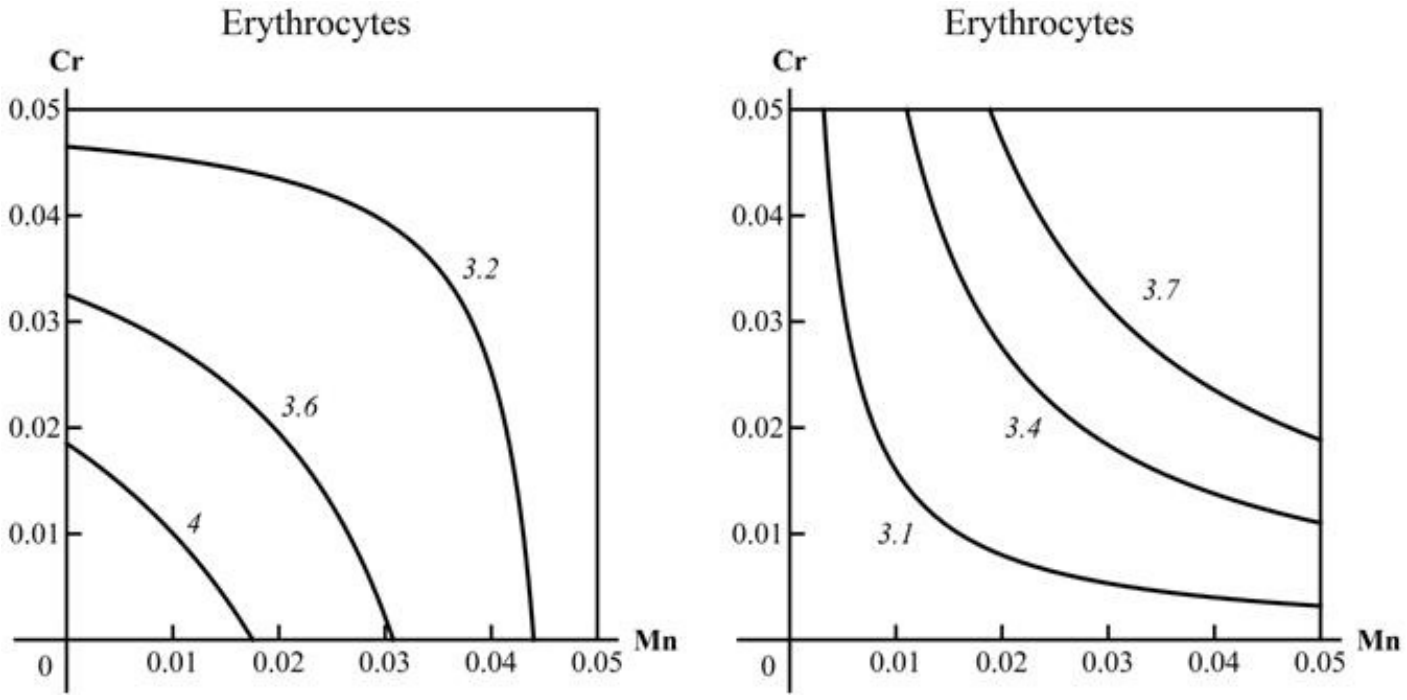
A novel approach to characterizing the type of three-factorial combined toxicity

We carried out an experiment in which outbred white rats were subjected to repeated injections with water solutions of either one of the toxics (Mn, Ni or Cr salts) in doses isoeffective in respect to the lethal acute toxicity, or any two of them, or all the three together in the same doses. Control rats were receiving injections of the same volume of distilled water. Judging by more than 30 indices for the organism's status, all the tested chemicals caused intoxication of mild to moderate strength. For each two-factorial exposure (manganese plus nickel, manganese plus chromium, or nickel plus chromium) we found by mathematical modeling that the binary combined toxicity (like it had been demonstrated by us previously for lead plus cadmium of lead plus fluoride combinations) either was of unidirectional additive type or departed from it (predominantly towards subadditivity) depending on the particular effect for which it was assessed, on this effect level, and on the dose level,

As concerns the full three-factorial toxic combination, we proposed a novel approach to characterizing its effects based on a consideration whether the addition of a third toxic to two others led to the type of binary combined action becoming either more or less adverse (?lasses A and B, respectively) or remaining basically unchanged (?lass C) We have revealed some stable patterns of this classification fully or partly reproduced when considering, one by one, various metals as the third component of a combination. Thus for the absolute majority of effects, the classification proved inherently consistent.



Isobolograms for combined decreasing action of manganese and chromium on the RBC count: (a)

without nickel (subadditivity), (b) against the background of nickel at the dose equal to 0.05 LD50 (synergism). The axes of coordinates show the doses of the Mn and Cr as fractions of respective LD50, and numbers at the isoboles show the level of effect on which the isobole is constructed.

We believe that the relevance of the proposed classification to health risk analysis and management is as follows. When assessing a total health risk due to exposure to three toxicants by the commonly accepted approach based on summation of one-factorial risks, it is essential to take into account the probability that the result of such assessment may underestimate the actual risk (if toxicologically important effects occur in Class A) or somewhat overestimate it (if they occur in Class B). The first variant is more important in terms of the precaution paradigm, while the second one may be considered as providing additional safety margin rather than justifying less conservative risk management scenarios.

Besides, we found a complicated reciprocal influence of combined metals on their retention in kidneys, liver, spleen and brain which might presumably be one of the possible mechanisms of combined toxicity, but not always the most important one.

Publication

Further development of the theory and mathematical description of combined toxicity: An approach to classifying types of action of three-factorial combinations (a case study of manganese-chromium-nickel subchronic intoxication).
Katsnelson BA, Panov VG, Minigaliyeva IA, Varaksin AN, Privalova LI, Slyshkina TV, Grebenkina SV
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