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Further development of mathematical description for combined toxicity: A case study of lead–fluoride combination

Vladimir G. Panov[b], Boris A. Katsnelson[a,*], Anatoly N. Varaksin[b], Larisa I. Privalova[a], Ekaterina P. Kireyeva[a], Marina P. Sutunkova[a], Irene E. Valamina[c], Olga Yu. Beresneva[c]

[a] Medical Research Center for Prophylaxis and Health Protection in Industrial Workers, 30 Popov Str., 620014 Ekaterinburg, Russia[1]
[b] Institute of Industrial Ecology, the Urals Branch of the Russian Academy of Sciences, 20 Sofia Kovalevskaya Str., 620990 Ekaterinburg, Russia[2]
[c] Ural State Medical University, 3 Repin Str., 62028 Ekaterinburg, Russia[3]

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ABSTRACT

In this article, we check and develop further some postulates of the theory and mathematical modeling of combined toxic effect that we proposed earlier [1]. To this end, we have analyzed the results of an experiment on rats exposed during 6 weeks to repeated intraperitoneal injections of lead acetate, sodium fluoride or both. The development of intoxication was estimated quantitatively with 54 functional, biochemical and morphometric indices. For mathematical description of the effect that lead and fluorine doses produced alone or in combination, we used a response surface regression model containing linear and cross terms (hyperbolic paraboloid). It is shown that the combination of lead and fluoride features the same 10 types of combined effect that we found previously for the lead and cadmium combination. Special attention is given to indices on which lead and fluorine produce an opposite effect.

1. Introduction

In our previous paper [1] we discussed the state of the art in the complicated and controversial domain of the combined toxicity theory and its mathematical modeling and investigated this problem taking as a case study an experiment on rats subjected to lead–cadmium subchronic intoxication.

We analyzed the findings of that experiment in order to identify the types of combined toxicity using either common sense considerations based on descriptive statistics or two mathematical models based (a) on ANOVA and (b) on Mathematical Theory of Experimental Design, which correspond to the widely recognized paradigms of effect additivity and dose additivity (Loewe additivity), respectively. This analysis has led us to the following conclusions:

(1) these two paradigms are virtually interchangeable and should be regarded as different methods for modeling combined toxicity rather than as concepts reflecting fundamentally differing processes;

* Corresponding author. Tel.: +7 343 3717 721; fax: +7 343 3717 740; mobile: +7 922 126 30 90.
E-mail addresses: bkaznelson@etel.ru, bkaznelson@ymrc.ru (B.A. Katsnelson).
[1] info@ymrc.ru.
[2] iie@ecko.uran.ru.
[3] usma@usma.ru.

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(2) within both models, there exist more than three traditionally recognized types of combined toxicity (additivity, subadditivity and superadditivity), and we have found at least 10 variants of it depending on exactly which effect is considered and what its level is, as well as on dose levels and their ratio.

Later on, these postulates were in principle confirmed based on the same approach in an analysis of experimental data on the combined toxicity of chromium (VI) and nickel [2].

In these papers we touched but tangentially upon the special case of toxic agents acting oppositely on some indices of organism's status where the combined effect equal to the algebraic sum of effects induced by separate exposures in other words, formal additivity can hardly be interpreted otherwise than toxicological antagonism. As well as Tallarida et al. [3] in a similar pharmacological situation, we proposed to model it in the same manner as used for a combination of toxics acting unidirectionally. In this connection, we dwelt upon some terminological issues and proposed to discriminate between "hidden antagonism" (in the case of subadditivity of unidirectional effects) and "explicit antagonism" (in the case of formal additivity of opposite effects).

Earlier Timbrell [4] proposed to distinguish terminologically between "functional antagonism where the effects are opposite and therefore counterbalanced; chemical antagonism in which a complex is produced; dispositional antagonism in which the absorption, distribution, metabolism or excretion of the toxic compound is influenced; and receptor antagonism where two substances interact with the same receptor and thereby reduce the toxic response". Such distinctions (given that no mathematical description has been provided by this author) are, in our opinion, more interesting for understanding or for searching for an understanding of the mechanisms of combined toxicity rather than for developing its working classification. It should be noted in this connection that "functional antagonism" has virtually the same meaning as our term "explicit antagonism" while the other three types of action considered by Timbrell are, in fact, the different mechanisms of what we propose to call "hidden antagonism", and these mechanisms are not alternatives but may be characteristic of one and the same combination of toxics. For instance, the "dispositional antagonism" was found by us not as a unique type but along with other types of combined chromium-nickel toxicity [2]. Moreover, when one toxic influences the metabolism of another, the net result may be not only antagonism but also potentiation of toxicity as it was demonstrated, for instance, for the naphthalene–lead combination [5].

We deemed it worthwhile to check the above-considered fundamental propositions by means of the most efficient mathematical tool, using, however, some other toxic combinations based, like in our previous paper, on certain experimental findings from our laboratory that had already been published without a mathematical analysis of this kind. To this end, we chose lead–fluoride subchronic toxicity [6], for which we had a sufficiently long list of toxicodynamic and toxicokinetic indices some of which suggested the possibility of an opposite effect.

Originally, we had turned just to this toxic combination because it is typically present in a range of urban areas contaminated with both fluorides (due, first of all, to emissions from electrolytic aluminum and superphosphate production facilities) and inorganic lead compounds (due to primary and secondary metallurgy of lead, copper and alloys of these metals and to persistent environmental contamination with lead accumulated over a long period of automotive transport's operation on leaded gasoline). Besides, a combined lead–fluoride pollution of workroom and ambient air is possible in the ceramic industry where sodium silicofluoride is used along with lead glazes. Finally, this issue attracted our attention in connection with the old discussion about the benefits and risks of water treatment with fluoride (as a method of preventing caries), specifically in connection with fact that in a number of cities in the eastern states of the USA there are still sections of water supply piping made of lead. An evaluation of lead content of the blood in more than 280 000 children in the State of Massachusetts revealed that water treatment with fluoride raised this index as well as the related prevalence of neuropsychiatric disorders [7].

Both lead and fluoride are characterized by high toxicity, affecting adversely a lot of systems in the organism, often with similar targets of toxic action [8–12].

Noteworthy, in particular, is the relationship between the toxicodynamics of both elements and the calcium metabolism and the toxic effects of both elements on the thyroid gland and on the bone tissue. However, there was in the scientific literature very little factual data prior to our experiment on the combined toxicity of lead and fluoride. Thus it was shown in an experiment on rats that when lead was added to the drinking water in combination with fluoride the concentration of this metal rose in both blood and teeth, whereas lead and fluoride combination did not influence the accumulation of fluoride in the same tissues [13]. A reduced learning ability was discovered in the offspring of female rats exposed to a combined effect of lead and fluoride, in comparison with the action of lead alone or of fluoride alone [14]. In the same offspring, exposure to this combination produced the greatest reduction in the glutamate content of the brain (hippocampus), glutamate being the principal mediator of excitation in the central nervous system and playing an important role in the learning processes.

To sum, the proposed analysis of the combined lead–fluoride toxicity along the lines considered above is of not only theoretical but also practical interest

2. Materials and methods

2.1. Animal experiment

This experiment was carried out on outbred white female rats (from our own breeding colony) with an initial age of about 4 months and body weight of 180–190 g, 15 animals in each exposed and control group. All rats were housed in conventional conditions, breathed unfiltered air and were given standard balanced food and clean