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Study on the variation rules of the joint effects for multicomponent mixtures containing cyanogenic toxicants and aldehydes based on the transition state theory

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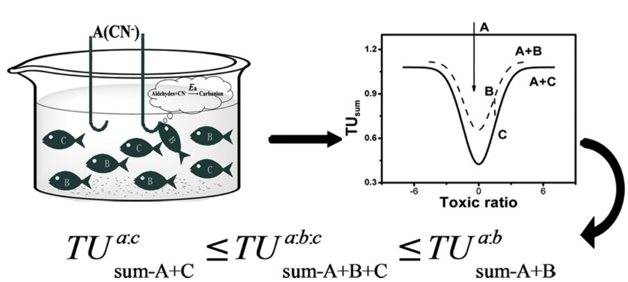
HIGHLIGHTS

- The fishing hypothesis was proposed based on the transition state theory.
- The hypothesis was used to reveal variation rules of joint effects of mixtures.
- Joint effects of multicomponent mixtures are among those of binary mixtures.
- Answer to the question why joint effect of binary equitoxic mixtures is the strongest.
- Joint effects of multicomponent mixtures can be predicted using the hypothesis

GRAPHICAL ABSTRACT



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ABSTRACT

Although the study of the variation rules of the joint effects for multicomponent mixtures has gained increasing attention, it still remains unclear how the variation occurs and what the relationships between the joint effects of multicomponent mixtures and their corresponding binary mixtures are. To explain how the variation occurs, this study first proposes a hypothesis on the variation rules of the joint effects using the well-known transition state theory. The hypothesis concluded that the joint effect of multicomponent mixtures is among the joint effects of the corresponding binary mixtures. This hypothesis was named the fishing hypothesis because there is a similarity between the action process of the joint effects and the fishing process. Next, the hypothesis was validated by use of the experimental data by evaluating the joint effects of binary, ternary and quaternary mixtures containing cyanogenic toxicants and aldehydes on *Photobacterium phosphoreum*. The application of the fishing hypothesis can explain the rule as to how the joint effects of a multicomponent-mixture vary with its number of components and their ratios. This study provides a good method to predict the joint effects of multicomponent mixtures using the joint effects of their corresponding binary mixtures. An improvement in the fishing hypothesis will be needed in our future studies due to the approximate assumptions used in the deduction of the hypothesis

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1. Introduction

Organisms in real environments are seldom exposed to single chemicals but are frequently exposed to multicomponent chemical mixtures [1,2]. However, current environmental quality standards and ecological risk assessments are mostly based on the experimental toxicity data of a single component [3]. As is well known, interactions among components in a mixture might cause intricate and substantial variations in the apparent properties of its constituents; thus, the joint effects of mixtures cannot be predicted by only using the toxicities of single components [4–6]. Furthermore, it is impossible for us to detect all of the toxicities for all of the possible mixtures. Consequently, the prediction of the toxicities of the mixtures is important and considerable research has focused on this issue. For example, Faust et al. assessed the joint toxicities of 16 biocides using independent action (IA) models [7]. Rosal et al. employed the combination index (CI) to assess the interactions of mixtures [8,9]. Our previous work predicted the joint effects of binary mixtures using Quantitative Structure Activity Relationship (QSAR) models [10]. However, although these methodologies fostered the assessment of the joint effects of mixtures, there is still a lack of general methodologies to identify or predict the occurrence of the toxicities of mixtures, as noted by Altenburger et al. [11,12]. This is because these methodologies usually focus on certain types of mixtures rather than reveal the variation rules of the joint effects for mixtures in general, i.e., the rules that govern how the joint effect of a multicomponent-mixture will vary with its number of components and their ratios. It is therefore necessary to reveal the various joint effect rules, which will provide a theoretical basis for prediction of the joint effects for multicomponent mixtures.

In the field of environmental toxicology, the study on the variation rules of the joint effects for multicomponent mixtures is becoming a hot issue [13–17]. A pioneering work proposed a hypothesis to explain the variation in the toxicities of equitoxic mixtures of nonspecific toxicants (narcotics) and found that the synergistic or antagonistic effects (interactions) will weaken as the number of components in the mixtures containing narcotic chemicals increased. The figure showing this effect seems to resemble a funnel, and therefore, it was named the funnel hypothesis (Fig. A1, see Appendix A in the supporting information) [18].

A climax hypothesis was then proposed in our previous work to reveal the variation of the joint effects for mixtures of reactive toxicants (Fig. 1) [19]. It was demonstrated that the joint effect at equitoxic ratios was the strongest, i.e., a climax was seen at the equitoxic ratios in the figures with TU plotted vs the toxic ratios. In this hypothesis, each figure has a climax, and therefore, it was named the climax hypothesis.

However, the hypothesis only discussed the climax phenomenon that states that the joint effects of binary mixtures at equitoxic ratios are stronger than that at non-equitoxic ratios. It was still impossible to predict the joint effects of multicomponent mixtures. By now, the joint effects of binary mixtures can be readily obtained and abundant data have been obtained. This raised the following questions: can the abundant binary mixture data be used to predict the joint effects of multicomponent mixtures; what is the relationship between the joint effects of binary mixtures and multicomponent mixtures; and do some variation rules exist within the relationships? If it was found that some variation rules exist, this study strove to answer the question as to why do such rules exist? These were the questions that we strove to answer in the present study.

As is well-known, transition state theory (TST) is usually used to estimate the reaction rate constant and explain how chemical reactions occur [20–22]. Many previous studies have demonstrated that the application of TST could provide an approach to revealing the essence of a chemical reaction process [23,24]. Li et al. studied the atmospheric reactions of nitrogen dioxide with different aldehydes (formaldehyde, acetaldehydes, propanal and butyraldehyde) in the environment using TST [20]. The calculated rate constants using the TST were consistent with the experimental results, which concluded that the rate constant of butyraldehyde was smaller than for the other aldehydes. This indicates that the TST can be employed to investigate the variation rules of chemical reactions of multicomponent mixtures. Our previous study found that the joint effects between cyanogenic compounds and aldehydes are very interesting; their joint effects vary from addition to synergism and antagonism [25]. In addition, we further revealed that these interesting results were due to the intracellular chemical interactions between the individual chemicals [17,26,27]; cyanogenic compounds were hydrolyzed to release CN^-, and then, CN^- reacted with the aldehydes and generated a cyanohydrin carbanion intermediate (Fig. 2). Consequently, the TST can also be employed to explain how these intracellular chemical reactions occur and to reveal the joint toxicological mechanism and the variation rules of the joint effects for these mixtures.

Furthermore, it was also found based on these studies that the chemical interaction process for mixtures was similar to a fishing process. For example, for a ternary mixture containing one cyanogenic compound (A) and two aldehydes (B and C), the joint effect of the mixture was related to its intracellular chemical reaction [10]. In the intracellular chemical reaction, the cyanogenic compound in the mixture was first hydrolyzed to release cyanide ions (CN^-) under the action of enzymes. Then, the CN^- reacted with the aldehyde that possessed the stronger reactivity. It was assumed that the reactivity of aldehyde C was stronger than that of aldehyde B. After a while, the reaction of CN^- with aldehyde C weakened and the reaction of CN^- with aldehyde B was triggered. If CN^- (or the cyanogenic compound) was observed as a fishhook, aldehydes B and C could be observed as different types of fish. The reactivity between CN^- and the aldehydes was seen as the bait in Fig. 3. The amount of the fish hooked should be related to the amounts of the different types of fish and the attractiveness of the bait to the different types of fish. The fish with a larger population or a stronger attraction to the bait will be hooked first. Obviously, the fishing process is similar to the action process of the mixture toxicity. Based on their similarity, the present study proposed a fishing hypothesis to further explain the variation rules of the joint effects for mixtures containing cyanogenic compounds and aldehydes.

The purposes of the present study were therefore to use TST to investigate the process of the intracellular chemical reactions of mixtures containing cyanogenic compounds and aldehydes by a proposed fishing hypothesis, to find the variation rules of the

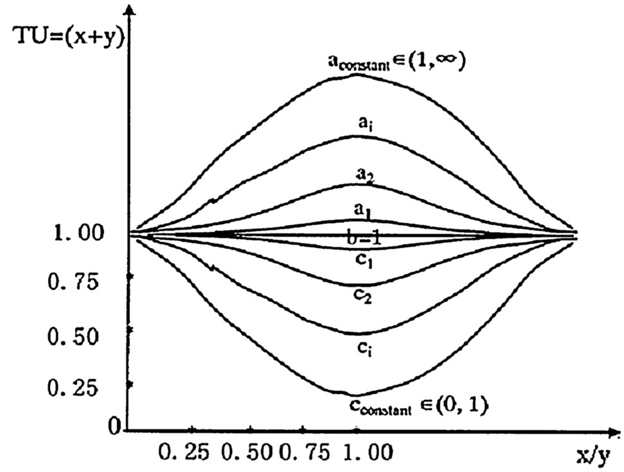

Fig. 1. Schematic of the climax hypothesis (from Lin et al. [19]).