

# Research Progress on Toxicity Assessment Methods of Mixed Pollutants

Yilun Dai<sup>1, 2, 3, 4, 5, \*</sup>

<sup>1</sup>Shaanxi Provincial Land Engineering Construction Group Co., Ltd., China

<sup>2</sup>Institute of Land Engineering and Technology, Shaanxi Provincial Land Engineering Construction Group Co., Ltd., China

<sup>3</sup>Key Laboratory of Degraded and Unused Land Consolidation Engineering, Ministry of Natural Resources, China

<sup>4</sup>Shaanxi Provincial Land Consolidation Engineering Technology Research Center, China

<sup>5</sup>Land Engineering Technology Innovation Center, Ministry of Natural Resources, China

\*Corresponding author

## Abstract

Since the 1930s, the field has used the following three models to evaluate the toxic effects of mixed pollutants: concentration addition model, independent action model and interaction model. The first two are applicable to the case that there is no interaction between the mixed components and do not affect each other, and the third is mainly applied to the case that there is an interaction between the components, which may lead to the enhancement or reduction of toxicity. In the environment, mixtures are not always simply composed of chemicals with similar or different effects, and it may be necessary to consider multiple models applied together during the toxicity assessment process, especially for mixture contamination in complex environments.

## Keywords

Toxicity Assessment Methods; Mixed Pollutants; Concentration Addition Model, Independent Action Model and Interaction Model; Multiple Models Applied.

## 1. Concentration Addition and Independent Action

Both concentration addition (CA) and independent action (IA) are applied to non-interaction models, so the evaluation of mixture toxicity is mostly based on the assumption that the components of the mixture do not interact or do not interfere with each other. In theory, the concentration addition model applies to a class of chemical substances in which the sum of the single toxicity of the components in a mixture is equal to the toxicity of the whole mixture. The model assumes that different components in the mixture have the same toxic mechanism and target sites, and do not dilute or affect each other's toxicity. Each component in the mixture will contribute to the total toxicity according to its own single toxic effect at the corresponding concentration, so even if the concentration level of each component in the mixture is below the toxicity threshold, its total toxicity may also be due to the addition effect. Li Menghan et al. studied the combined toxicity of heavy metal Pb and antibiotics to luminous bacteria, and the results showed that when Pb co-existed with tetracycline antibiotics and sulfonamides antibiotics, the acute toxicity of the mixture increased sharply, and the toxic unit (TU) value of PB-tetracycline antibiotics-sulfonamides antibiotics was between 0.8 and 1.2, indicating the additive effect between the three. Chen et al. studied the combined toxicity of new aromatic embroidery and green disinfection byproducts on Qinghai Lake Bacillus, and the results

showed that the binary mixture showed synergistic effects at 50% effect concentration (EC50), 20% effect concentration (EC20) and 10% effect concentration (EC10) levels. The effective concentration level and concentration ratio are the main factors affecting the synergistic effect. Independent action, also known as reaction addition, means that the toxicity between the components of the mixture is independent, they have different toxic mechanisms and different biological targets, so their toxicity will not affect each other. As long as all components in a mixture of pollutants are at sub-toxic levels, the whole mixture can be considered to be non-toxic. For the purposes of risk assessment, if there is evidence that the toxicity of the mixture is not additive, it is usually assumed that the mixture has an independent effect.

## 2. Interaction

In some cases, there are interactions between the components of the mixture that result in the total toxicity being stronger or weaker than predicted. Usually enhancement or synergy occurs when one chemical in the mixture changes the way another chemical is metabolized. At present, it has been found that there are two main ways for a substance to change the metabolism of another substance. First, the first substance induces the expression of the enzyme involved in the activation of the second substance, so that the second substance is activated faster; The second is that one substance prevents the degradation of another substance by inhibiting the expression of enzymes involved in detoxification. Takahiro et al.] studied the synergistic inhibition experiment of macrolide antibiotics and ketoconazole on *selenophylla*, and the results showed that the two could produce strong synergistic effects at different proportions of concentrations, enhancing the growth inhibition effect on *selenophylla*. The mechanism of action may be because ketoconazole inhibits the metabolism of macrolide antibiotics by *selenophylla* as a CYP inhibitor. Michele et al. studied the inhibitory strength and synergistic potential of different azole fungicides against *Daphnia* zoea and insect larvae, and the results showed that the azole fungicides enhanced the toxicity of alpha-cypermethrin in *daphnia* zoea and inhibited cytochrome P450 activity to varying degrees.

Another case of interaction is called antagonism. When the toxicity of a mixture is less than predicted using the concentration addition model, antagonism is considered to be present in the mixture. Antagonism may be due to the interaction between the components of the mixture, competition for the target of action, or changes in metabolism. Marcelo et al. studied the single and combined toxicity of three common antibiotics (amoxicillin, Enrofloxacin, and oxytetracycline) on *Lemna mino*, a duckweed plant. The results showed that oxytetracycline inhibited plant growth and cell division, and the other two antibiotics showed no toxic effect at tested concentrations. However, the combined toxicity results showed that the toxicity of oxytetracycline was inhibited in the presence of amoxicillin or enrofloxacin or both.

## Acknowledgments

This work was supported by the Scientific Research Item of Shaanxi Provincial Land Engineering Construction Group (2021WHZ0092).

## References

- [1] H., Dooley, M., et al. Effect of azole fungicide mixtures, alternations and dose on azole sensitivity in the wheat pathogen *Zymoseptoria tritici*[J]. *Plant Pathology*, 2015.65(1):124-136.
- [2] Giavini E, Menegola E. Are azole fungicides a teratogenic risk for human conceptus[J]. *Toxicology Letters*, 2010, 198(2): 106-111.
- [3] Brauer V S, Rezende C P, Pessoni A M, et al. Antifungal Agents in Agriculture: Friends and Foes of Public Health[J]. *Biomolecules*, 2019, 9(10): 521-534.

- [4] Escher B I, Baumgartner R, Koller M, et al. Environmental toxicology and risk assessment of pharmaceuticals from hospital wastewater[J]. *Water Research*, 2011, 45(1): 75-92.
- [5] Thomas K V, Hilton M J. The occurrence of selected human pharmaceutical compounds in UK estuaries[J]. *Marine Pollution Bulletin*, 2004, 49(5/6): 436-444.
- [6] Hof H. Critical Annotations to the Use of Azole Antifungals for Plant Protection[J]. *Antimicrobial Agents & Chemotherapy*, 2001, 45(11): 87-90.