WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 19, 347-352. Review Article ISSN 2277–7105

TOXICOKINETIC STUDY OF FUNGICIDES

Kanchan Choudhary*[1] and Dr. S. S. Sisodia[2]

*[1]PG Scholar, Department of Pharmacology, Bhupal Nobles' College of Pharmacy,Udaipur, Rajasthan.

*Professor and Head of Pharmacology Department, Bhupal Nobles' College of Pharmacy, Udaipur, Rajasthan.

Article Received on
14 September 2023,

Revised on 04 Oct. 2023,
Accepted on 25 Oct. 2023

DOI: 10.20959/wjpr202319-30091

***Corresponding Author**
Kanchan Choudhary
PG Scholar, Department of Pharmacology, Bhupal Nobles' College of Pharmacy, Udaipur, Rajasthan.

ABSTRACT

Toxicokinetic studies provide important data on the amount of toxicant delivered to a target as well as species-specific metabolism. From many years, fungicides are used to protect plants from fungal spores or fungal attack. Exposure of fungicides on agricultural products causes various toxicants effects to human's health on consumption of this product. The toxicokinetic data of these fungicides remains unclear. So, it's important to study the toxicokinetic of fungicides.

KEYWORDS: Toxicokinetic, Fungicides, Toxicants, exposure, Risk assessment, Endocrine disruptor.

INTRODUCTION

Fungicides are the biocidal chemical compounds or biological organisms/substances that are used to eradicate parasitic fungi or their spores[1] from plants and other agricultural products. Fungicides have been known to cause irritation of eyes and skin. Although fungicides causes low acute toxicity but its prolonged exposure can result in severe adverse effect. Coughing, throat irritation and squeezing can be seen when spray mist or dust is inhaled from the pesticides. The toxicity of the product and the concentration of product exposure are responsible for the health risk assessment with fungicides. (Hazard=Toxicity x Exposure) i.e. the product can even if harmful if it has low toxicity but a high exposure level. It has been reported that fungicides are known to cause disruption in endocrine cells which thereby affects the reproduction and developmental process. Fungicides can lead to endocrine disruption even in low concentration and thereby affects the reproduction and developmental process; they can be toxic to endocrine cells. Some fungicides have been reported to act as

reproductive endocrine disruptor like fenarimol which act as antiandrogen by inhibiting aromatization of testosterone to 17β-estradiol within the brain and hence causes infertility in male rats[2] whereas 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is known to cause inhibition of testosterone synthesis in male adult rats.[3]

The data obtained from toxicity study of compound alone isn't sufficient for the determination of the exposure risk assessment to humans. So, it is necessary to determine the toxicokinetic of compound and this data will provide the ability to interpret exposure assessments and reduce uncertainty in risk assessments.

Toxicokinetics

Toxicokinetics deals with the study of absorption, distribution, biotransformation & excretion of chemicals in the organism. It includes the rate at which a chemical enters the body as well as its fate inside the body, such as its metabolism and elimination once it is within. The substance concentration over time on and in the body is described by toxicokinetics.[4] It measures the level of exposure of compound in plasma samples by determining its concentration in plasma with respect to time.[5] Toxicokinetic studies provide important data on the amount of toxicant delivered to a target as well as species-specific metabolism. The toxicokinetics method is one of the potential tools for assessing the risks to human health. It plays crucial role in evaluation the toxicity of chemicals and contaminants.[6] From *in-vitro* to *in-vivo* studies, from chemical exposure to systemic dose in risk assessment, toxicokinetics serves as a bridge for extrapolating chemical concentrations across different species.[7] The vast majority of animal toxicity data cannot be extrapolated to ensure human safety without the knowledge of kinetics, hence toxicokinetics-related investigations are important for assessing chemical safety.[8] An important parameter in toxicokinetics is the variation of blood or plasma concentration of the toxicant with time. With the help of toxicokinetics principles one can determine the chemical concentrations at which toxic effects are produced, the rate and extent at which ADME process occurs in body and the duration of action and also the extent of drug-drug interaction.[9] Understanding kinetic principles is crucial as they demonstrate the connection between a chemical's concentration in the body and its toxicological effects.[10] Important data on the "rate, extent and duration of systemic exposure across dose, species, strains, gender, and life stages within a toxicology programme" are generated through toxicokinetics studies. Toxicokinetics data can be collected from various species like rat, mouse, rabbit by giving chemical through different route like gavage, dietary,

dermal.[11]

Movement of xenobiotic from site of administration to systemic circulation is termed as absorption. Absorption of toxicant chemicals can occur through lung inhalation, skin and through oral route.[12] The chemical's solubility profile, its size, concentrations of chemicals and external factors like presence of hydrolytic enzymes, presence of food and surface area of absorption influences the rate of absorption of chemical.[4] The absorbed toxicant is distribution from the bloodstream to body tissues and organs. Distribution behaviour of toxicant in body tissues can be studied by determining the volume of distribution of chemical in body. For risk assessment purpose, volume of distribution is an important parameter for assessing the biological uptake of toxicants.[12] Toxicants consumed undergo a variety of chemical transformations with enzymes generated by human cells within the liver. Harmful and less toxic metabolites are produced upon metabolism of chemical by Phase I and Phase II reactions. Phase I reaction involves oxidation, reduction and hydrolysis of chemical whereas in phase II, the chemical in combination with an endogenous substance forms various conjugates like glucoronide, methylated and amino acid conjugates. Animal tissues and human tissues can be used to obtain information upon the species differences on metabolism of chemical.[11] Metabolites are excreted through kidney and/or liver through excretion process. Excretion is the process by which a chemical is removed from the body to protect it from the impacts of harmful substances.

Parameters of toxicokinetic

Systemic exposure parameters such as AUC, t, C-curve is a quantifiable result of the ADME processes and is the deciding factor for the potential systemic adverse health effects and thereby playing major role in developing toxicity studies.[5] Tmax (the time taken to reach Cmax), Cmax (the maximum concentration recorded) AUC Area Under the Curve (a measure of the exposure to the drug) are the important assessment for determining exposure.[13]

- Peak plasma concentration **(Cmax)**: The point at which there is maximum concentration of chemical in plasma is known as peak plasma concentration. It is represented in units of weight/volume.
- **Time of peak concentration (Tmax):** Time taken by the chemical to reach the peak concentration in plasma is known as Tmax. It is expressed in hours and helps in determining the rate of absorption.
- **Area under curve (AUC):** The AUC determines the extent of exposure of chemical. It is

expressed in units of weight/volume/time.

- **Plasma half-life:** The time taken by the plasma concentration of chemical to reduced to half of its original value. Elimination rate of chemical can be predicted by knowing the plasma half –life of chemical. Elimination rate of chemical is slow when the half- life of chemical is long and when the half-life of chemical is short the elimination rateis fast.

$$T_{1/2} = 0.693 \times \frac{V}{CL}$$

- **Clearance:** The body's ability to eliminate the chemical is known as clearance or it may be defined as complete removal of chemical from the volume of plasma per unit time. It is expressed in units of volume/time.

CL = Rate of elimination/C Where C is the plasma concentration

- **Volume of distribution:** The volume of distribution relates the amount of drug in the body to the concentration of drug in the plasma.

Vd= amount of drug in the body/ Plasma drug concentration

Toxicokinetic study for risk assessment of Fungicides

Toxicokinetics studies are required for accurate risk assessment of chemical. Parameters involved in risk assessment are hazard identification, dose response assessment, exposure assessment and risk characterization. These parameters facilitate accurate predictions of actual risk.

Hazard identification, the first step in risk assessment includes identifying toxicants that are harmful to human, determining the environmental concentrations at which they are present, describing the particular toxicities (such as neurotoxicity and carcinogenicity) that the substances under consideration can cause, and assessing the circumstances in which these toxicities may manifest in exposed people.

Quantitative relationship is determined between the dosage and the toxic reaction in Dose-response assessment. An evaluation of response variations, such as differences in susceptibility between young and old people, may be a part of this stage. The route of exposure is identified in Exposure assessment. The duration and the dose level of toxicant can be assessed through blood and urine samples. Information is gathered from all the parameters and the total risk of exposure to a chemical is characterized in Risk characterization.[14]

CONCLUSIONS

Fungicides being used on agricultural plants and products cause some toxic effects to humans on exposure of the chemical. These toxic effects sometimes can be severe and may damage organ cells, as it was reported earlier that fungicides causes disruption of endocrine cells and hence affects reproductive system. To understand these toxic effects of fungicide, toxicokinetic study serve as an essential tool. Data obtain on toxicokinetic study will help in assessing the risk associated with the human health by studying the Phase I and Phase II metabolism. Toxicokinetic study can be easily carried on liver microsomes, tissues and cells, etc hence implementing 3R Principle.

REFERENCES

1. Compare the Difference Between Similar Terms [Internet]. 2022 [cited 2023 May 18]. What is the Difference Between Fungicides and Pesticides. Available from: https://www.differencebetween.com/what-is-the-difference-between-fungicides-and-pesticides/
2. Andersen HR, Vinggaard AM, Rasmussen TH, Gjermandsen IM, Bonefeld-JørgensenEC. Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity in vitro. Toxicol Appl Pharmacol, 2002 Feb 15; 179(1): 1–12.
3. Gupta P. Chapter 37. Herbicides and Fungicides. In 2017.
4. Heringa MB. Integration of toxicokinetics and toxicodynamics.
5. Ploemen JP, Kramer H, Krajnc E, Martin I. The Use of Toxicokinetic Data in Preclinical Safety Assessment: A Toxicologic Pathologist Perspective. Toxicol Pathol, 2007 Feb 1; 35: 836–9.
6. Sandhya. Toxicokinetics an essential tool in drug discovery: A review article. IP Int J Compr Adv Pharmacol, 2021 May 28; 6: 5–9.
7. Dixit R, Riviere J, Krishnan K, Andersen ME. Toxicokinetics and physiologically based toxicokinetics in toxicology and risk assessment. J Toxicol Environ Health B Crit Rev, 2003; 6(1): 1–40.
8. Dixit R, Riviere J, Krishnan K, Andersen ME. Toxicokinetics and physiologically based toxicokinetics in toxicology and risk assessment. J Toxicol Environ Health B Crit Rev, 2003; 6(1): 1–40.
9. Gupta PK. Principles and basic concepts of toxicokinetics. In, 2016; p. 87–107.
10. Gupta PK. Principles and basic concepts of toxicokinetics. In, 2016; p. 87–107.
11. Terry C, Hays S, McCoy AT, McFadden LG, Aggarwal M, Rasoulpour RJ, et al.

Implementing a framework for integrating toxicokinetics into human health risk assessment for agrochemicals. Regul Toxicol Pharmacol RTP, 2016 Mar; 75: 89–104.

12. Burcham P. Toxicokinetics: The Behaviour of Chemicals in the Body. In, 2014; p. 53–90.
13. Dixit R, Riviere J, Krishnan K, Andersen ME. Toxicokinetics and physiologically based toxicokinetics in toxicology and risk assessment. J Toxicol Environ Health B Crit Rev, 2003; 6(1): 1–40.
14. Toxicology NRC (US) C on A of TT to P. Overview of Risk Assessment. In: Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment [Internet]. National Academies Press (US); 2007 [cited 2023 Oct 9]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK10201/