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Implementing a framework for integrating toxicokinetics into human health risk assessment for agrochemicals

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ABSTRACT

A strategic and comprehensive program in which toxicokinetic (TK) measurements are made for all agrochemicals undergoing toxicity testing (both new compounds and compounds already registered for use) is described. This approach provides the data to more accurately assess the toxicokinetics of agrochemicals and their metabolites in laboratory animals and humans. Having this knowledge provides the ability to conduct more insightful toxicity studies, refine and interpret exposure assessments and reduce uncertainty in risk assessments. By developing a better understanding of TK across species, including humans via in vitro metabolism studies, any differences across species in TK can be identified early and the most relevant species can be selected for toxicity tests. It also provides the ability to identify any non-linearities in TK as a function of dose, which in turn can be used to identify a kinetically derived maximum dose (KMD) and avoid dosing inappropriately outside of the kinetic linear range. Measuring TK in key life stages also helps to identify changes in ADME parameters from in utero to adults. A robust TK database can also be used to set internal concentration based "Reference Concentrations" and Biomonitoring Equivalents (BE), and support selection of Chemical Specific Adjustment Factors (CSAF). All of these factors support the reduction of uncertainty throughout the entire risk assessment process. This paper outlines how a TK research strategy can be integrated into new agrochemical toxicity testing programs, together with a proposed Framework for future use.

1. Introduction

Toxicokinetics (the study of how the body absorbs, distributes, metabolizes, and excretes chemicals and drugs) has played a central role in the safety assessment of pharmaceuticals for decades (ICH, 1995) and it is widely acknowledged that this type of data can also provide valuable information for chemical and agrochemical risk assessment. However, historically, little toxicokinetic (TK) data has been routinely generated in toxicology studies within the agrochemical industry. This is because traditional toxicology studies for this sector have been conducted using the 'Maximum Tolerated Dose (MTD)' approach, which is an external dose metric. Risk assessments are usually also conducted on the basis of external exposure: consumer exposures are generally estimated on the basis of residue levels in food (e.g., mg/kg food commodity) together with food consumption data (e.g., kg commodity eaten/day); operator/worker and bystander exposures are generally estimated based upon predictive models of potential dermal and inhalation exposure with potential for hand to mouth exposures (Fig. 1A). However, evolving methods in analytical technology, toxicology and in exposure assessment are shifting the chemical risk assessment process towards a focus on internal dose and early biological effects (Fig. 1B). The shift towards reliance on internal dose and indicators of early biological effects presents an opportunity to reduce uncertainties in the risk assessment process by shrinking the degree of extrapolation in the dose–response continuum.

Likewise, there is a shift to the use of biomonitoring data to assess exposures to chemicals and agrochemicals amongst the human population (Sexton et al., 2004) and this shift to measuring exposures via internal dose metrics requires a greater understanding of TK to be able to interpret in a risk assessment context

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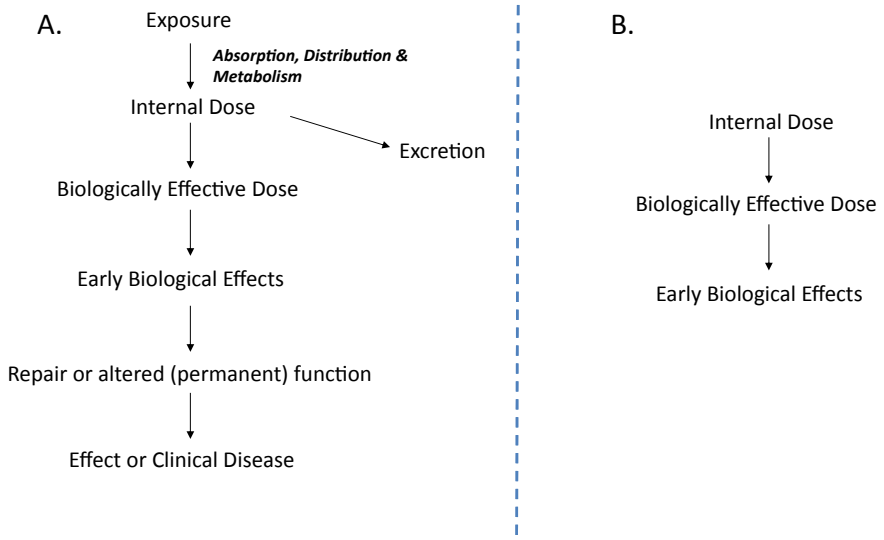

Fig. 1. Comparison of the old (A: current) and new (B: internal dose based) risk assessment paradigms. The old risk assessment paradigm involves deriving a dose–response relationship in which dose is defined as external dose (mg/kg/d or ppm in air) and response is a disease incidence. The new risk assessment paradigm involves deriving a dose–response relationship in which dose is defined as internal dose (concentration of parent compound or active metabolite in blood – ng/L) and response is defined using a precursor response event identified from an in vitro assay.

(Hays et al., 2012). Shifting towards the use of TK in toxicity studies and dose–response assessments, along with the use of biomonitoring for exposure assessment, has the potential to substantially reduce the uncertainty in agrochemical risk assessments (Hays et al., 2012).

Assessment of internal dose in hazard and dose–response assessment is occurring through the use of directly measured internal dose metrics in animal studies, incorporation of pharmacokinetic data and models in the dose–response assessment process, and increasingly, through reliance on in vitro toxicological methods. Integration of TK analysis into all toxicity studies follows principles from the International Life Sciences Institute/Health and Environmental Sciences Institute – Agricultural Chemical Safety Assessment Technical Committee (ILSI/HESI-ACSA). The ACSA project included industry, government, academia and non-governmental organization (NGO) scientists. Their 'base set' of principles includes the use of TK to help guide an integrated approach to evaluating systemic toxicity, life-stage effects and dose level selection (Barton et al., 2006; Carmichael et al., 2006; Cooper et al., 2006).

Regulatory initiatives are now advancing this move towards collecting TK data (Table 1). An example is the new EU Regulation (1107/2009 EC) for agrochemicals, which explains the objectives of obtaining TK data as: to describe the systemic exposure achieved in animals and its relationship to the dose levels and the time course of the toxicity studies; to relate the achieved exposure in toxicity studies to toxicological findings and contribute to the assessment of the relevance of these findings to human health, with a particular regard to vulnerable groups; to support the design of a toxicity study (choice of species, treatment regimen, selection of dose levels) with respect to kinetics and metabolism; and to provide information which, in relation to the findings of toxicity studies, contributes to the design of supplementary toxicity studies (Annex to SANCO/11802/2010 Rev. 0 (POOL/E3/2010/11802/11802R0-EN.doc)).

Integrated TK in toxicity studies has become routine at Dow AgroSciences since 2006. The approach is described in detail in Saghir et al., 2012, where it is concluded that integrating TK measurements into the full range of guideline studies required for a new agrochemical (without using additional satellite animals) generates important information on the "rate, extent and duration of systemic exposure across dose, species, strains, gender and life stages within a toxicology program". This involves more than simply measuring internal dose (peak, average and area under the curve of blood concentration) associated with test dosing regimes, but also includes characterizing the rates and extent of absorption, distribution, metabolism and excretion (ADME) of parent compounds and their metabolites. This additional information provides valuable insights towards understanding species differences in ADME and often with respect to mode of action (MOA).

This manuscript outlines how this additional information helps improve risk assessments for agrochemicals with a particular focus on how this initiative has become standard practice within Dow AgroSciences (Fig. 2). Case studies are provided for numerous applications of TK in agrochemical risk assessment highlighting the value of this new paradigm. An integrated approach to utilizing TK is proposed for risk assessments of agrochemicals and involves:

- Characterizing TK in concert with conducting toxicology studies
- Measuring internal reference concentrations
- Deriving risk assessments based on internal dosimetry (Biomonitoring Equivalents)
- Biomonitoring for exposures to agrochemicals
- Conducting risk assessments using Biomonitoring Equivalents and biomonitoring data.

2. Hazard identification

Hazard identification is primarily the process of identifying the types of adverse effects that can be caused by exposure to a compound. Secondary, but equally important, objectives should be identification of the mode of action (MOA) for each type of effect and/or identification of the dose metrics most closely related to the observed effects. Both primary and secondary objectives can be better achieved by developing an understanding of TK in the studies used to identify the adverse effects. For agrochemicals, often the proximate toxicant is known, and most often it is the