Modelling human pesticide kinetics based on oral and dermal exposure data derived in a controlled setting

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Primary Objective: To collect human data of the kinetics of pesticides after a single oral or dermal dose to create a physiology-base pharmacokinetic (PBK) model. Secondary Objective(s): The models that will be parameterised with these data will...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON53236

Source
ToetsingOnline

Brief title
Human kinetics of pesticides

Condition

- Other condition

Synonym
N/A

Health condition

Er wordt geen aandoening onderzocht omdat het om een kinetiek studie gaat

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universiteit Nijmegen
Source(s) of monetary or material Support: EU

Intervention

Keyword: dermal, kinetics, modelling, pesticides

Outcome measures

Primary outcome

Concentration of parent compound(s) and/or its metabolite(s) in blood, urine,

faeces and skin after a single oral or dermal exposure.

Secondary outcome

• Relative metabolite conversion factors/recovery

• Excretion pattern of parent/metabolite excretion over 96h after exposure

• Pesticide residue levels on and in skin after dermal exposure

• Microbiome of the stool after pesticide exposure

Study description

Background summary

The current research contributes to the Sustainable Plant Protection Transition (SPRINT) Project (see https://sprint-h2020.eu/) in the EU Horizon Programme and is part of a work package on Exposure Assessment. Plant protection products (PPP, in this protocol referred to as *pesticides*) are primarily taken up as residues from the diet. In addition, there is a contribution from so-called non-dietary sources which may vary in the general population, depending on sub-group (e.g. applicators such as farmers or *neighbours* who live close to agricultural land). Dietary exposure is by ingestion and non-dietary exposure may be related to inhalation (e.g. spray drift) or dermal absorption (direct skin contact) at relatively high levels during application or at much lower levels in a home next to an agricultural field where pesticides are applied (so-called bystander exposure).

In the SPRINT project we study exposure in three subgroups from the general population: farmers, neighbours and consumers. The main study method will be by human biological monitoring (HBM). For interpretation of the HBM results understanding the kinetic process of uptake, distribution, metabolism and excretion (ADME) is vital. In the current protocol we propose to do a study at low dose in human volunteers to describe these kinetic parameters that will later be used for physiology-based biokinetic (PBK) modelling to support interpretation of the HBM findings and calculate the dose in target tissues.

The collection of HBM data in the population-based observational study (HBM-survey) was already completed according to an approved study protocol registered under dossier number: 2020-7248 and NL-number: NL76296.091.20 (1). Based on this study outcome we were able to pre-select pesticides for the current human volunteer study according to occurrence and hazard, using the hazard quotient (HQ) approach to identify the highest priority pesticides by ranking from high to low HQ (2).

Humans are exposed to pesticides through several routes. In the general population, pesticide residues on food cause dietary intake of pesticides. In addition, non-dietary exposure occurs through household use of pesticides, e.g. use of insecticide sprays indoors in or around a private home, potentially leading to inhalation or dermal absorption. In addition, farmers are exposed in an occupational setting during application of pesticides to crops. This multi-route exposure, combined with a lack of knowledge on toxicokinetics, makes it difficult to estimate whether the ADI for pesticides is exceeded. Improved understanding of pesticide kinetics will aid in the determination of human exposure in the general population.

Understanding human pesticide kinetics is crucial for transitioning towards more sustainable plant protection. The EU has established the Farm-to-Fork strategy within the European Green Deal, aiming to make food systems fair, healthy and environmentally friendly. The Commission aims at achieving a 50% reduction in the overall use and risk of chemical pesticides in 2030. Increased understanding of human kinetics will aid in the transitioning towards safer harvest protection.
According to EU regulations the pre-market evaluation of a new PPP does not require a human volunteer study aimed at characterisation of the kinetics of uptake, distribution, metabolism and excretion in humans. For the proposed pesticides there is currently not sufficient knowledge on kinetics in humans to be able to interpret the results of our HBM survey with respect to the toxicokinetics.

Several similar human toxicokinetic models already exist for pesticides, such as that of Auton et al. for dermal exposure or Oerlemans et al. for tebuconazole(3, 4). However, using human kinetic data to create a PBK model to predict intake of specific pesticides is not yet available for most pesticides.
In addition, the development of a generic human PBK model for pesticides

requires empirical data on multiple pesticides to verify that the PBK model works for a broad chemical spectrum.

The study will add new information on the kinetics of selected pesticides after oral and dermal exposure, and to what extent differences between and within males and females can be expected. For several pesticides some toxicokinetic data has been published based on human (volunteer) studies. This is summarized in section 6.3. This information will help to aid the understanding pesticide kinetics, and contribute to the development of computational models to predict oral or dermal exposure to pesticides in the general population.

Study objective

Primary Objective:
To collect human data of the kinetics of pesticides after a single oral or dermal dose to create a physiology-base pharmacokinetic (PBK) model.

Secondary Objective(s):
The models that will be parameterised with these data will also be used to:
a. perform calculations of the dose of the parent and its metabolites in internal organs for follow-up testing of specific organ toxicity;
b. perform back-calculations (reverse-dosimetry) related exposure scenarios observed in real life to evaluate how HBM findings are related to currently established safe values.

Study design

The design is a laboratory-based controlled kinetic study. Study subjects (see section 4) will be their own reference as we will start to collect samples of body fluids before the pesticide of interest will be administered. All study participants will receive the same dose and samples of body fluids will be collected over time. A similar study design has been used in our research group by Oerlemans et al. to study kinetics of tebuconazole in healthy volunteers (3).

Study participants will be asked to participate in two single exposure scenarios (oral and skin absorption) separated by a wash-out period of at least one week to avoid carry-over.
Exposure at baseline will be verified before the administration of the pesticide of interest. Study subjects will be advised to avoid foods and beverages known to contain high residue levels of the pesticide of interest, and document this prior to their visit. During the visit the research department food and beverages will be provided.

The dose will not exceed the ADI for that pesticide. One session will be dedicated to oral administration and the other session involves dermal exposure of the substance of interest dissolved in a volatile organic solvent (ethanol)

that will evaporate, leaving a known topical dose on the skin surface. For reasons of comparison, each volunteer will be exposed to the same substance orally and dermally.

Intervention

Oral exposure to a pesticide
Dermal exposure to a pesticide

Study burden and risks

Participants will not experience any benefits from taking the investigational product used in this study.

The potential risks of short-term exposure have been summarized in the International Chemical Safety Cards (ICSCs) for the following pesticides:
ICSC 0859 - LAMBDA-CYHALOTHRIN (ilo.org)
ICSC 0246 - CYPERMETHRIN (ilo.org)
ICSC 0247 - DELTAMETHRIN (ilo.org)
ICSC 0160 - GLYPHOSATE (ilo.org)
ICSC 1347 - PIPERONYL BUTOXIDE (ilo.org)
ICSC 1303 - IMAZALIL (ilo.org)
ICSC 0033 - 2,4-D (ilo.org)

The risks of other pesticides have been summarized by Haz-Map:
Tebuconazole - Hazardous Agents | Haz-Map
Acetamiprid - Hazardous Agents | Haz-Map
Cyprodinil - Hazardous Agents | Haz-Map
Bromoxynil - Hazardous Agents | Haz-Map

Risks of fluopyram exposure has been summarized by the Ctgb (the Netherlands):
Fluopyram: Ctgb Toelating: Luna Sensation

Information on the hazard of fluazifop-P can be found on the manufacturers label: 00394108-001-002.pdf (nufarm.com)

(see also: pg. 26 and 27 in the study protocol

Contacts

Public
Radboud Universiteit Nijmegen

Heyendaalseweg 135

Nijmegen 6525 AJ
NL
Scientific
Radboud Universiteit Nijmegen

Heyendaalseweg 135
Nijmegen 6525 AJ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Good general health i.e. no use of prescribed or OTC medication (except oral contraceptives) that could change the kinetics of pesticides during the study period ;
- Age between 18 and 55 years;
- BMI between 20 and 25;
- Alcohol consumption (on average) less than two standard glasses a day;

Exclusion criteria

- People using OTC or prescribed medication that induces or decreases CYP-enzyme activity, or could otherwise influence metabolism.
- Pregnancy or (partner) intention to become pregnant during the study period;
- Lactating mothers;
- Skin disorders, e.g. sensitivity to natural or synthetic pyrethroids, atopic eczema, psoriasis, or other chronic skin diseases that causes hyperkeratosis;
- Skin abnormalities on the non-dominant forearm, e.g. scars and injuries;
- Smoking;
- Any direct contact with pesticides (e.g. work-related).

- Participation in other studies

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2023
Enrollment:	78
Type:	Anticipated

Ethics review

Approved WMO Date:	02-10-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-11-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL84110.091.23