3. Pesticide exposure

3.1 Why evaluate pesticide exposure?

Exposure to pesticides is strongly associated with acute and chronic health effects in humans. However, total elimination of the use of pesticides is not possible even though it would be preferable (see fact sheet 1: Introduction to pesticides). In order to prevent future acute and chronic pesticide poisonings it is essential to be able to understand how salesmen, farmers and consumers are getting exposed to pesticides, how pesticides enter the body, in which ways pesticides affect the organ systems in the body, and how pesticides are excreted.

Risk assessment is a tool that is used to calculate the adverse effects of an individual's current or future exposure to pesticides (1). The health risk depends on the toxicity of the pesticide and the amount of exposure to the pesticide. Furthermore in order to expand knowledge on the relationship between different pesticides and health hazards it is necessary to conduct more epidemiological studies among humans. Therefore knowledge on how to collect data of exposure is also essential.

3.2 Routes of exposure

There are three primary ways by which pesticides can enter the human body. These include inhalation, oral ingestion and skin absorption (2). In addition multiple exposure with several toxic substances that enter the body through different routes of exposure is also possible (2).

- Oral ingestion: can occur from the consumption of contaminated food or water, the use of contaminated eating tools, contaminated hands, or individuals drinking pesticides by accident or in order to commit suicide (3).
- Inhalation: the vapors of pesticides or aerosol droplets smaller than 5 μm in diameter are absorbed through the lungs. Inhalation can occur from breathing vapors while spraying or as bystanders to a field being sprayed (3).
- Skin absorption: occurs from skin contact with pesticides, for example by handling sprayers or pesticide containers. Absorption resulting from skin exposure is the most important route of uptake for exposed workers (3), and it is considered to be the most frequent means of pesticide exposure (4).

Exposure from mother to child: the fetus can be exposed through the placenta or a newborn by drinking breast milk contaminated by pesticides (5).

For further reading on assessment of pesticide exposure:

- Groups in risk of getting exposed see fact sheet 2: Health effects of pesticides
- IPCS: International Programme on Chemical Safety, Environmental health criteria 214, Human exposure assessment: http://www.inchem.org/documents/ehc/ehc/ehc214.htm
- Sheldon, Lisa S. Exposure Framework in Krieger, Robert: Hayes handbook of pesticide toxicology, Academic Press, 2010

3.3 Biological reactions

Knowing the biological reactions provoked by pesticide exposure is important in order to understand the poisonous effects of pesticides. The biological reactions are processes of absorption, metabolism and excretion of pesticides also referred to as toxicokinetics (13). In general terms, how does pesticides enter the body, where does it go and what happens to it?

3.3.1 Absorption

Absorption is defined as the translocation of the pesticide from an external source of exposure to the bloodstream (6). A chemical is absorbed when it crosses the small intestine, the alveoli in the lungs or the epithal layers in the skin:

- Gatrointestinal absorption: chemicals are usually absorbed into the bloodstream from the gastrointestinal tract by passive diffusion. They enter the portal circulation and are delivered directly to the liver where they may be metabolized before reaching the systemic circulation. The toxic substance or its metabolites are excreted by the bile to the intestine, where it can possibly be absorbed again. Some highly lipophlic (fat-soluble) substances such as organochlorine pesticides are absorbed into the lymphatic system by active or facilitated transport similar to the transport of nutritional fats (6).
- Absorption from the respiratory tract: gases and vapors may be absorbed through the respiratory tract depending on their physiochemical properties and the physiology of the region. They diffuse across cell membranes in the direction of the concentration gradient until equilibrium is established. Hydrophilic (water-soluble) and reactive gases and vapors tend to be absorbed in the mucus layer of the upper respiratory tract, whereas lipophlic and nonreactive gases and vapors are absorbed from the deeper regions of the respiratory tract. When toxic gases and vapors have been deposited in the respiratory tract they can enter the blood or the gastro-intestinal canal (6).
- Skin absorption: toxic substances are absorbed through the skin by passive diffusion. Hydrophilic substances are absorbed through sweat glands and hair follicles, and lipophilic substances are absorbed through the top layer (stratum corneum) of the skin. The rate of

absorption of hydrophilic substances is dependent on the blood-flow, whereas the rate of absorption of lipophlic substances is determined by diffusion. Many lipophilic pesticides enter the dermis and epidermis in the skin and do not necessarily traverse the full thickness of the dermis. There are various factors that can influence absorption of pesticides through the skin: absorption through different body parts, pesticide formulation and mixtures as well as environmental factors such as temperature and humidity. For example changes in air temperature can alter lipid fluidity in the lipids of the stratum corneum, and high relative humidity can increase skin hydration (6).

3.3.2 Metabolism

Metabolism of toxic substances is often referred to as biotransformation (7). The liver is the primary site of pesticide biotransformation. The purpose of biotransformation is detoxification through the excretion of hydrophilic products. Therefore only lipophilic substances undergo two phases of biotransformation to become more hydrophilic:

- Phase I: OH-. SH-, or NH_2-group is added to the lipophilic toxic substance. This process occurs by oxidation, reduction or hydrolysis. By oxidation the toxic substance deliver electrons, and by reduction the toxic substance absorbs electrons. Enzymes usually catalyze the reactions. Cytochrom P450 enzymes have a crucial role in catalyzing oxidation processes. Hydrolysis is the cleavage of a chemical by the uptake of water (7).
- Phase II: hydrophilic group (usually Glutathion-S-transferase) is added to the toxic substance in order to make the toxic substance become hydrophilic (7).

There are different physiological factors that affect biotransformation. These include developmental effects, gender differences, genetic factors, tolerance and resistance (7). Although the purpose of biotransformation is detoxification, there are exceptions where biotransformation results in a more toxic product. Such reactions are generally referred to as activation reactions (7).

For further reading on absorption and metabolism:

- Absorption: Baynes, Ronald E. and Riviere, Jim E.: Absorption in Krieger, Robert: Hayes handbook of pesticide toxicology, Academic Press, 2010
- Metabolism: Hodgson, Ernest: Metabolism of pesticides in Krieger, Robert: Hayes handbook of pesticide toxicology, Academic Press, 2010

3.3.3 Excretion

Hydrophilic substances are primarily eliminated by the kidneys (renal excretion) or the liver (fecal excretion). The liver handles larger molecules than the kidneys. Lipophilic substances must

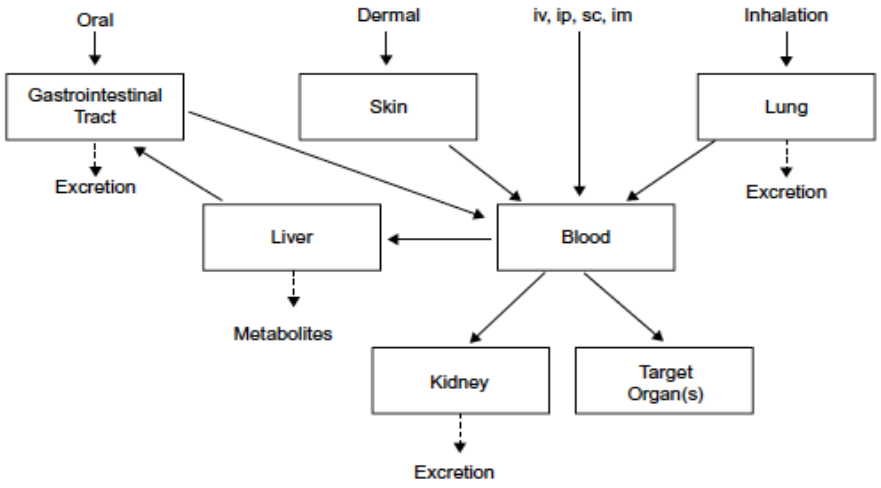
undergo phase I and II of biotransformation to become more hydrophilic before they can be eliminated through renal or fecal excretion (8).

- Renal excretion: in the kidneys blood is filtrated across the basal membrane. The excretion of toxic substances through the kidneys therefore depends on the ability of toxic substances to bind to plasma proteins and their physical-chemical properties (8).
- Fecal excretion: toxic substances can be excreted from the liver to the intestine by the bile. Highly hydrophilic metabolites will usually be excreted through feces (8).
- Exhalation: vapors and aerosols can be excreted through exhalation dependent on vapor pressure, the solubility of the substance in blood and its binding to plasma proteins (8).

3.3.4 Bioaccumulation

Highly lipophilic substances that don't undergo biotransformation may be excreted as the parent chemical by a number of alternative routes or it may bioaccumulate in adipose tissue (8, 9). They will tend to build up in the body with increasing age. For example lipophilic organochlorines are sequestered in lipid rich tissues in all organisms. They can then be passed on to the next generation across the placenta and in the breast milk (9).

Figure 3.1: Representation of the absorption, distribution, metabolism, and excretion of toxicants (6).



For further reading on excretion and bioaccumulation:

- Excretion: Hodgson, Ernest: Pesticide excretion in Krieger, Robert: Hayes handbook of pesticide toxicology, Academic Press, 2010
- Bioaccumulation: Franke C, Studinger G, Berger G, Böhling S, Bruckmann U, Cohors-Fressenborg D, Jöhncke U (1994) The assessment of bioaccumulation. Chemosphere 29: 1501-1514.

3.4 How to calculate health risk?

The health risk of using pesticides depends on the toxicity of the pesticide used, the concentration and amount of pesticide applied, how often the pesticide is applied and who or what has contact with the pesticide. The risk of adverse effects due to pesticide poisoning can according to the Environmental Protection Agency (EPA) be expressed as (10):

$$\text{Risk} = \text{Exposure} \times \text{Toxicity}$$

1. The toxicity of a pesticide: pesticides are classified in groups from low to high toxicity (see fact sheet 1: Introduction). The toxicity depends on the amount of active ingredient in the pesticide formulation and the chemical class of the pesticide. The active ingredient is the chemical component in the pesticide that controls the pest (11). Because the health risk depends both on toxicity and the amount of exposure, even pesticides that are low in toxicity can be hazardous if the exposure is high.

2. Pesticide exposure: the amount of exposure to the pesticide is determined by the dose, the frequency of exposure, the route of exposure and the individual sensibility to the particular pesticide (12).

3.5 How to assess adverse effects of pesticide exposure?

The EPA has developed a science-based approach to assess potential risks of chemicals to human health. It consists of four key activities (10):

1. Hazard identification: identifies toxicological properties of a chemical substance. This identification is done through the conduct of toxicological studies that address the duration of exposure and the different routes of exposure. Endpoints of toxicity are for example reproductive toxicity, genotoxicity, carcinogenicity, etc. (13).

2. Dose-response assessment: considers the dose levels at which adverse effects were observed in test animals and uses these dose levels to calculate an equal dose in humans (10).

3. Exposure assessment: identifies the source and route of exposure (10).

4. Risk characterization: combines the hazard, dose-response and exposure assessments to describe the overall risk from a pesticide. It explains the assumptions used in assessing exposure as well as the uncertainties related to the dose-response assessment (10).

Box 3.1 Health risk evaluation

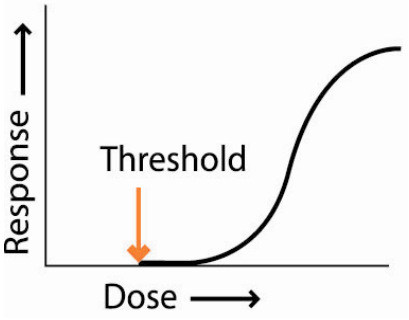
When the health risk of a chemical is evaluated in toxicological studies, the following factors are considered (14):

1. Toxicity threshold
2. NOAEL and LOAEL
3. LD_{50} and LC_{50}

3.5.1 Toxicity threshold

The toxicity threshold is the exposure level or dose of a toxic substance above which toxicity or adverse health effects can occur, and below which toxicity or adverse health effects are unlikely to be seen (14).

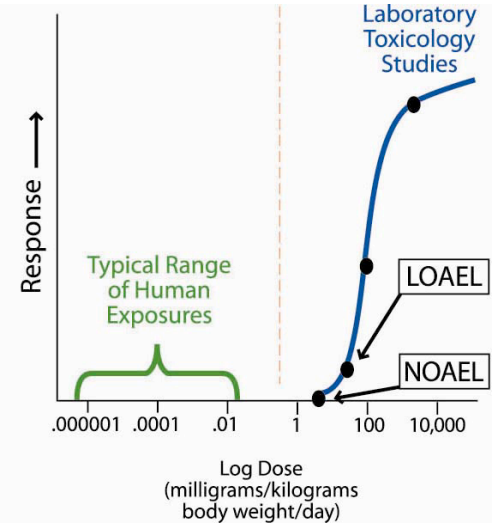
Figure 3.2: Example of dose-response curve showing a toxicity threshold (14)



3.5.2 NOAEL and LOAEL

NOAEL is the "No Observable Adverse Effect Level", which can be used for determining safe levels of exposure. LOAEL is the "Lowest Observable Adverse Effect Level", which is the lowest dose an adverse effect could be detected in an experiment (14).

Figure 3.3: Example of dose-response curve indicating NOAEL and LOAEL (14)



3.5.3 LD_{50} and LC_{50}

LD_{50} and LC_{50} represent the individual dose or concentration required to kill 50 percent of a population of test animals and are measurements of acute toxicity. LD_{50} is the lethal dose for oral and dermal exposure, and LC_{50} is the lethal concentration for respiratory exposure. A pesticide with a low LD_{50} or LC_{50} is more toxic than a pesticide with a high LD_{50} orLC_{50} because it takes less of the pesticide to kill half of the test animals (12).

For further reading on toxicity and safety evaluation of pesticides:

- Hanson, Lindsay and Ritter, Leonard: Toxicity and safety evaluation of pesticides in Krieger, Robert: Hayes handbook of pesticide toxicology, Academic Press, 2010
- EPA: assessing health risks from pesticides: http://www.epa.gov/opp00001/factsheets/riskassess.htm
- EPA: Glossary of terms: methods of toxicity testing and risk assessment: http://www.epa.gov/opp00001/science/comptox-glossary.html

3.5.4 Tests

A number of different tests can be performed to assess the risk of toxic substances to human health (15). They are often done on experimental animals in a laboratory before releasing the pesticide for use:

- The acute toxicity test: assesses the effects of short-term exposure to a single dose of pesticide (oral, dermal, and inhalation exposure, eye irritation, skin irritation, skin sensitization, neurotoxicity).
- The sub-chronic toxicity test: assesses the effects of intermediate repeated exposure (oral, dermal, inhalation, nerve system damage) over a longer period of time (30–90 days).
- The chronic toxicity test: assesses the effects of long-term repeated exposure lasting for most of the test animal's lifespan and is intended to determine the effects of a pesticide product after prolonged and repeated exposures (e.g., chronic non-cancer and cancer effects)
- The developmental and reproductive tests: assess any potential effects in the fetus of an exposed pregnant female (i.e., birth defects) and how pesticide exposure may influence the ability of a test animal to reproduce successfully
- The mutagenicity test: assesses the potential of a pesticide to affect the genetic components of the cell.
- The hormone disruption test: measures the pesticides potential to disrupt the endocrine system

3.5.5 Biomarkers

Biomonitoring is the measurement of chemicals in human biological specimens such as blood, urine, skin, hair (14).

- Acetylcholinesterase tests: are used for acetylcholinesterase-inhibiting insecticides (organophosphates and carbamates). These pesticides may interfere with acetylcholinesterase, which is an enzyme that controls muscle movement and reduce acetylcholinesterase levels in the blood (16).
- Urine metabolites: are the most commonly used biomarkers of orgaophosphate exposure in both adults and children. The sample is relatively easy to collect but can be seen as problematic since urinary metabolites are elimination products rather than direct markers of exposure or internal dose (17).
- Blood analysis: is used to diagnose most herbicide, fungicide and non-acetylcholinesterase-inhibiting insecticide exposure and poisonings. The blood serum can constitute a good indicator of body burden, especially when the pesticide residue levels are expressed at the lipid base. Persistent chlorinated pesticides or their metabolites can be measured readily in blood and serum, and have been used to provide an estimate of long-term body burden. Some pesticides such as organophosphate compounds have relatively short half-lives in the body and are therefore not easily measurable in blood or serum (17).

For further reading on tests and biomarkers of exposure:

- Wagida A. Anwar: Biomarkers of human exposure to pesticides, Environmental health perspectives 105 (Suppl 4): 801-806, 1997
- Nigg, Herbert N. and Knaak, James B.: blood cholinesterase as human biomarkers of organophosphorus pesticide exposure in Ware, George W.: Reviews of environmental contamination and toxicology, vol.163, 29-112
- Damalas, Christos A. and Eleftherohorinos, Ilias G.: pesticide exposure, safety issues and risk assessment indicators, Int J Environ Res Public Health 8(5):1402-19 (2011)

Educative session

Educative video:

1. Handling of pesticides - mix, spray and wash: We see a farmer before, during and after pesticide use. He is mixing pesticides, spraying with pesticides and cleans himself after spraying.

Study questions

1. Consider aspects that influence the farmer's health risk during and after spraying with pesticides.
2. Consider through which routes the farmer is at risk of getting exposed to pesticides?
3. What precautions does the farmer take to reduce his risk of pesticide exposure?
4. What could the farmer have done differently to further reduce his risk of getting exposed to pesticides?
5. Which factors affect health risk and how is risk calculated?
6. How would you measure the farmer's exposure to pesticides? Mention possible barriers for doing this.

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4. Perry MJ, Marbella A, Layde PM. Compliance with required pesticide-specific protective equipment. American Journal of Industrial Medicine. 2002;41.
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7. Hodgson E. Metabolism of pesticides. Hayes handbook of pesticide toxicology: Academic Press; 2010.
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11. EPA. Glossary of terms: methods of toxicity testing and risk assessment. United States Environmental Protection Agency; [cited]; Available from: http://www.epa.gov/opp00001/science/comptox-glossary.html
12. Pennsylvania State University. Pesticide safety fact sheet: potential health effects of pesticides; 2009
13. Hanson L, Ritter L. Toxicity and safety evaluation of pesticides Hayes handbook of pesticide toxicology: Academic Press; 2010.
14. Hood RR. The importance of toxicity thresholds for biomonitoring; 2009
15. Damalas CA, Eleftherohorinos IG. Pesticide exposure, safety issues, and risk assessment indicators. IntJEnvironResPublic Health. 2011;8:1402-19.
16. Nigg HN, Knaak JB. Blood cholinesterase as human biomarkers of organophosphorus pesticide exposure. Reviews of environmental contamination and toxicology. 2000;163.
17. IPCS. International Programme on Chemical Safety, Environmental Health criteria 214, Human exposure assessment: International Programme on Chemical Safety; 2000