August
2025

TECHNICAL DOCUMENTATION

Bayer Safety Standard *for* Operator Safety

Table of Contents

IMPORTANT NOTICE
This document details the 2nd version of the voluntary safety standard that Bayer applies to operator safety. It concerns the baseline standard that Bayer plant protection products must meet for operator safety in countries where no risk-based assessment for operator safety is in place. It contains the associated dataset, the models, and the methods used.

This document is not an announcement of a new standard; rather it is an outline of the standard that already underpins our decision-making as it relates to product safety for operator exposure worldwide.

PREFACE

The application of a safety standard as a consistent baseline for all plant protection products sold by Bayer is a key element for a safe and sustainable crop protection portfolio. Bayer endorses 'The International Code of Conduct on Pesticide Management' of the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). In addition to the regulatory requirements in countries where we register our products, we apply our own internal safety standard for risk assessment that ensures a globally consistent baseline for product safety. This standard reflects the guidelines and standards of international organizations like FAO, WHO and the Organization of Economic Cooperation and Development (OECD), as well as those of reference regulatory authorities around the world. It continuously evolves based on the latest scientific knowledge. Our safety standard is consistently applied for new product evaluations and label extensions in countries with only limited regulatory environments.

We apply a risk-based approach by following the three pillars of a reliable safety standard: (i) data collection to determine the hazard of the product and the potential exposure of operators, (ii) risk assessment to compare hazard and exposure as well as (iii) risk management to ensure that the requirements of the risk assessment are realized (implemented).

In this document, we describe the internal baseline operator safety standard we apply to our products. Details are presented such as the hazard determination for an active ingredient, and which algorithms are used to identify the absorption behavior of each active ingredient. Information is provided on the operator exposure models applied, as well as strategies to implement certain risk mitigation measures.

We will continue to work together with multiple internal and external stakeholders on operator safety. We encourage all stakeholders to join an open dialogue and provide suggestions for improvement.

1.1 COMMENT ON VERSION 2:

Since the publication of the first version of our Operator Safety Standard in 2021, we have received a wide range of feedback. While much of it has been positive, there has also been constructive criticism that has prompted us to seek further improvement. To this end, we engaged a panel of independent, global experts to review the standard. The key outcomes of this review are summarized in the meeting minutes, which are publicly available on Bayer's transparency website: Bayer Scientific Review Panel Meeting Minutes[1]. Details on how we considered the comments from the reviewers in this document are highlighted in Appendix A1 of this document.

Considering this feedback, we have made several adaptations to the Operator Safety Standard. We have incorporated cutting-edge technical developments, such as the use of in silico tools for predicting dermal absorption, the introduction of advanced algorithms for seed treatment and sowing, and the inclusion of guidance for drone (UAV) application of plant protection products.

[1] https://www.bayer.com/sites/default/files/Bayer_Scientific_Review_Panel_Meeting_Minutes_Final.pdf

2. COMMITMENT TO FAO CODE OF CONDUCT AND PARTICIPATION IN GLOBAL PROJECTS

At Bayer, we are committed to the principles laid out in the International Code of Conduct on Pesticide Management issued by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO)[2].

The International Code of Conduct on Pesticide Management, the most recent version of which was issued by the FAO and WHO in 2014[3], is a voluntary framework that guides the private sector, governments, civil society, and other stakeholders on best practices in managing crop protection products throughout their life cycle, from invention to ultimate use and finally, discontinuation. Its main objective is to maximize product potential and sustainability and minimize risks to human and animal health and the environment. The FAO-WHO Code is our overarching guidance for managing pesticides throughout the product life cycle.

Additionally, we recognize the importance of tools like the FAO Pesticide Registration Toolkit[4] in supporting responsible pesticide regulation. Bayer supports the development and utilization of all resources that strengthen the regulatory environment and enhance risk-based decision-making in pesticide registration processes.

We demonstrate this commitment through our active participation in the international ICPPE project[5] , which has been active since 2021. This collaborative initiative focuses on improving operator safety in countries that do not so far have regulations relating this area by developing data-driven risk assessment models tailored to the unique agronomic conditions in those regions, with the goal of integration into the FAO Pesticide Registration Toolkit.

Our own internal registration guidance adheres to the principles of the FAO Toolkit and will continue to do so in the future. While technical aspects of our procedures may differ, we continue to follow a consistent risk-based approach in our assessments to ensure the safety of all our new products, independent of the region where they are used.

[2] https://www.bayer.com/de/file/270596/download?token=cwrcmIeA
[3] https://www.fao.org/pest-and-pesticide-management/pesticide-risk-reduction/code-conduct/en/
[4] https://www.fao.org/pesticide-registration-toolkit/registration-tools/en/
[5] https://wwwcp.umes.edu/sans/aes/icppe/

3. BAYER SAFETY STANDARD FOR OPERATOR SAFETY – INTRODUCTION

For operator safety evaluation (e.g., safety of farmers handling and spraying a PPP or treating seeds), Bayer follows the FAO code of conduct[6] and its requirement to determine the potential risk for operators applying a plant protection product. Based on this guidance, we assess both hazard and exposure using conservative and realistic information to reliably determine potential operator risk. We then use risk management tools to ensure operator safety.

The following figure illustrates in three pillars how we apply our operator safety standards to our products.

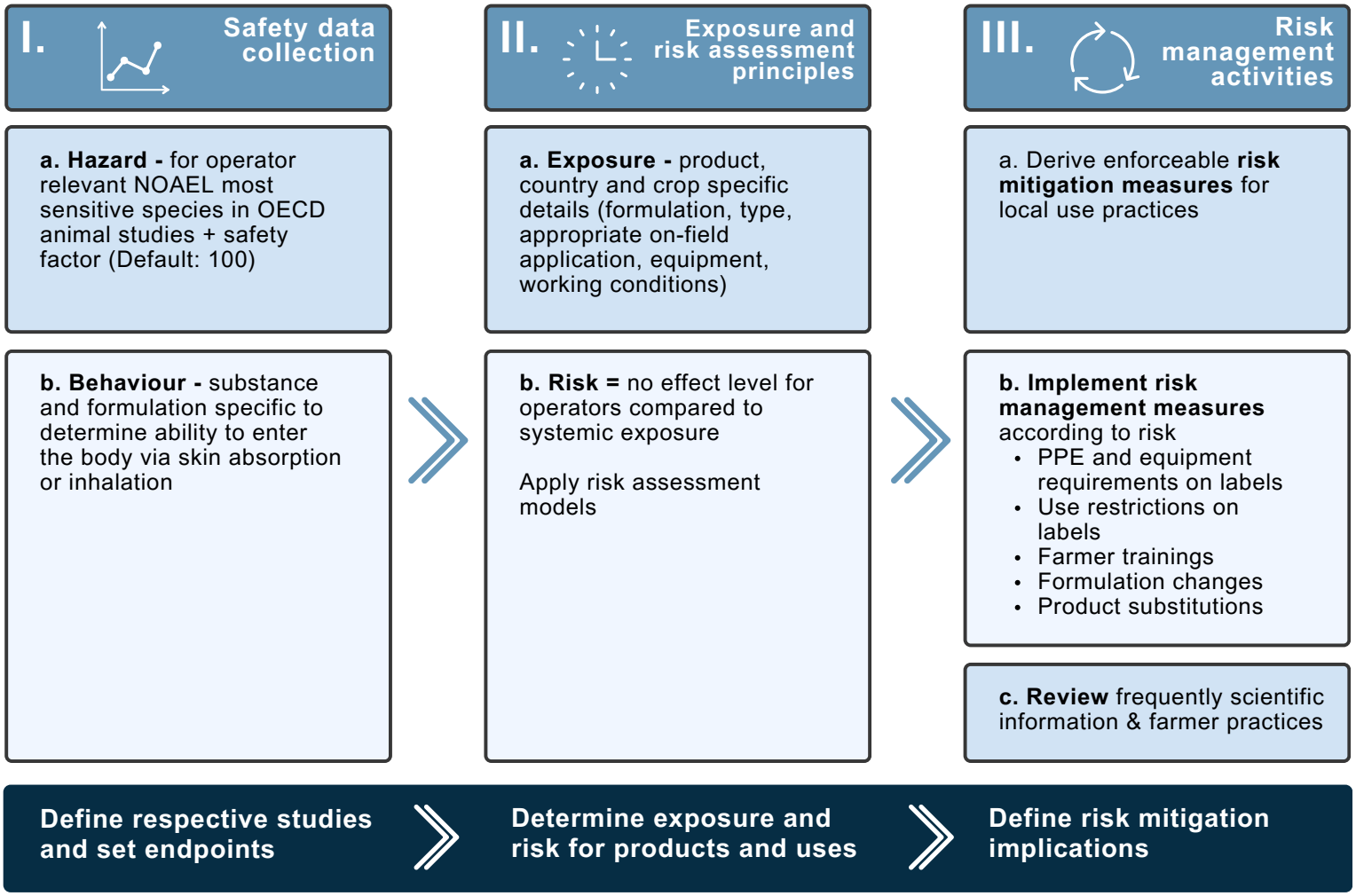

Figure 3.1: *Generic illustration of the operator safety standard framework*

I. **Safety data collection:** We conduct studies and assessments to understand the toxicity properties of our active ingredients and products to characterize their hazard and behavior in the body. In addition, we determine routes of exposure and how an active ingredient can enter the human body (dermal/ inhalation/oral absorption).

II. **Exposure and risk assessment principles:** We conduct tests and gather information to understand local practices, equipment used, operator behavior and potential sources of exposure to our products during their application. The more data we can collect from actual field use, the more reliable our assessments of risk.

III. **Risk management activities:** Risk management ensures that the requirements of the risk assessment are realized. Our risk management approach needs to be realistic and appropriate by considering current local practices and environments, and providing safe use trainings.

[6] The international Code of Conduct on Pesticide Management – World Health Organization (WHO) and Food and Agriculture Organization of the United Nations, version 2017

In the following chapters, the details of the internal operator safety standards are explained to assess potential operator exposure to PPPs and to allow a level of operator safety even when existing country regulations do not specifically require this level of assessment. For countries that meet the criteria below, Bayer relies on country regulatory guidelines to ensure operator safety:

I. Operator Safety Assessments follow a risk-based approach.
II. Risk assessments are consistently applied for all new products.
III. The regulation and decision-making process is transparent and comprehensible.

Among other examples, the regulatory environments in OECD countries such as the US, EU27 or Australia meet the above-mentioned criteria.

If a registration is recognized in a country as outlined in this chapter (such as the US or EU27), and the planned regulatory use scenario is the same (covering application rate, equipment, crop, etc.), we can steward it accordingly. In such cases, considering the registration and evaluation by the authority, an additional internal assessment is not required. For use scenarios that vary, our internal safety standards, as detailed above, will be applied.

The coverage of exposure scenarios that will be considered in risk assessment is highly variable and is depending on local agronomic use conditions. While some exposure scenarios, such as a PPP application with a handheld device in a normal field crop structure, are addressed in almost all registration processes, some scenarios are currently not in the focus of regulators. This can be for multiple reasons, starting from the non-relevance of certain exposure scenarios in certain countries to the fact that for certain new technologies, the data necessary to conduct a reliable risk assessment are not yet available.

As a globally acting company, it is our objective to cover all possible use scenarios compliant with Good Agricultural Practice (GAP) to close modelling gaps – either by creating data (e.g., conducting exposure studies) or by developing new risk assessment approaches, and amending our assessments accordingly.

Our overarching goal is to support authorities in developing or refining regulations for operator safety and adopting harmonized safety standards. For instance, specific operator exposure studies conducted by Bayer have been provided free of charge to PROHUMA, a local industry association in Brazil that collaborates closely with Brazilian regulators, to support their work on the development of an operator exposure model. In addition, Bayer supports an initiative by FAO for the development of a global harmonized operator exposure model for developing countries.

4. SAFETY DATA COLLECTION FOR OPERATOR SAFETY ASSESSMENT

4.1 HUMAN SAFETY: DETERMINATION OF HAZARD

The pesticidal effect of a chemical plant protection product is driven by the active ingredient. Therefore, a hazard assessment of the active ingredient (as well as for the corresponding plant protection product) and its potential residues is performed.

Numerous toxicological studies are conducted to determine the potential for short- and long-term effects, including CMR studies (Carcinogenicity (C), mutagenicity (M), reproductive toxicity (including embryotoxicity and teratogenicity) (R)) as well as studies which investigate how a chemical is processed by a living organism. The results of all these studies are used to derive a value called AOEL (Acceptable Operator Exposure Level) which is a threshold to characterize a safe dose for non-dietary exposure (including a large safety margin). For more information on the studies that are conducted and how the AOEL is derived, please refer to Appendix A2.

The primary ways operators can be exposed to substances are typically through skin contact (dermal exposure) and breathing them in (inhalation exposure), rather than ingesting them (oral route). When assessing the risk of systemic effects (effects that impact the entire body), it's crucial to understand how much of a substance that comes into contact with the body's exterior (for example, landing on the hand) actually gets absorbed into the body (becomes bioavailable). This means we need to accurately measure how much of the active ingredient can enter the body through the skin and through the lungs. Knowing the extent of this absorption is essential for correctly estimating the systemic exposure, which is further elaborated in the next chapter.

4.2 BEHAVIOR (DERMAL AND INHALATION ABSORPTION)

As already mentioned in the previous chapter, operators are mainly exposed to plant protection products (PPPs) via two routes:

I. Dermal exposure to the concentrated product and the diluted spray mix and,
II. Inhalation exposure to dust particles (for solids) or aerosols (for liquids).

Besides the risk evaluation of local effects on skin, eyes, and the respiratory system - e.g. skin and eye irritation or lung inflammation (please refer to Appendix A.2 for more information on acute local effects) - it is important to determine the fraction that may enter the circulatory systems of the operator by systemic exposure. An active ingredient can only cause systemic effects if it is absorbed and distributed to other parts of the body where it can interact with cells, tissues, and organs such as the liver or kidney. In other words, adverse systemic effects can only occur if there is systemic exposure.

The skin is a multi-layered organ that forms a natural barrier to absorption of foreign substances, including PPP active ingredients. Dermal (percutaneous, skin) absorption is a general term that describes the transport of chemicals from the outer surface of the skin to the systemic circulation. Given that the skin is the major route of non-dietary exposure, it is important to be able to quantify both the extent of external exposure and the amount / proportion of this external dose that can enter the body. Hence, dermal absorption is a key parameter used in operator risk assessments for agrochemicals. In internal risk assessments, Bayer uses, as a first step, either defined default values in the absence of data or measured absorption values from *in vitro* human skin studies. Generally, the default absorption values are more conservative, i.e., higher than is normally obtained from absorption studies because they are based on empirical 95th percentile values from a very large dataset of study data (Aggarwal *et al.* 2015)[7].

[7] M.Aggarwal, P.Fisher, A.Hüser, F.M.Kluxen, R.Parr-Dobrzanski, M.Soufie, C Strupp C.Wiemann, R.Billington: Assessment of an extended dataset of in vitro human dermal absorption studies on pesticides to determine default values, opportunities for read-across and influence of dilution on absorption, Regulatory Toxicology and Pharmacology, Volume 72, Issue 1, June 2015, Page 58-70

Dermal *in vitro* absorption studies are conducted to determine the dermal absorption of an active ingredient in a formulated product. These studies use formulated product where the active ingredient is usually radiolabelled (14C) in order to determine and quantify its distribution following application. The radioactivity found in the skin layers and in the receptor fluid provides means of quantifying the degree of absorption of the active ingredient of interest.
More recently, an *in silico* tool based on the paper by Kuester *et al.* (2022)[8] has been used to predict dermal absorption as a refinement option in the absence of study data.

For exposure via the inhalation route, a worst-case situation is assumed, i.e. .e. that 100% of the inhaled amount is absorbed via the respiratory system and taken up systemically.

The following chapter provides an overview of the determination of dermal absorption values for pesticide active ingredients, including default dermal absorption values, active ingredient-specific dermal absorption derived from in vitro human skin studies, and the use of in silico prediction tools for dermal absorption.

4.2.1 DEFAULT DERMAL ABSORPTION VALUES

When no measured data are available for a given active ingredient to determine active ingredient -specific dermal absorption values, default values according to Aggarwal *et al.* 2015[9] are used. These defaults were derived from 295 GLP- and OECD guideline-compliant human *in vitro* dermal absorption studies. The assessment covered 152 agrochemicals, 19 formulation types and representative ranges of spray concentrations. The analysis of the data used EFSA's worst-case dermal absorption definition (i.e., an entire skin residue, except for surface layers of stratum corneum, is absorbed). Therefore, the 95th percentile values which were derived empirically from the data (i.e., no modelling) were:

I. Dermal absorption default values of 6% for liquid and 2% for solid concentrates, irrespective of the active ingredient concentration.
II. Dermal absorption default values of 30% for all spray dilutions, irrespective of the formulation type.

4.2.2 ACTIVE INGREDIENT-SPECIFIC DERMAL ABSORPTION VALUES

4.2.2.1 SCIENTIFIC EVALUATION OF STUDY RESULTS

For the derivation of appropriate active ingredient -specific dermal absorption[10] values, data from in vitro human skin studies are used. These studies are conducted with formulated products under GLP and in accordance with OECD guideline No. 428.[11] The dermal absorption is hereby calculated as:

Dermal absorption = Directly absorbed + tape-stripped skin + (Stratum corneum (tape strip 3…X))

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[8] Kuster et al. (2022) - In silico prediction of dermal absorption from non-dietary exposure to plant protection products, Computational Toxicology, Volume 24, November 2022, 100242, https://doi.org/10.1016/j.comtox.2022.100242

[9] M.Aggarwal, P.Fisher, A.Hüser, F.M.Kluxen, R.Parr-Dobrzanski, M.Soufie, C Strupp C.Wiemanng, R.Billington: Assessment of an extended dataset of in vitro human dermal absorption studies on pesticides to determine default values, opportunities for read-across and influence of dilution on absorption, Regulatory Toxicology and Pharmacology, Volume 72, Issue 1, June 2015, Page 58-70

[10] EFSA (European Food Safety Authority), Buist H, Craig P, Dewhurst I, Hougaard Bennekou S, Kneuer C, Machera K, Pieper C, Court Marques D, Guillot G, Ruffo F and Chiusolo A, 2017. Guidance on dermal absorption. EFSA Journal 2017;15(6):4873, 60 pp. https://doi.org/10.2903/j.efsa.2017.4873

[11] OECD Guideline for the Testing of Chemicals, Guideline 428. Skin Absorption: in vitro Method (April 2004)

In the European Union, the European Food Safety Authority (EFSA) provides guidelines for studying how substances are absorbed through the skin in laboratory settings. According to these guidelines, absorption is deemed to be effectively complete if more than 75% of the substance that eventually ends up in the receiving fluid (measured at the end of the observation period, typically 24 hours) has already done so by the midpoint of that period (usually at 12 hours). In such instances, it is recommended to disregard all layers of the outermost skin (stratum corneum) collected by tape stripping.

Our approach is somewhat similar. However, to avoid overly conservative estimates that might not be necessary (known as compounded conservatism), and in line with the empirical method used for setting default values, Bayer opts to consider only the maximum value of absorption. We do not add a standard deviation to calculate a higher percentile value, a method suggested in some other guidelines for further safety margins. This decision is made to maintain a balance between safety and practicality in our assessments.

4.2.2.2 THE DETERMINATION OF ACTIVE INGREDIENT-SPECIFIC DERMAL ABSORPTION VALUES

In a first-tier approach, we decided to define active ingredient -specific dermal absorption values in a “multi-to-one” approach when measured data from in vitro human skin studies are available on a given active ingredient. Therefore, for each active ingredient three data pools were established:

I. Dermal absorption of the concentrate for
- Liquids or for
- Solids

II. Dermal absorption of the dilution (it is assumed that solid and liquid formulations act similarly once diluted in water)

Depending on the number of independent studies which are available for each active ingredient, the following workflow is used to define active ingredient -specific default dermal absorption figures for each data pool.

Table 4.1: *Approach to consider the variability of different products. This standard approach might be adapted depending on literature and expert judgement, depending on the similarity of formulations tested and assessed.*

Number of independent studies (n=)	Approach taken	Comment
1	Study result * 2	The safety factor of 1.5 or 2 is needed to cover potential variability. If the so derived value exceeds the defined default dermal absorption, the used value is limited to 30%.
2	Highest study result * 1.5	
>3	Highest study result	

In conclusion, the following decision tree was followed:

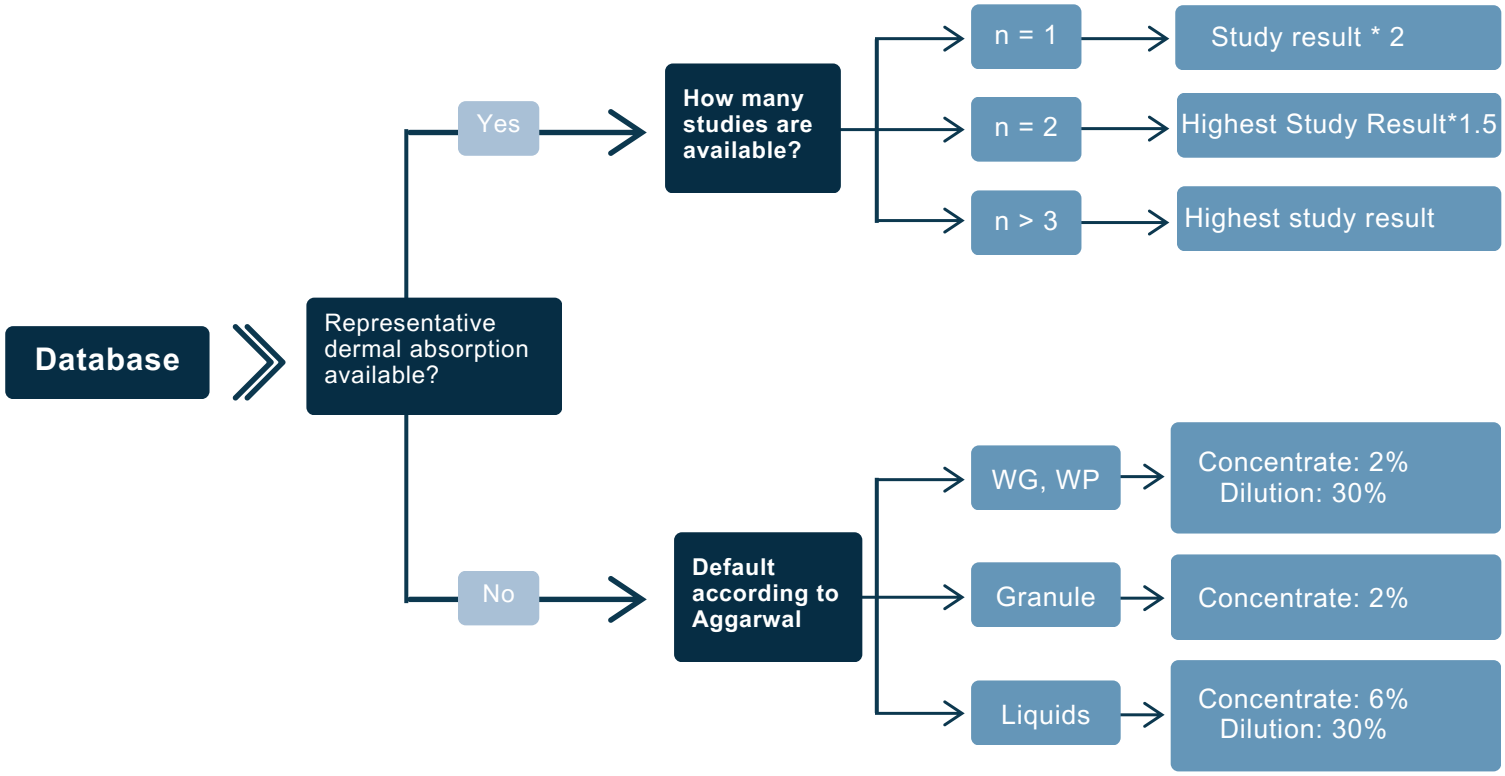


Figure 4.1: *Workflow to determine active ingredient -specific default dermal absorption values.*

In a second-tier approach, when a product-specific *in vitro* dermal absorption study exists for the active ingredient in the formulation of concern, product-specific measured values can be used.

4.2.2.3 SPECIFIC CONSIDERATION OF DERMAL ABSORPTION FOR SEED TREATMENT FORMULATIONS

Dermal absorption rates for seed treatment formulations, whether liquid or solid concentrates, are generally comparable to those of concentrated spray products. However, the situation changes when it comes to dilution. Unlike spray application products, which are often significantly diluted (commonly at ratios of 1/100 to 1/500) and thereby increase the relative dermal absorption of the active ingredient, seed treatment products are usually less diluted in slurry mixes, typically ranging from 1:2 to 1:10 ratios. Our internal studies indicate that the proposed default value of 6% for dilutions aligns closely with observed measured values. As a result, it is justified to apply this 6% default value to diluted seed treatment products as well.

4.2.2.4 SPECIFIC CONSIDERATION OF ACTIVE INGREDIENTS THAT PERSIST IN THE STRATUM CORNEUM

The absorbable dose, as defined using all the material in the receptor fluid plus that in the tape-stripped skin and stratum corneum, is a worst-case assumption. There are, however, active ingredients with certain physicochemical properties (e.g., lipophilic active ingredients) where their affinity for the lipophilic environment in the stratum corneum can limit dermal absorption, leading to the formation of reservoirs which are more likely to be removed by desquamation than by systemic uptake. For those molecules, this can lead to a considerable overestimation of the amount of the active ingredient that is likely to become systemically available. This concern has been expressed by the German Federal Institute for Occupational Safety and Health[12].

[12] BAuA; Dermal absorption values for anticoagulant rodenticides: Alternative approach for the occupational setting. Agreed at Human Health Working Group meeting WG-I-2021. Publication date: 1 June 2021

Thus, as a potential tier 2 approach, where the percentage found in the stratum corneum is considered to be relatively high and a relatively low percentage is found in the receptor fluid, an alternative, maximum dermal flux-based approach can be applied[13,14] . This alternative approach can more adequately account for the cases where only a proportion of the absorbable dose becomes systemically available and thereby derive more realistic estimates of the percentage of absorption.

4.2.3 THE USE OF *IN SILICO* PREDICTION TOOLS FOR DERMAL ABSORPTION

In 2022, Bayer developed an *in silico* model designed to predict the skin penetration of active ingredients in plant protection products (PPPs). The model was developed using a machine learning technique known as random forest, and it was trained using a dataset that combines in vitro human skin studies from the EFSA dermal absorption database augmented with additional in-house data from Bayer. Alongside the applied dose, the model also employs various relevant physicochemical properties as parameters.

To make the model's predictions usable for regulatory compliance, it has been integrated with a precautionary percentile-based approach. An external validation using an independent dataset confirmed the model's readiness for practical application. The methodology and assessment tool have been published in a peer-reviewed journal (Kuster et al., 2022).[15]

For our non-dietary risk assessments, we employ a tiered decision tree approach, which includes the use of this in silico dermal absorption prediction model as part of a comprehensive safety evaluation of PPPs. The decision to utilize the *in silico* tool as a higher-tier approach is made by technical experts on a case by case basis.

4.3 3RD PARTY ACTIVE INGREDIENT CONSIDERATIONS

To enable risk assessments, we derive the AOEL and dermal absorption figures for 3rd party active ingredients by considering publicly-available authority evaluations, e.g., from EFSA or US EPA. Where study reports are not available, we rely on the evaluation provided by regulatory authorities. For dermal absorption values, we optionally use the *in silico* prediction tool to determine a dermal absorption value where applicable.

[13] WHO (2006). Dermal Absorption. Environmental Health Criteria (EHC) 235. ISBN 978 92 4 1572 35 4

[14] Kluxen, F ; et al (2023), Practical guidance to evaluate in vitro dermal absorption studies for pesticide registration: An industry perspective, Regulatory Toxicology and Pharmacology, Volume 142, August 2023, https://doi.org/10.1016/j.yrtph.2023.105432.

[15] Kuster et al. (2022) - In silico prediction of dermal absorption from non-dietary exposure to plant protection products, Computational Toxicology, Volume 24, November 2022, 100242, https://doi.org/10.1016/j.comtox.2022.100242

5. EXPOSURE AND RISK ASSESSMENT PRINCIPLES

The operator exposure estimations are based on models built from experimental data conducted with PPPs under realistic field conditions, where farmers were monitored during their normal operations for one working day in a defined scenario, and the residues on clothing and skin as well as potential inhalation exposure were analyzed. This data, compiled from multiple studies, is statistically analyzed, and evaluated to develop a model that allows estimations of operator exposure in certain scenarios (Figure 5.1). The equipment type used to apply a PPP is a critical factor that influences operator exposure, with different application methods leading to varying levels of exposure.

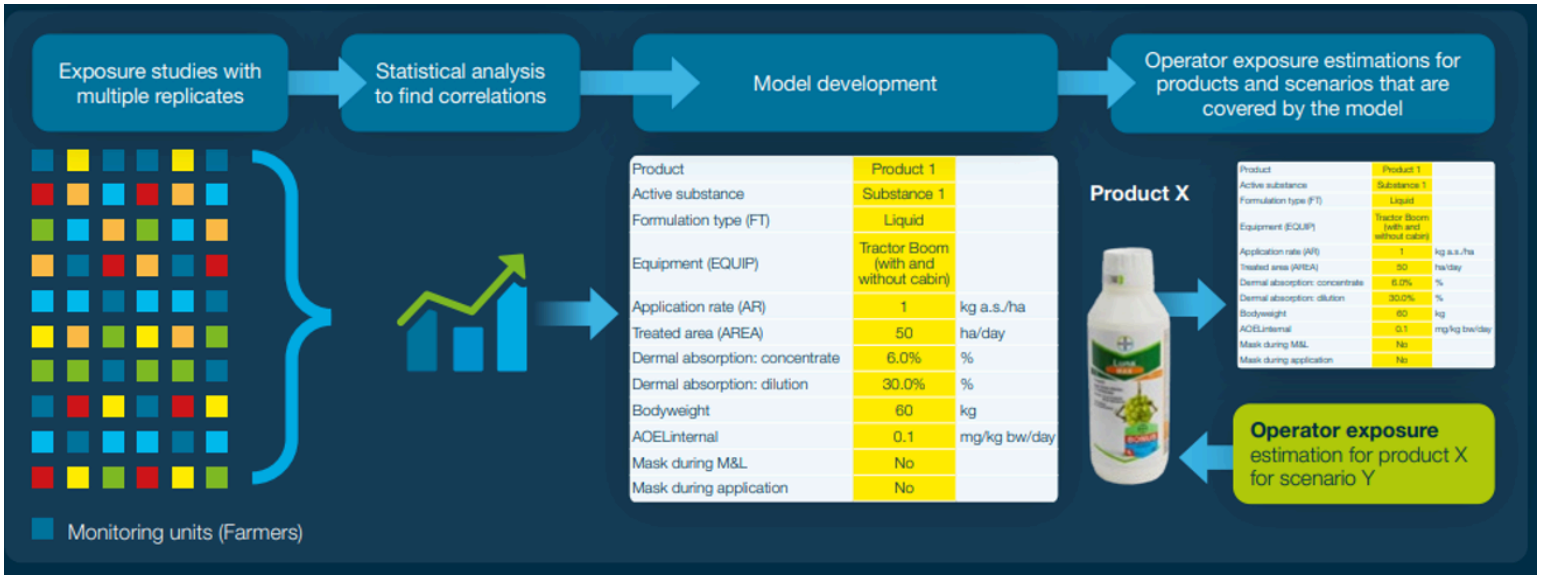
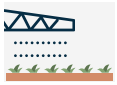


Figure 5.1: Principle of operator risk assessment based on generic model approaches

Bayer compared existing model approaches set by international bodies to decide which model fits best for operator exposure assessments, considering the quality and transparency of the underlying exposure database and the reliability of the statistical analysis. While opting to use models proposed by the FAO pesticide registration toolkit, Bayer also developed an operator exposure model using handheld data from various regions around the globe to cover use scenarios common in low- and middle-income countries (LMICs) not addressed by current exposure models. The following Table 5.1 provide an overview of the models used for different exposure scenarios:

Table 5.1: Bayer operator risk assessment approach

	Spray Application							Granule Application		Seed Treatment		
	Ground-boom	Airblast	Handheld (normal crop)	Handheld (dense crop)	Aerial (airplane)	Drone	Drip Irrigation	Manual application	Application via tractor	Professional facility	On-farm high troughput	Small-scale equipment
												
Origin of the approach	Europe	Europe	Bayer	Bayer	FAO	Bayer	Europe	FAO	FAO	Europe	Bayer	Bayer

The assumptions for assessing operator risk to PPP are explained in detail in the following sub-chapters, focusing on a risk-based approach and consistent risk assessments for all new products, following transparent and comprehensible regulation and decision-making processes.

Bayer's objective is to cover the most relevant use scenarios compliant with Good Agricultural Practice to close modeling gaps, either by creating data through exposure studies, or by developing new risk assessment approaches and amending assessments accordingly.

The following figure illustrates the concept of a risk-based approach including parameters that influence exposure. Risk management approaches are important to decide whether the outcome of a risk assessment reflects the reality or additional stewardship measures needs to be initiated to, e.g., increase the acceptance of PPE:

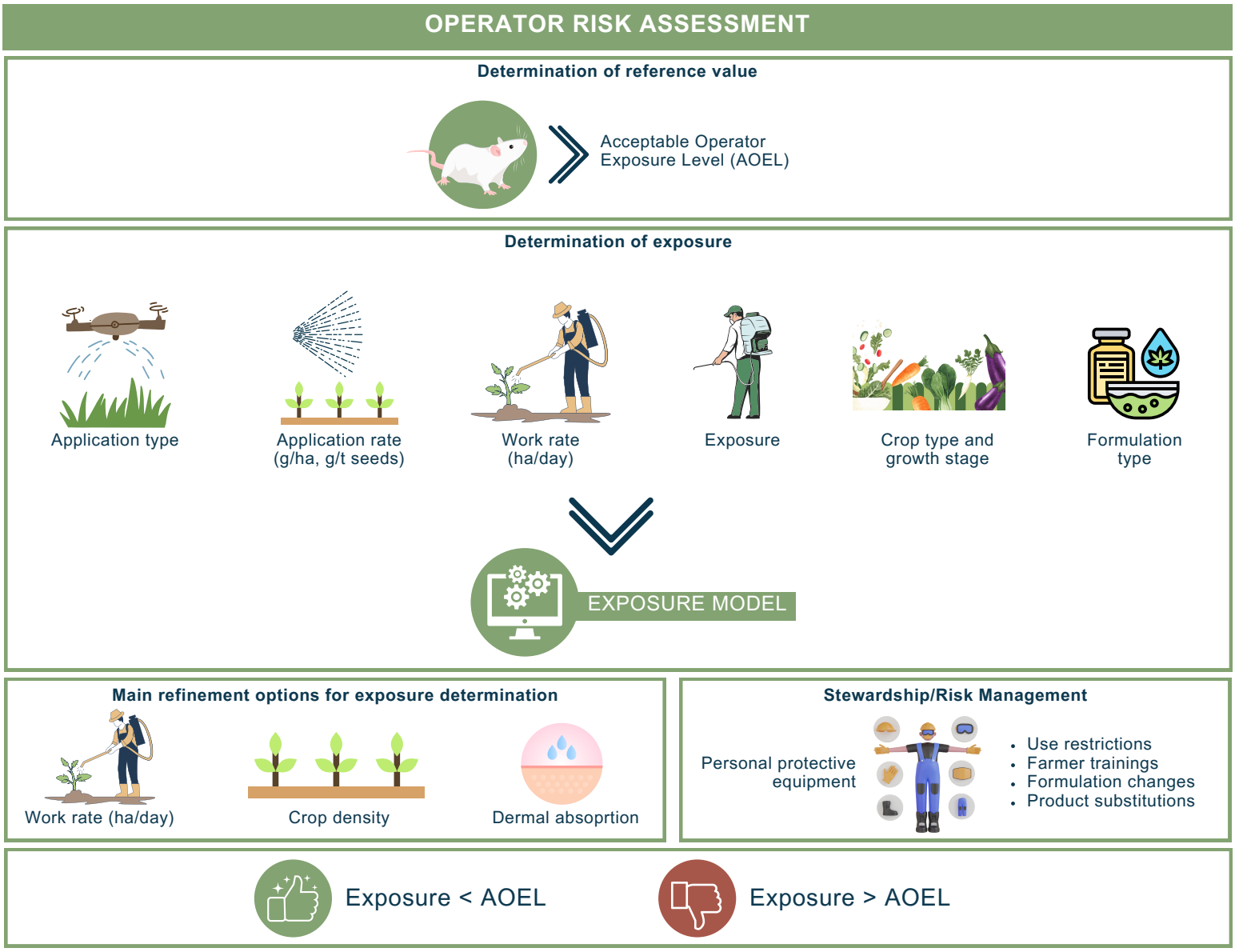


Figure 5.2: *Illustration on the operator risk concept including hazard determination, exposure and risk assessment as well as risk management.*

5.1 OPERATOR EXPOSURE

Operator exposure estimations are usually linear or log-linear correlated with the amount of active ingredient handled in one working day. This holds true for spray application as well as for seed treatment uses. However, other parameters also have an influence on the exposure. The following questions need to be answered thoroughly to allow a reliable operator exposure assessment to be conducted.

5.1.1 QUESTIONS TO BE ANSWERED TO ALLOW A RELIABLE RISK ASSESSMENT

How is the product formulated?

Spray application: We distinguish between 'Wettable Powders' (WP), 'Wettable Granules' (WG) and 'Liquids' (e.g. EC, SC, OD). This is important, because different formulation types can lead to higher or lower operator exposure during mixing and loading of the product. As an example, the use of dusty formulations (WP) results in higher inhalation exposure than the use of liquid or granule formulations. Alternatively, exposure of the hands is higher when using liquids as opposed to WGs. For less common formulation types, we use the algorithms developed for WP, WG, or liquid formulations as surrogates. For instance, a water-soluble granule (SG) is treated as if it were a WG formulation for the purpose of exposure assessment. A comprehensive list of common formulation types for plant protection products is available on the website of the Federal Office of Consumer Protection and Food Safety.

Seed Treatment: Here, we categorize formulations into two main types: liquids and solids. Liquid formulations include Flowable Concentrates for Seed Treatment (FS), while solid formulations encompass powders for Dry Seed Treatment (DS). The type of formulation is crucial for determining dermal absorption rates as well as understanding the application process. For example, powder formulations like DS are often directly mixed with seeding material such as potatoes. In contrast, FS formulations are typically mixed in slurry tanks and are then applied in liquid form.

What is the application rate per hectare or dose rate per ton seed?

As already mentioned, exposure is often correlated with the amount of active ingredient handled: the higher the application rate per hectare for spray application products, the more likely the occurrence of high operator exposure to the active ingredient. The same applies for seed treatment, in relation to the dose of active ingredient per ton of seed.

What is the relevance of the treated area per day for spray application and sowing of treated seeds and the capacity of the seed treatment equipment for seed treatment products?

Similarly, this holds true for the treated area per day: the larger the area treated via spray application or sown with treated seeds, the more active ingredient is handled per day during mixing/loading and application of the spray or loading and sowing of the treated seedsand the more likely the chance of higher operator exposure to the active ingredient, The daily throughput in seed treatment facilities is related to the potential amount of active ingredient handled per day connected with a likelihood for higher exposure in facilities with larger treatment capacity.

What kind of equipment is used?

The type of equipment used to apply pesticides is one of the most important factors influencing operator exposure. However, in terms of risk assessment it is difficult to judge what is the worst case. For example, during spray application the risk of exposure to spray liquid is higher for a handheld application than for a tractor-mounted ground-boom application. On the other hand, the assumed treated area per day and accordingly the amounts of product handled are much higher for a ground-boom application. Also, to be considered that water rates could differ which might impact the respective dermal absorption rate. The question which equipment scenario should be considered as the worst case, can thus not be answered in general, but needs to be a case-by-case decision. Therefore, if many different equipment scenarios per use are can realistically be assumed, multiple exposure assessments for each equipment type need to be conducted. In cases where equipment-specific exposure data are not available or the database is insufficient, an expert judgement may be helpful to estimate operator exposure. In others, however, one could consider experimental data generation.

In general, Bayer is prepared to support authorities to establish trial programs for new technologies, like drone application of PPPs.

It's important to note that certain application techniques and types of equipment do not align with good agricultural practices or the professional application of plant protection products. Addressing these scenarios requires stewardship measures such as training and education. Collaboration between the industry and local regulators is essential to develop less exposure-intensive solutions. For instance, in the case of manual seed treatment, employing a drum mixer or even a shovel technique for mixing seeds - along with the use of chemical-resistant gloves - can substantially reduce operator exposure compared to hand mixing, which is not supported by Bayer.

What kind of personal protective equipment (PPE) is worn by the operator?
The protection of the operator by using appropriate PPE is a key element to reduce exposure significantly. During mixing and loading of the PPP, mainly the hands are exposed. The use of chemical resistant gloves during mixing and loading or hand sowing of treated seeds can therefore reduce exposure to a large extent. Another example is the mixing and loading of 'Wettable Powders'. Here, operators can significantly reduce their exposure via inhalation by wearing a particle filtering mask (FFP1 type).

We consider local agronomic conditions in developing countries to be able to estimate exposure under local use conditions. Besides specific crop, climate, and equipment factors, this also includes a realistic view on the use of appropriate PPE during pesticide application. For instance, Bayer does not assume the use of unrealistic "advanced" PPE, like the use of impervious clothing under hot and humid weather conditions. Together with external partners, we want to ensure that PPE provides sufficient protection and comfort, and that it leads to increased acceptance at farm level.

Spray application: Which crop is treated at which growth stage?
The combination of crop and growth stage indicates a specific exposure scenario with implications for the level of exposure. As an example, exposure during handheld application in a developed rice field (dense crop) is higher than during handheld application in a corn field at an early growth stage (normal crop). If operators are in contact with sprayed foliage, exposure is usually increased. To distinguish, in a first-tier approach, whether a crop can be considered as 'dense' or 'normal,' please refer to Appendix A3.1.

Seed Treatment: What seed varieties are treated?
For seed treatment, it is important to note that different types of seeds require distinct treatment techniques, making it difficult to compare them directly. For example, corn seeds are commonly treated with specialized equipment that uniformly applies a liquid pesticide formulation. The inclusion of stickers in this process enhances the adhesion of the pesticide to the corn seeds. These stickers not only improve the treatment's efficacy but also minimize operator exposure during sowing by reducing abrasion of seed, and thus the generation of dust. On the other hand, treating potatoes often involves manually applying a powder formulation like DS (powder suitable for dusting) to the tubers, which increases the potential for dermal and inhalation exposure of the operator.

5.1.2 THE SELECTION OF OPERATOR EXPOSURE MODELS

Once the above-mentioned questions are answered, operator exposure assessments are conducted, assuming different model approaches. The following exposure models are used in internal risk assessments by Bayer:

Use scenario [2]	Equipment used	Model used	Work rate
Spray application	Tractor mounted boom sprayer	Europe: AOEM	50 ha/day
	Airblast without cabin	Europe: AOEM	10 ha/day
	Airblast with cabin	Europe: AOEM	10 ha/day
	Aerial (airplane)	CLI – PoR OPEX (AHED-based model)	500 ha/day
	Drone (UAV)	Handheld, normal crop as surrogate[1]	4 ha/day for surrogate
	Handheld, normal crop	Bayer model	1-4 ha/day
	Handheld, dense crop	Bayer model	1 ha/day
Irrigation	Drip irrigation	Europe: AOEM M&L tank	50 ha/day
Granule application	Manual granule application	CLI – PoR OPEX (AHED3-based model)	2 ha/day
	Solid broadcast spreader	CLI – PoR OPEX (AHED3-based model)	80 ha/day
Seed treatment			
Slurry treatment	Seed treater, commercial facility – standard technical level	SeedTROPEX	75 tons/day
	Seed treater, mobile – on farm treatment, high throughput	Bayer on-farm, mobile study	10 tons/day
	Seed treater, on-farm (Drum Mixer/ Small batch treaters)	Bayer study	2 hours/day
Seed sowing	Mechanical drill sowing	SeedTROPEX	8 hours/day

[1] Will be replaced by model, currently in development based on Bayer two studies (Kuster et al. (2023)[16a] and Felkers et al. (2024))[16b]

[2] Other special scenarios like manual sowing/planting are subject to expert evaluation

Technical details on the European model (AOEM) can be found on EFSA's website.[17] Technical details on the CLI PoR OPEX model can be found CropLife International's website, as well as a download link to the model.[18]

[16a] Kuster et al. (2023), Pesticide Exposure of Operators from Drone Application: A Field Study with Comparative Analysis to Handheld Data from Exposure Models, ACS Agric. Sci. Technol. 2023, 3, 12, 1125–1130

[16b] Felkers et al. (2024), Pesticide exposure of operators during mixing and loading a drone: towards a stratified exposure assessment, Pest Management Science by John Wiley & Sons Ltd on behalf of Society of Chemical Industry, DOI 10.1002/ps.8574

17] https://efsa.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.2903%2Fj.efsa.2014.3874&file=3874Ax1-sup-0001.zip

[18] https://croplife.org/downloads/#accessForm%0D

5.1.3 UNMANNED AERIAL VEHICLES (UAV/DRONES) FOR PESTICIDE APPLICATION

Application of pesticides with Unmanned Aerial Vehicles (UAV)/drones, is a relatively new but rapidly evolving technology. In many regions – especially in Asia/Pacific – it is beginning to replace to a significant degree applications that, up to now, have been performed with handheld application equipment, e.g., applications performed in rice fields. Contrary to handheld uses, the UAV is operated from outside the field. This avoids contact with the treated crop and accordingly eliminates the most critical operator exposure pathway. In this respect – as a replacement for handheld equipment - UAV use has the potential to become a "game changer" in terms of operator (applicator) exposure.

Nevertheless, it must be acknowledged that for the time being limited data are available for the development of an UAV-specific operator exposure model and official model approaches have not yet been established (OECD. Report on the State of the Knowledge 2023)[19]. Some regulatory frameworks, e.g., in the US, permit drone uses if aerial application is registered. Our current approach assumes that where application with handheld equipment is safe for the operator - assuming normal crop architecture - an application by UAV is also acceptable from an operator exposure perspective. Results of an operator exposure study conducted by Bayer in Thailand in 2022 (using 'Brilliant Blue G' as a tracer for the determination of operator exposure) supports that surrogate approach (Kuster *et al.* 2023).[20a] In Kuster *et al.* (2023) and Felkers *et al.* (2024)[20b], it has been demonstrated that for drone application the exposure of operators occurs mainly during the mixing and loading process on hands. The use of chemical resistant gloves can effectively minimize exposure.

Figure 5.3: Typical UAV/Drone used for pesticide application.

[19] OECD. Report on the State of the Knowledge – Literature Review on Unmanned Aerial Spray Systems in Agriculture, ENV-CBC-MONO (2021) 39. OECD Series on Pesticides, No. 105, OECD Publishing, Paris 2023

[20a] Kuster *et al.* (2023), Pesticide Exposure of Operators from Drone Application: A Field Study with Comparative Analysis to Handheld Data from Exposure Models, ACS Agric. Sci. Technol. 2023, 3, 12, 1125–1130

[20b] Felkers *et al.* (2024), Pesticide exposure of operators during mixing and loading a drone: towards a stratified exposure assessment, Pest Management Science by John Wiley & Sons Ltd on behalf of Society of Chemical Industry, DOI 10.1002/ps.8574

5.1.4 DEVELOPMENT OF THE BAYER HANDHELD APPLICATION MODEL - OVERVIEW

As for many other models, we developed a two-step approach, considering exposure during mixing and loading separately from exposure during application. For exposure during mixing and loading, we used the exposure figures from the European AOEM model. For operator exposure during handheld application, we distinguished between three application scenarios:

I. Handheld application in normal crops, spray direction: upwards and downwards
II. Handheld application in dense crops, spray direction: upwards
III. Handheld application in dense crops, spray direction: downwards

We defined a dense crop scenario as follows: if the operator has considerable contact with the treated crop, the scenario is defined as “dense”. Spraying sideward the application may reduce the contact to contaminated foliage but was deemed often impractical under realistic use conditions. Whether a use scenario can be considered “dense crop” is dependent on the crop, the cultivation type, and the growth stage at the time of application. For more information, please refer to the chapter “5.1.1. Spray application: Which crop is treated at which growth stage?”.

In Appendix A3, detailed information on the handheld application scenarios in normal and dense crops can be found, along with the exposure algorithms developed by Bayer for operator risk assessments.. The appendix includes data from multiple studies conducted in Europe, the US, and South Korea, covering both field and greenhouse environments. The statistical analysis utilized the non-parametric method of quantile regression for modelling, with specific equations provided for dermal and inhalation exposure in different clothing scenarios. Additionally, the appendix contains figures illustrating exposure during handheld applications in both normal and dense crop scenarios, along with a summary table of the exposure algorithms used for operator risk assessments.

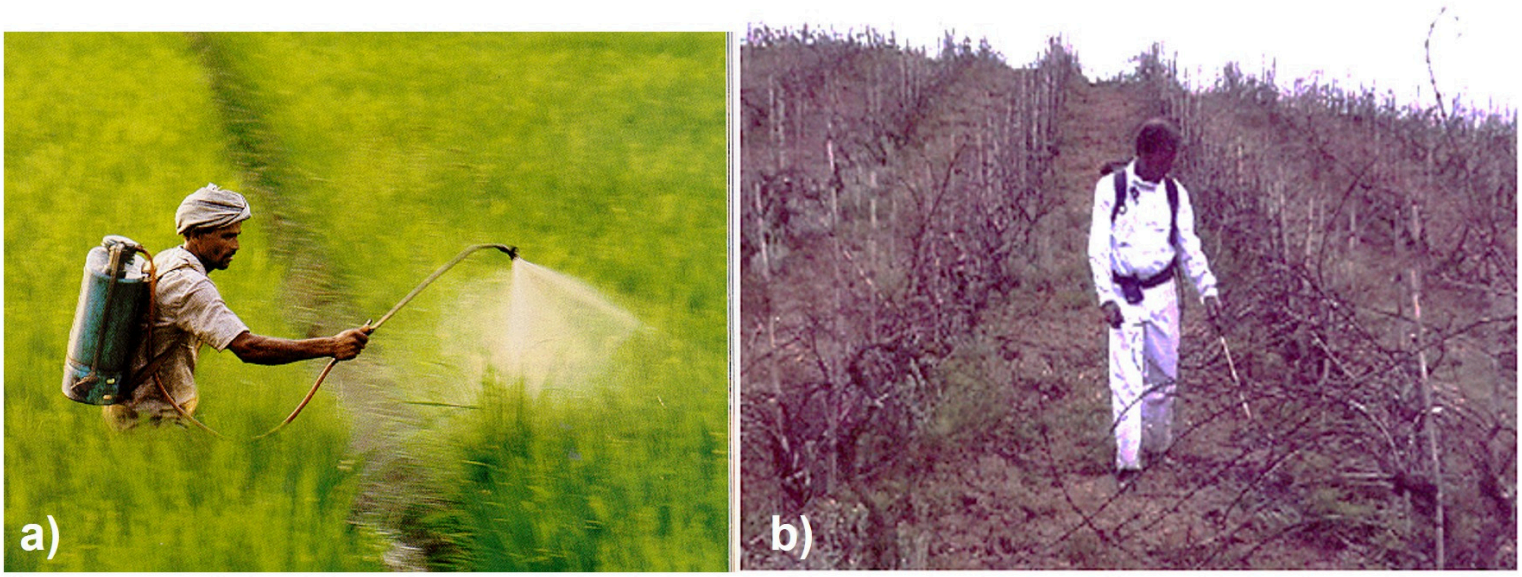


Figure 5.4: Handheld application scenarios, examples: a) Dense Crop, b) Normal Crop

5.1.5 SEED TREATMENT EXPOSURE ALGORITHMS

During seed treatment, operators can be exposed to chemicals through dermal contact during tasks such as mixing/loading, calibration, bagging and cleaning, as well as potential inhalation exposure. The use of appropriate Personal Protective Equipment (PPE) is crucial to minimize operator exposure and ensure safety during seed treatment activities. Understanding the specific exposure scenarios and implementing the appropriate safety measures is essential for mitigating potential risks to operators during seed treatment processes.

In the appendix, detailed exposure scenarios and algorithms are provided for various seed treatment equipment, including commercial seed treaters, mobile seed treaters, and on-farm seed treaters. For commercial seed treaters, the appendix includes information on the SeedTROPEX model, surrogate values used for exposure modeling, and systemic operator exposure calculation during different work tasks. Additionally, exposure algorithms are presented for mobile seed treaters and on-farm seed treaters, including drum mixers, along with normalized operator exposure results. The appendix also explains the potential ways in which operators can be exposed during seed treatment, providing a comprehensive overview of the safety considerations and exposure assessment for different seed treatment scenarios.

Figure 5.5: Typical working scenarios in commercial seed treatment facilities

Figure 5.6: Drum-type mixers used for seed treatment

5.1.6 SEED SOWING EXPOSURE ALGORITHMS

During seed sowing, operators may be exposed to chemicals through activities such as handling treated seeds and operating sowing equipment. Dermal contact and inhalation exposure are key pathways for potential and actual chemical exposure during seed sowing activities. Adhering to safety protocols and utilizing recommended PPE can help mitigate operator exposure and ensure safe practice during seed sowing operations.

In the appendix, detailed exposure scenarios and algorithms are provided that relate to drill sowing of treated seeds, and the use of personal protective equipment to mitigate exposure. Exposure estimates for tractor-driven sowing are outlined in detail, including the use of specific surrogate values and systemic operator exposure calculations. Additionally, the appendix explains the assumptions and considerations for the use of personal protective equipment, including advanced PPE (see also chapter 5.1.7), to ensure safe practices and minimize operator exposure during pesticide application.



Figure 5.7: Mechanical sowing of treated seeds

5.1.7 PERSONAL PROTECTIVE EQUIPMENT TO MITIGATE EXPOSURE.

The operator risk assessment answers the question “under which conditions is the exposure of the operator considered to be without unacceptable risk”? To achieve this, the estimated systemic exposure has to be lower than the Acceptable Operator Exposure Level (AOEL).

The operator exposure, (see section 5) is corrected for the absorption rate (section 4) according to the route of exposure to derive the systemic operator exposure. This value is then compared to the toxicological endpoint relevant for operators (AOEL).

Besides considering specific crop, climate, and equipment factors, an appropriate operator risk assessment also includes a realistic view of the use of personal protective equipment (PPE) during pesticide application. In our risk assessments, we only assume protective clothing for operators, the use of which can be considered realistic under local practical and climatic conditions. In most of the countries in scope, we consider the use of one layer of long-sleeved, long-trousered clothing. In addition, chemical resistant gloves and a simple particle filter mask (FFP1) can be considered.These are then directly incorporated either as a default protection factor (e.g., mask: 80% protection for inhalation exposure) or using measured exposure figures in our models. This assumption also complies with the PPE recommendations made by FAO for applying agricultural pesticides[21].

[21] FAO & WHO (2020) – International code of conduct on pesticides management – Guidelines for personal protective equipment when handling and applying pesticides

6. RISK MITIGATION

6.1 PRODUCT-SPECIFIC MEASURES

Bayer aims to obtain new registrations only for product uses that meet the Bayer safety standard.

Depending on use-specific circumstances, risk mitigation measures, such as a reduction in the product application rate or application frequency, or the use of advanced personal protective equipment such as impervious clothing can be applied. In some markets, additional engineering measures such as drift-reducing nozzles, a closed cabin on a tractor, dust extraction during seed treatment, or the use of a closed transfer system can be considered to further mitigate exposure.

Precautionary statements on product labels are basic measures to mitigate health risks for operators. Bayer has established a Good Labeling Practice procedure which makes sure that operators apply products safely, if they follow the label.

For crop protection products, we have committed to the voluntary standard set by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO): The International Code of Conduct on Pesticide Management (2014)[22]. Details of our commitments can be found on our transparency website.

6.2 GENERAL MEASURES

6.2.1 SAFE USE TRAININGS

We provide targeted training to farmers, seed treatment professionals, other users, and distributors, emphasizing effective and safe product usage to ensure operator safety. Training covers safe product handling, transport, storage, and disposal, along with calibration of application equipment, proper use of PPE, and first aid measures, amongst other topics. We adapt training topics for specific groups, crops, or products - based on local needs. Our materials come in various formats, including on-site presentations, brochures, videos, posters, manuals, and live chats. We combine training with events such as product launches and field days, and our safety videos are available online.

Through our Bayer Safe Use Ambassador initiative, we partner with 50+ universities in Asia/Pacific and Africa to train agricultural students in safe product use, empowering them to educate farmers during their internships. We conduct webinars and online events on sustainable product use. We also provide guidance to physicians and poison control centers on treatment following product poisoning or snake bite.

6.2.2 LICENSE TO SPRAY

For countries with no mandatory training or licensing requirements, professional spray services (e.g., Spray Service Providers), offer an effective way of avoiding unsafe use. This approach is being pioneered in several African countries. Bayer supports initiatives and partnership projects that aim to ensure that PPPs are only handled by trained operators.

[22] https://www.bayer.com/en/file/270596/download?token=cwrcmIeA

6.2.3 INNOVATION IN APPLICATION TECHNOLOGY

In countries with small agricultural field sizes which typically feature backpack spraying, innovations in application technology such as the use of unmanned aerial vehicles (UAVs/drones) or mechanized ground spraying for the application of PPPs, offer the opportunity to significantly reduce operator exposure during the application of the product. Proper use of appropriate PPE is required when mixing/loading PPPs for drone use, as for other modes of application. When flying the drones, the pilot does not require PPE, but it must be used again when contact with the drone resumes after the application. Stewardship guidance for use of UAVs is available on CropLife International's website.[23]

6.2.4 MONITORING

We follow up on every incident relating to our crop protection and seed products reported anywhere in the world and manage the incidents with the aid of a dedicated incident management system. Our incident management system and continuous product use screenings form the key reference points when it comes to monitoring the safety of our products and to identifying necessary improvements. In general, steps to mitigate risk range from increased training efforts, change of formulation, revised application recommendations and use limitations, to product withdrawal. Further, our incident management system also analyzes data from national poison control centers, where available. We work with hospitals and poison control centers to further improve their incident management capability and data quality, also with the support of CropLife International. Since 2022, we have engaged with medical professionals through our Bayer Safe Use Ambassador Initiative, in which we encourage physicians in LMICs that do not have national incident monitoring institutions to report any incidents related to PPPs.

[23] https://www.bayer.com/en/file/270596/download?token=cwrcmIeA

7. UNCERTAINTIES

"All models are just simplifications of the reality and only as good as the data and the assumptions from which the model is built". This statement is an alternative variant of the famous sentence by the British statistician George E.P. Box, *"all models are wrong, but some are useful"*. It means that more data and more solid assumptions lead to better predictions. When constructing a model, one leaves out all the details which, with the knowledge at one's disposal, are considered inessential. Models may not be absolutely true, but it is important that they are applicable, and whether they are applicable for any given purpose must, of course, be investigated. This also means that a model is never final, only on trial. This general perception of modelling also holds true for our current operator risk assessment approach, which is not perfect by far, but we are working continuously to improve it.

7.1 MISSING DATA

The safety standard created by Bayer covers the most common pesticide application scenarios. We hereby cover more exposure scenarios than are considered by many leading regulatory authorities, because we also consider local requirements and practices, which can often be drivers of high exposure levels. However, our current modelling approaches do not cover all possible ways of working with plant protection products, because insufficient data is available to estimate operator exposure accurately for some of the less common application scenarios. If a use scenario is not covered by our exposure models we may also consider bridging from a more conservative exposure scenario (e.g., handheld -> drone).

A PPP application according to the label recommendations results in a safe use scenario for operators. Thus, it is our objective that farmers work according to Good Agricultural Practice by following the individual use restrictions on the label of each PPP. However, many use scenarios are not supported by us, because they are not according to Good Agricultural Practice and often lead to high-risk scenarios. It is our overarching objective to train farmers to effectively reduce these high exposure scenarios by further professionalizing the application of plant protection products according to the label instructions.

7.2 COMPOUNDED CONSERVATISM OR SCIENCE VS. REGULATORY SCIENCE

The safety standard approach created by Bayer, exposure models were developed a priori, based on the best scientific knowledge and the clear objective to estimate operator exposure in a realistic manner. We are aware that pesticide risk assessments are uncertain by nature, based on assumptions in the absence of data, such as estimating exposure and extrapolating toxicity across species. Regulatory agencies usually resolve those uncertainties in a health protective (conservative) manner; however, only inter- and intraspecific uncertainties are explicitly addressed by a safety factor (SF). When setting the toxicological threshold. Other uncertainties are also addressed (e.g., by consistently using "worst case" or conservative assumptions and high exposure percentiles), but here, a safety factor cannot be determined . Cochran and Ross (2017)[24] developed a methodology to quantify hidden uncertainty factors routinely applied by many leading authorities globally. This quantification leads to the conclusion that adding multiplicative factors is not only scientifically questionable, but also helpful neither to risk managers´ policy decisions, nor to a comprehensive risk-benefit analysis.

[24] Roger C. Cochran & John H. Ross (2017) A method for quantitative risk appraisal for pesticide risk assessments, Journal of Toxicology and Environmental Health, Part A, 80:1, 1-17, DOI: 10.1080/15287394.2016.1224747

DEFINITIONS (EXTENDED FROM FAO GUIDELINE)

- **A.I.** (Active Ingredient) is the biologically active ingredient of a plant protection product.
- **AOEL** (Acceptable Operator Exposure Level) is a systemic endpoint relevant for non-dietary risk assessment.
- **Co-formulant** means a non-active ingredient component of a formulated product, added for various purposes (e.g., to stabilize the mixture of active ingredients).
- **Exposure** to pesticides means any contact between a living organism and one or more pesticides.
- **FAO** (Food and Agriculture Organization) is an agency of the United Nations leading international efforts to defeat hunger, improve nutrition and ensure food security.
- **Formulation** means the combination of various ingredients (active ingredients, co-formulants and solvents) designed to render the product useful and effective for the purpose claimed and for the envisaged mode of application.
- **GLP** (Good Laboratory Practice) is a quality system of management controls for research laboratories and organizations to ensure the uniformity, consistency, reliability, reproducibility, quality, and integrity of products through analytical tests.
- **Hazard** means the inherent property of an active ingredient, agent or situation having the potential to cause undesirable consequences (e.g., properties that can cause adverse effects or damage to health, the environment or property).
- **Mode/mechanism of action** describes a functional or anatomical change, resulting from the exposure of a living organism to an active ingredient.
- **NOAEL** (No Observed Adverse Effect Level) is a dose level in toxicological animal testing studies at which no adverse effects have been observed.
- **OECD** (Organization for Economic Co-operation and Development) is an intergovernmental economic organization with 37 member countries to stimulate economic progress and world trade.
- **Operator** is a professional who is involved in activities relating to the application of a PPP; such activities include mixing/loading the product into the application machinery, operation of the application machinery, repair of the application machinery whilst it contains the PPP and emptying/cleaning the machinery/containers after use.
- **Pesticide** means any active ingredient or mixture of active ingredients of chemical or biological ingredients intended for repelling, destroying or controlling any pest or disease, weeds or regulating plant growth.
- **Pesticide management** means the regulatory and technical control of all aspects of the pesticide life cycle, including production (manufacture and formulation), authorization, import, distribution, sale, supply, transport, storage, handling, application and disposal of pesticides and their containers to ensure safety and efficacy and to minimize adverse health and environmental effects and human and animal exposure.
- **PPP** (Plant Protection Product) means a formulated product, containing one or more pesticides and often co-formulants. Plant protection products are usually ready-to-use liquids or solid formulations, like granules. The term PPP includes spray application as well as Seed Treatment uses.
- **Risk** is the probability and severity of an adverse health or environmental effect occurring as a function of a hazard and the likelihood and the extent of exposure to a pesticide.
- **Risk management:** A systematic process of identifying, assessing, and mitigating risks to prevent harm and ensure safety. It involves developing and implementing strategies that are realistic and suitable within local contexts, including the provision of training and necessary protective equipment.
- **Stewardship:** The practice of managing and safeguarding resources or practices with a focus on ethical, sustainable, and responsible use. It aims to ensure the long-term welfare of both people and the environment by promoting adherence to guidelines and sustainable practices.
- **Use Scenario:** Conditions and parameters for applying pesticides that are assumed for operator risk assessment. This includes the application rate, the area treated, the equipment used, and other relevant factors to ensure effective and safe use.

APPENDIX

A1 - CONSIDERATION OF REVIEWER COMMENTS

On April 21-22, 2021, an external review panel was held with eight external scientists, including academics and current and former regulators, who were asked to provide feedback on the first version of the operator safety standards. The scientists pre-reviewed the standards and provided feedback to directed questions on the quality of the standards. During the meeting they were able to elaborate on their feedback, ask Bayer questions, and Bayer was able to clarify. Their feedback is now used to improve the standards' technical content and readability. The panel's feedback has been instrumental in guiding these improvements.

- **Simplification and Audience Segmentation:** To make the standard more accessible, Bayer has simplified the main document by moving complex technical considerations to the appendix. This approach ensures that the content remains comprehensive while being more accessible to a broader audience.
- **Collaboration and Capacity Building:** Bayer has joined the ICPPE project to work collaboratively with industry leaders, regulators, and academic experts to improve operator safety, particularly in low and middle-income countries. The revised standards reflect a commitment to the FAO Code of Conduct and the need for industry-wide support in promoting best practices and responsible supply to prevent inappropriate product use.
- **Dermal absorption:** The revision includes a detailed justification for the choice of dermal absorption values and progress on an in-silico prediction tool, which has been published and made available for public use.
- **Data Collection and Modeling:** Bayer has expanded its safety standard to include models for seed treatment exposure modeling and drone applications.
- **Local Studies and Industry Collaboration:** The company is actively contributing to and sharing data with the ICPPE project and has published a peer-reviewed study on operator exposure during drone applications. Bayer acknowledges the need for an industry-wide response to generate robust datasets that reflect local operator practices and conditions.

In conclusion, the revised operator safety standards reflect a concerted effort by Bayer to integrate expert feedback, enhance safety for operators, and foster collaboration with global stakeholders to achieve improved and localized risk assessments. The company remains committed to continuous improvement and the responsible stewardship of its products.

For more details on the expert panel, please refer to the meeting minutes, which are published on our transparency website.

25

[25] https://www.bayer.com/en/sustainability/transparency

A2 – TOXICOLOGICAL STUDIES TO DETERMINE THE HAZARD

The pesticidal effect of a chemical plant protection product is driven by the active ingredient. Therefore, a hazard assessment of the active ingredient (as well as for the corresponding plant protection product) and its potential residues is performed.

Toxicological studies with the active ingredient are conducted to determine the potential for:

- I. Short- and long-term adverse effects on all major organs/systems including liver, brain, kidney, thyroid, reproductive organs, nervous system etc.
- II. Carcinogenicity (C), mutagenicity (M), reproductive toxicity (including embryotoxicity and teratogenicity) (R) and endocrine disrupting (ED) properties of the active ingredient. These effects are often referred to as CMR-ED.
- III. The absorption, distribution, metabolism and excretion (ADME) pathways in the mammalian system including a toxicological characterization of relevant metabolites (break-down products).
- IV. The maximum dose at which No Adverse Effects (NOAEL) were observed in at least three mammalian species (mouse, rat, dog).

For human health effects, Bayer complies with section 4 of the OECD Guideline for the Testing of Chemicals.[26]

As an orientation, this would comprise around 50 different tests to characterize the properties of one single active ingredient.

The following listed studies are an extract that are conducted to get a full toxicological profile of an active ingredient.

A2.1 TOXICOLOGICAL STUDIES

A2.1.1 ACUTE TOXICITY STUDIES

Acute toxicity describes the adverse effects of an active ingredient that result either from a single exposure or from multiple exposures in a short period of time (usually less than 24 hours). active ingredients, as well as formulated products, are tested for acute systemic and local effects, using in silico, in vitro and in vivo test methods, to assess the main routes of exposure and endpoints:

- I. **Acute oral** toxicity
- II. **Acute dermal** toxicity
- III. **Acute inhalation** toxicity
- IV. **Skin irritation/corrosion** effects
- V. **Skin sensitization** effects (allergic reactions)
- VI. **Eye irritation/corrosion** effects

The purpose of acute toxicity studies is to provide information of adverse effects of an active ingredient (or a formulation) resulting from exposure in a short period of time. In most acute toxicity tests, relatively high doses of a test substance is given. The studies provide information on toxic effects and the potential of recovery, help to determine possible target organs that may be scrutinized in repeated dose tests and support dose selection for repeated dose studies, when no other toxicological data is available.

[26] https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals_72d77764-en

The results of these studies provide indication of the hazard of an active ingredient or the formulated product, which is translated in classification and labelling phrases to be included in the package and on the Material Safety Data Sheet (MSDS), following the GHS labeling (Global Harmonization System).

A2.1.2 SHORT-TERM TOXICITY (SUB-ACUTE AND SUB-CHRONIC)

In the assessment and evaluation of the toxic characteristics of a chemical, the determination of sub-chronic oral toxicity using repeated doses is usually carried out after initial information on toxicity has been obtained from acute toxicity tests. The 28-day (sub-acute) and 90-day (sub-chronic) study provides information on the possible health hazards likely to arise from repeated exposure and from repeated exposure over a prolonged period covering post-weaning maturation and growth into adulthood. The studies provide information on the major toxic effects, indicate target organs and the possibility of accumulation of test chemical and can provide an estimate of a no-observed-adverse-effect level (NOAEL) of exposure which can be used in selecting dose levels for chronic studies and for establishing safety criteria for human risk assessment. Sub-acute and sub-chronic toxicity studies will thus provide useful data for operators who are handling and using the pesticide, as well as for other persons who may be exposed sub-chronically. Usually, these toxicity studies are conducted in rats, mice, and dogs. This is important to cover potential interspecies variability in mammals, which is needed to judge the hazards for humans. In some cases, short-term studies can also be conducted to assess potential effects from dermal and or inhalation exposure.

A2.1.3 LONG-TERM TOXICITY (CHRONIC) AND CARCINOGENICITY (C)

When acute, sub-acute and sub-chronic toxicity studies reveal a favorable toxicological profile, long-term (chronic) studies with two mammalian species (rats, mice) are conducted. Chronic toxicity studies provide information on the possible health hazards likely to arise from repeated exposure over a considerable part of the lifespan of the species used. They provide information on the toxic effects of the active ingredient, indicate target organs and the possibility of accumulation.

Chronic toxicity studies are often combined with carcinogenicity studies in order to reduce the number of animals tested. The purpose of these studies, which are conducted in mice and rats, is to identify the carcinogenic properties of a chemical, including an increased incidence of neoplasms, increased proportion of malignant neoplasms or a reduction in the time to appearance of neoplasms, compared with concurrent control groups.

A2.1.4 NEUROTOXICITY STUDIES

Neurotoxicity is defined as an adverse change in the structure or function of the nervous system that results from exposure to a chemical, biological or physical agent. Neurotoxicity studies are conducted to detect potential neurobehavioral and neuropathological effects. These studies are not conducted routinely. They are only conducted if the agent under evaluation belongs to certain chemical classes which are known to have neurotoxic potential, or if findings in acute or sub-acute studies suggest a neurotoxic effect. A developmental neurotoxicity study is carried out, if potential effects on the nervous system and behavioral development following exposure in utero, during lactation and early phase of life until adulthood need to be investigated.

A2.1.5 MUTAGENICITY/GENOTOXICITY (M)

Genotoxicity describes the potential of chemical agents to damage the genetic information within a cell causing mutations, which may lead to cancer. The aim of these tests is to predict the potential of a chemical to cause genetic damage, identify and exclude genotoxic carcinogens at an early stage and elucidate the mechanism of action of some carcinogens. The genotoxic potential is tested in vitro, in vivo in somatic cells and in vivo in germ cells.

A2.1.6 REPRODUCTIVE TOXICITY (R)

Reproductive toxicity studies assess the potential for adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. Developmental toxicity pertains to adverse toxic effects to the developing embryo or fetus. Reproductive toxicity studies are multi-generational and evaluate effects on the integrity and performance of the male and female reproductive systems, including gonadal function, the oestrus cycle, mating behavior, conception, gestation, parturition, lactation, and weaning, and the growth and sexual development of the offspring. In addition, developmental toxicity testing is designed to provide information concerning potential effects of prenatal exposure on the pregnant test animal and on the developing offspring.

A2.1.7 ENDOCRINE DISRUPTING PROPERTIES

Endocrine disruptors are chemicals that can directly interfere with endocrine systems in the body controlled by hormones. Adverse effects are monitored and described in all toxicity studies. In addition, in some countries and regions a more detailed investigation is required to better understand the underlying mode/mechanism of action and to provide sufficient evidence whether the observed effect is mediated by an endocrine mode of action, or it is a consequence of altered homeostasis due to systemic toxicity. These studies also assess whether the effects seen in animals is relevant to humans (e.g., will the chemical effect occur in humans in the same way as in animals).

A2.2 DERIVATION OF THE AOEL

For operator risk assessment described in this standard, we follow a systemic exposure approach. This means, the toxicological threshold used for operator risk assessments (Acceptable Operator Exposure Level = AOEL) represents the internal (absorbed) dose derived from any route of exposure and is expressed as an internal level (mg/kg body weight/day).

To determine the AOEL, the lowest NOAEL (No Observed Adverse Effect Level) from the most sensitive species identified in sub-chronic studies is usually used as a starting point. Typically, toxicological studies are conducted in mice, rats, and dogs . With the default approach the derived NOAEL is divided by a safety factor of 10 to account for possible differences between humans and animals, and an additional factor of 10 to cover differences within the human population. Sometimes safety factors are adjusted to account for, e.g., study duration or severity of effects. In other words, the AOEL is by default 100 times lower than the dose that produced no adverse effects in animals. The determination of the endpoint is based on the following equation:

AOELsystemic (mg/kg bw/day) = (NOAELoral x A) / SF

Where:

- **NOAELoral** is the No Observed Adverse Effect Level from the most relevant oral study.
- **A** is the fraction of the active ingredient that is taken up by the body after oral administration (e.g., 60% oral absorption: A = 0.6).
  The AOEL will be corrected if the measured oral absorption is < 80%.
- **SF** is the assessment factor (Default 100 (10 x 10)).

The main routes of exposure for operators are usually via the dermal and inhalation routes, and not via the oral route. To compare a systemic endpoint (AOEL) with systemic exposure, it is important to know what fraction of initial external exposure (e.g., what lands on the hand) becomes bioavailable, i.e. absorbed into the body. Therefore, the behavior of the active ingredient on skin and via the respiratory tract needs to be determined to estimate systemic exposure properly.

A3 – DETAILS ON OPERATOR EXPOSURE MODELLING

A3.1 DENSE CROP SCENARIOS

The following figure A3-1 describes the logic to distinguish dense and non-dense scenarios that are relevant for handheld applications.

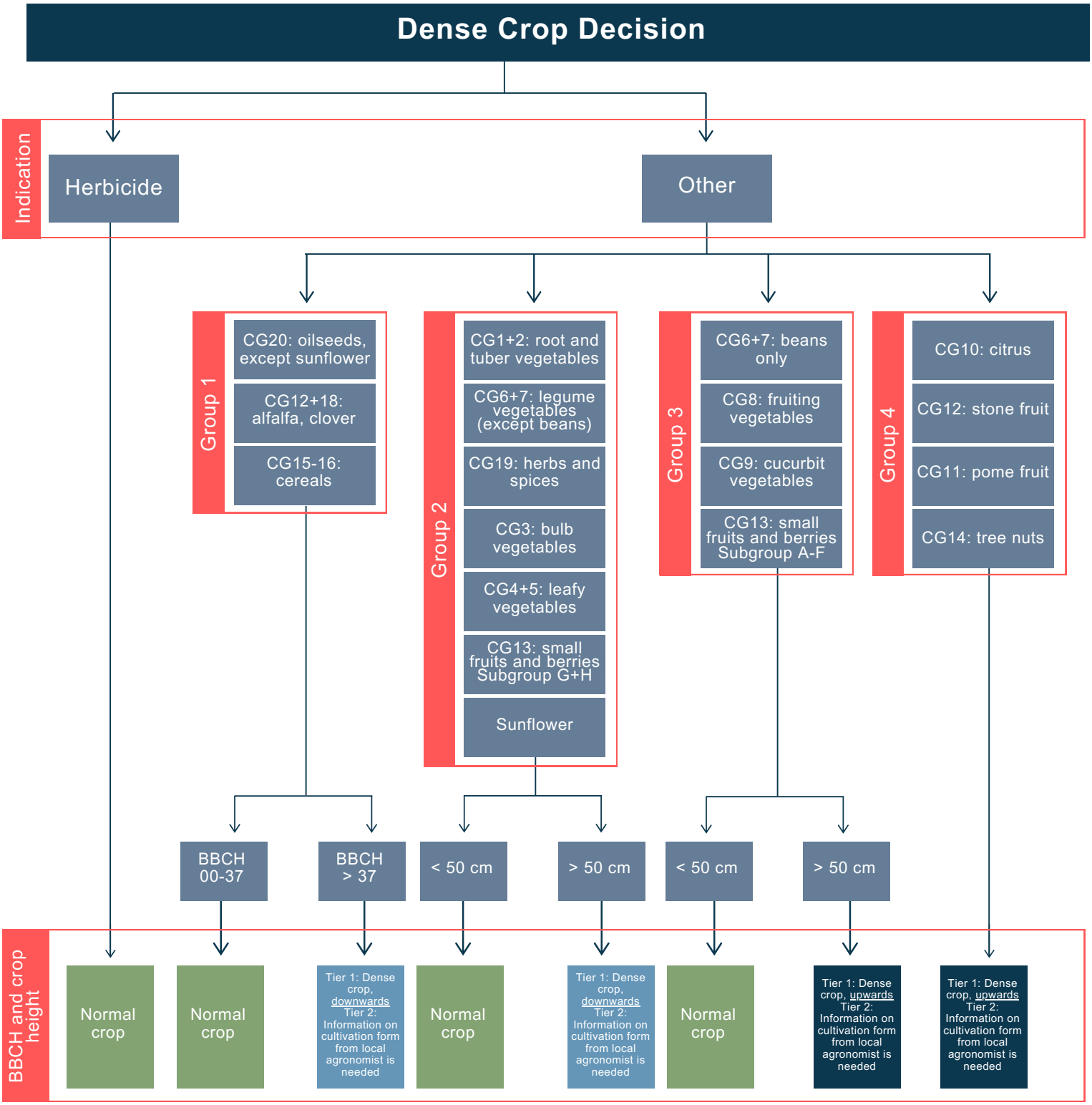


Figure A3.2: *Dense crop decision tree relevant for handheld uses. Remarks: Herbicide application is considered as a use in a normal crop scenario. For crop group 1 the BBCH (growth stage) was chosen to distinguish between dense and normal crop: at BBCH38 or higher, the crop height is usually more than knee height. For group 2 and 3 the use of the BBCH is not useful anymore. Therefore, information on the crop height were used as a parameter: (≤ 50 cm: normal crop; > 50 cm: dense crop). In Group 4, mainly trees, a dense crop scenario is always considered as tier 1. Crops were mainly grouped according to US EPA policy 3.*[27]

A3.2 HANDHELD APPLICATION

A3.2.1 HANDHELD APPLICATION IN NORMAL CROPS

We compiled more than 200 monitoring units (farmers) in one database. The underlying studies were conducted in Europe and the US[28], in the field and in greenhouses. For the statistical analysis, the non-parametric method of 75th quantile regression (Koenker, 2005)[29] was used for modelling. This was also the statistical approach used to develop the European AOEM. Two different clothing scenarios were modelled:

I. Operator wearing one layer of clothing, no gloves

225 independent data points were used for quantile regression. The analysis revealed that the exposure is log-linear correlated with the total amount (TA) of active ingredient handled per day. A pre-analysis revealed that the spray direction (upward or downward) does not have a significant effect on the overall exposure.

Assuming an outdoor scenario in a normal crop the equation to calculate operator exposure during spraying (not including mixing and loading) is as follows:

Dermal operator exposure:
Operator dermal exposure in µg/person = 10^(0.63602*LOG(TA) + 4.03613)
Inhalation operator exposure:
Operator inhalation exposure in µg/person = 10^(0.80252*LOG(TA) + 1.95944)

II. Operator wearing one layer of clothing, with gloves

216 independent data points were used for quantile regression. The analysis revealed that the exposure is log-linear correlated with the total amount (TA) of active ingredient handled per day. A pre-analysis revealed that the spray direction (upward or downward) does not have a significant effect on the overall exposure.

Assuming an outdoor scenario in a normal crop the equation to calculate operator exposure during spraying (not including mixing and loading) is as follows:

Dermal operator exposure:
Exposure µg/person = 10^(0.42129*LOG(TA) + 3.54578)
Inhalation operator exposure:
Operator inhalation exposure in µg/person = 10^(0.80252*LOG(TA) + 1.95944)

[27] US Environmental Protection Agency Office of Pesticide Programs, Science Advisory Council for Exposure (ExpoSAC) Policy 3, revised January, 2017

[28] Operator exposure data from study report AHE400 were considered in the development of the model with kind permission of the Agricultural Handlers Exposure Task Force (AHETF)

[29] Koenker, R.: Quantile regression; Econometric society monographs No. 38, ed.: Chesher, A. and Jackson, M., Cambridge university press 2005. Koenker, R.: quantreg: Quantile Regression; R package version 4.81 (2012), http://CRAN.Rproject.org/package=quantreg

Figure A3.2: Exposure during handheld applications, normal crop scenario, with and without gloves
Top picture: Example of operators applying PPP in a normal crop scenario.

A3.2.2 HANDHELD APPLICATION IN DENSE CROPS, DOWNWARD SPRAYING

For downward application in dense crop scenarios, we used 31 monitoring units from independent studies conducted in South Korea[30] on rice. A statistical analysis using quantile regression with the total amount of active ingredient handled per day like it was used for the normal crop scenario was technically not possible due to the variability of the study results and the small range of active ingredient handled. As an alternative, we defined the scenario "handheld downward application in dense crops" (e.g., rice from BBCH 38 onwards) as a sum of two sub-scenarios for the exposure during application (excluding mixing and loading):

I. Exposure from the actual spraying: It is reasonable to assume that the exposure from spraying is indeed like the exposure in a normal crop. Therefore, we considered exposure calculations using the same exposure figures as for the normal crop scenario.

II. In addition to the exposure from the actual spraying, an additional exposure from contact to the treated crop while walking through contaminated foliage can be assumed. Hereby, mainly the lower body part is exposed. Therefore, mean normalized leg and hip exposure values from the 31 low crop dense studies were taken into consideration. The maximum total amount of active ingredient handled per day in these studies were 0.12 kg a.s./day. As no clear correlation was observed, we used the mean value up to the maximum amount handled per day (0.12 kg a.s./day). Over 0.12 kg/day a linear extrapolation was used as a rather conservative approach, since without data we could at least not exclude a correlation for higher amounts handled. The mean value was deemed appropriate, because of the addition of two exposure scenarios. The use of a higher centile would have led to an unnecessary compounded conservatism.

[30] Operator exposure data from studies conducted in rice (South Korea, SNU, CBNU, KBSI) were considered in the development of the model with kind permission of the College of Agriculture and Life Sciences Seoul National University

We assume that the inhalation exposure is not dependent on the cultivation type (dense or non-dense). Therefore, the formula for both scenarios is identical.

Dermal operator exposure, no gloves (TA=total amount of active ingredient handled per day):
Exposure in µg/person = 10^(0.63602*LOG(TA) + + 4.03613) + if((TA) < 0.12; 4727; (TA)/0.12 * 4727))

Dermal operator exposure, with gloves:
Exposure in µg/person = 10^(0.42129*LOG(TA) + 3.54578) + if((TA) < 0.12; 4727; (TA)/0.12 * 4727))

Inhalation exposure:
Exposure in µg/person = 10^(0.80252*LOG(TA) - 0.5792 + 2.53864)

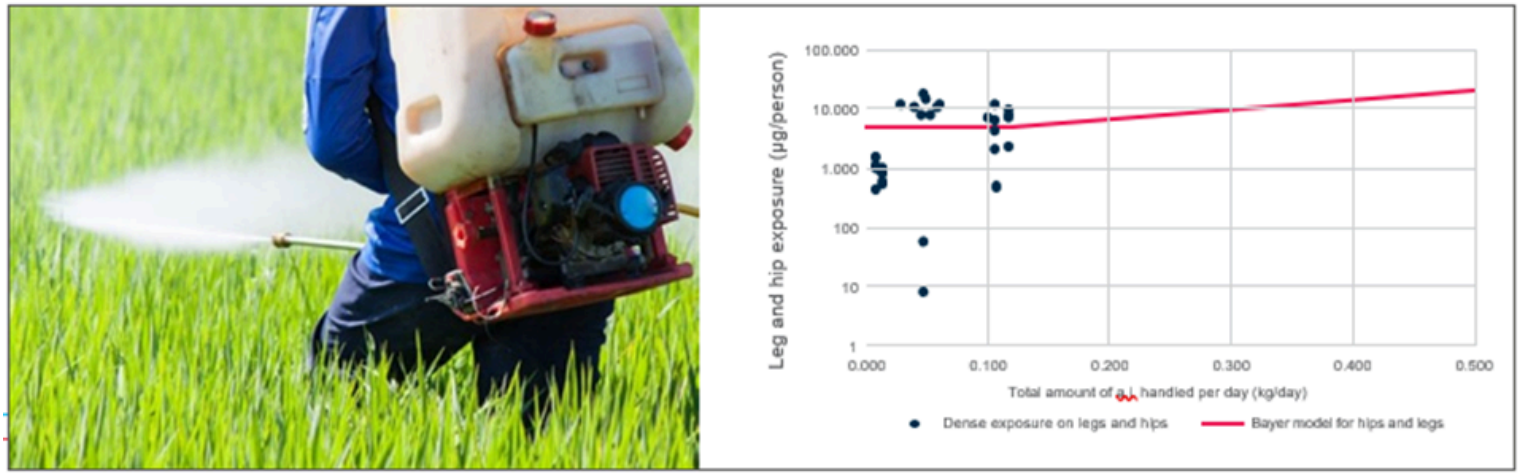


Figure A3.3: *Exposure of the legs and hips during handheld applications in a dense crop scenario (downward spraying)*
Picture left: *Example of operator applying PPP in a dense crop scenario (rice)*

A3.2.3 HANDHELD APPLICATION IN DENSE CROPS, UPWARD SPRAYING

40 Monitoring units from two European studies were used to determine operator exposure during upward spraying in dense high crops. The use of quantile regression was technically not possible, because no statistical correlation between exposure and TA was found. In contrast to the dense crop values for downward spraying, the total absolute amount of active ingredient handled per day was quite high, up to 2-5 kg a.s./day). Therefore, we decided to normalize the data in mg/kg a.s./day for both dermal and inhalation exposure but using a higher centile value (95th) in a conservative approach.

Dermal operator exposure, no gloves (TA = total amount of active ingredient handled per day):
Exposure in µg/person = 17666*(TA) + 49869*(TA) + 1363*(TA)

Dermal operator exposure, with gloves:
Exposure in µg/person = 357*(TA) + 49869*(TA) + 1363*(TA)

Inhalation exposure:
Exposure in µg/person = 186*(ta)

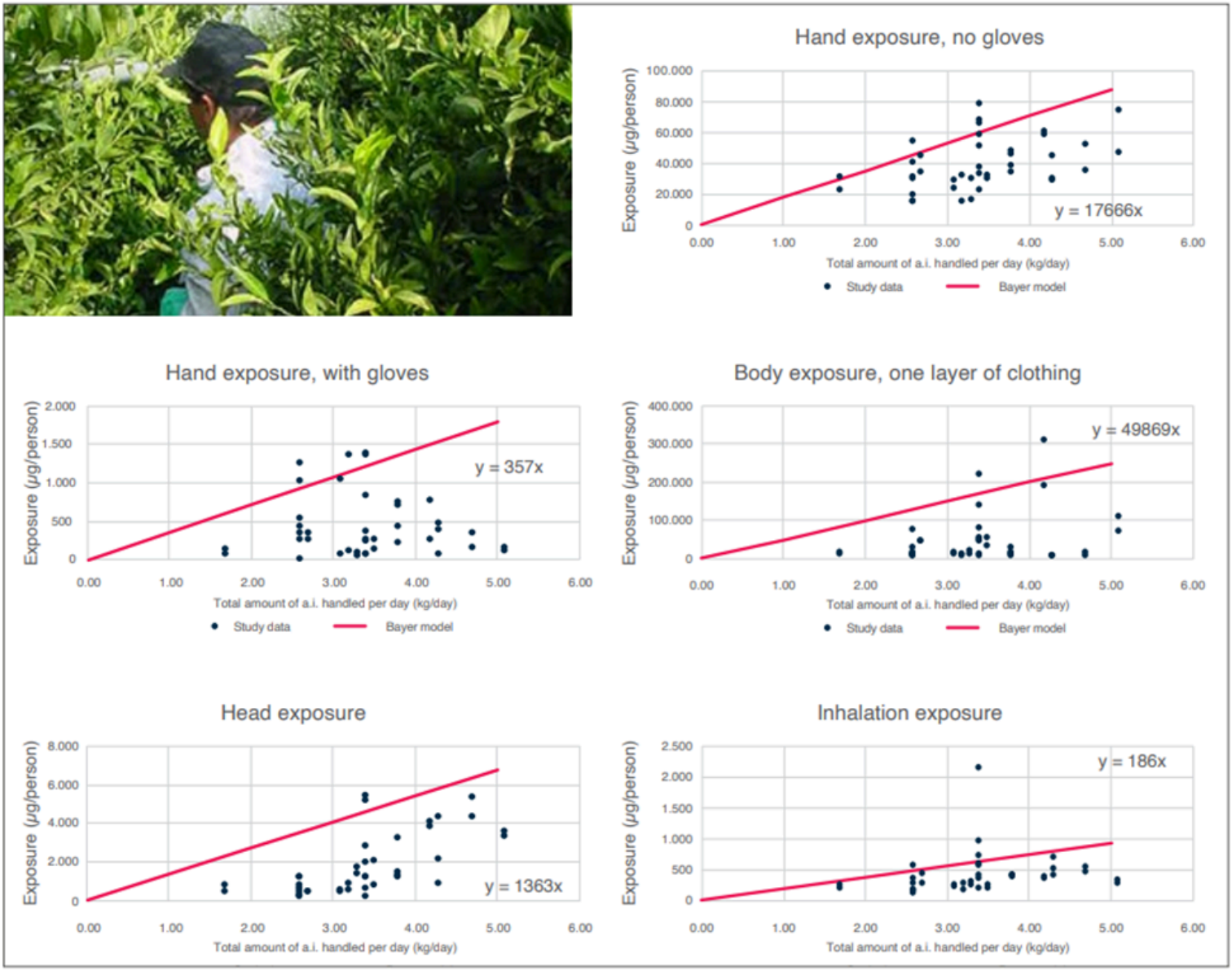


Figure A.3.4: *Exposure during handheld applications, dense crop scenario, exposure of different body parts*
Picture top-left: *Example of operator applying PPP in a dense crop scenario: upward spraying*

A3.2.4 HANDHELD APPLICATION IN NORMAL AND DENSE CROPS: SUMMARY

The handheld models developed by Bayer are described in the following:

Table A.3.1: Exposure algorithms of the Bayer handheld models used for operator risk assessments

	Normal crop Upward + Downward (µg/operator)	Dense crop, Downward (µg/operator)	Dense crop, Upward (µg/operator)
Exposure during mixing and loading	Europe: AOEM	Europe: AOEM	Europe: AOEM
Dermal exposure during application, one layer of clothing, no gloves	= 10^(0.63602*LOG(TA) + 4.03613)	= 10^(0.63602*LOG(TA) - 0.50321 + 4.53934) + if((TA) < 0.12; 4727; (TA)/0.12 * 4727))	= 17666 µg/kg*TA (hand) + 49869* TA (body) + 1363 µg/kg * kg a.s. / ha * ta (head)
Dermal exposure during application, one layer of clothing, with gloves	10^(0.42129*LOG(TA) + 3.54578)	= 10^(0.42129*LOG(TA) + 3.54578) + if((TA) < 0.12; 4727; (TA)/0.12 * 4727))	= 357µg/kg*TA (hands+gloves) + 49869 µg/kg* TA (body) + 1363 µg/kg*TA (head)
Inhalation exposure	10^(0.80252*LOG(TA) + 1.95944)	10^(0.80252*LOG(TA) + 1.95944)	= 186 µg/kg*TA

TA = total amount of active ingredient handled per day (kg/day): kg a.s. / ha * area treated Depending on the equipment either “Mixing and loading – tank” or “Mixing/loading – knapsack”

A3.3 SEED TREATMENT USES

A3.3.1 SEED TREATER, COMMERCIAL FACILITY – STANDARD TECHNICAL LEVEL

This type of seed treater is commonly found in commercial facilities and is designed to meet standard technical specifications. It is engineered for high precision and uniformity in seed treatment, minimizing operator exposure to chemicals. These machines are typically equipped with advanced safety features, including enclosed treatment chambers and automated dispensing systems, to ensure both effective treatment and operator safety. Exposure estimates for these types of equipment are provided by the SeedTROPEX model[31] . We specifically utilize the database of the French version of the model, as it offers the advantage of separating exposure by body parts. This feature facilitates the recommendation of appropriate Personal Protective Equipment (PPE) for operators. Nevertheless, normalization of the exposure data in the specific work tasks is according to the original Seed TROPEX model, i.e., for mixing/loading, calibration and cleaning surrogate values are expressed in mL slurry/ operation, and for bagging in mg a.s./hour. For initial, tier 1 assessments, we employ the SeedTROPEX model for slurry treatment with liquid formulations across all crops, except for tuber treatments. For more advanced, higher-tier assessments—such as those focusing on specific crops like corn and sugar beet, or on small grains in general—we rely on dedicated exposure studies. These specialized studies are particularly relevant for seed treatment facilities with advanced technical capabilities, as they provide a more accurate representation of operator exposure conditions.

[31] Hamey, P., Byron N.: SEED TROPEX predictive exposure model for seed treatment in plant and seed sowing: Interpretation by UK PSD, not published

The following surrogate values were extracted from the database and applied in exposure modelling. Available data were generated for operators wearing one layer of cotton/polyester work clothing and in addition chemical resistant gloves during mixing/loading, calibration and equipment cleaning. Additional protection via impermeable coverall or particle filtering half mask will be addressed via protection factors (impermeable coverall 0.5, particle filtering half mask FFP2 0.1).

Table A.3.2: Surrogate values used for operator exposure modelling.

TASK	Inhalation Exposure (ml/op)*	Body Potential (ml/op)*	Body one layer of clothing (ml/op)*	Hands Potential (ml/op)*	Hands protected (ml/op)*
Calibration Mixing / Loading Bagging (mg/hr) Cleaning	0.001 0.0001 0.0054 0.016	0.008 0.0038 1.110 0.400	0.001 0.0005 0.135 0.030	0.097 0.0070 0.379 0.199	0.006 0.0002 0.038 0.003

Systemic operator exposure during the work tasks is calculated according to the established algorithm of the Seed Tropex model as presented below:

	Systemic exposure
Mixing/loading Calibration, Cleaning	Esys=((DEbody +DEhand) x DA + IE) x Conc x WR / BW With: Esys: Systemic exposure (mg/kg bw/day) DEbody: Dermal exposure body (mL /operation) DEhand: Dermal exposure body (mL /operation) IE: Inhalation exposure (mL/operation) DA: dermal absorption (%) Conc: (mg a.s./ mL) WR: Work rate (operations/day) BW: body weight (kg) Dermal absorption: Mixing/loading, calibration, bagging: concentrate, cleaning: in use dilution
Bagging	Esys=((DEbody +DEhand) x DA + IE) x WR / BW With: Esys: Systemic exposure (mg/kg bw/day) DEbody: Dermal exposure body (mg /hour) DEhand: Dermal exposure body (mg /hour) IE: Inhalation exposure (mg/hour) DA: dermal absorption (%) WR: work rate (hours/day) BW: body weight (kg)



Figure A.3.5: Typical working scenarios in commercial seed treatment facilities

A3.3.2 SEED TREATER, MOBILE – ON FARM TREATMENT, HIGH THROUGHPUT

Mobile seed treaters are designed for on-farm use and are capable of high-throughput operations. These units are often trailer-mounted, allowing for easy transport and flexibility in treatment location. While they offer the advantage of convenience, it's crucial for operators to follow safety guidelines rigorously. This is particularly important as the mobile nature of these units can sometimes lead to less controlled environments compared to commercial facilities.

Exposure algorithms for this scenario were derived from a study conducted in 2006, Worker Exposure During On-farm and Commercial Seed Treatment of Cereals were analyzed. Sixteen trials assessed agricultural workers' exposure to imidacloprid residues during cereal grain seed treatment and planting. Twelve trials involved on-farm treater/planters and four with commercial applicators. The seed was treated with liquid formulations for seed treatment. The mixing method involved open pouring of the formulation into various containers. Workers' actual dermal exposure was measured using body dosimeters, hand rinses, and face/neck wipes. Inhalation exposure was gauged using a personal air sampling pump.

A summary of the normalized exposure results is given in the table below. As surrogate for the exposure calculation the 75th percentile of the dermal and inhalation exposure was selected.

Table A.3.3: Normalized operator exposure results for mobile seed treaters

	Exposition µg/kg a.s. handled				
	Inner Dosimeter	Hand Washes	Face-Neck Wipes	Total Dermal	Inhalation (20.8 L/min)
NT003-06X	40.2	286	4.02	330	2.94
NT004-06X	20.6	34.7	2.62	57.9	6.53
NT005-06X	9.75	5.5	1.78	17.1	1.41
NT006-06X	50.7	122	3.24	176	5.53
NT007-06X	10.3	117	1.02	128	0.50
NT008-06X	210	313	4.19	527	4.71
NT009-06X	153	47.4	10.3	210	77.47
NT010-06X	12.9	49.9	1.26	64.1	0.87
NT011-06X	7.16	14.1	0.83	22.1	0.92
NT013-06X	62.9	14.9	0.85	78.6	2.42
NT015-06X	7.2	13.1	0.11	20.4	0.19
NT016-06X	91.3	18.2	2.28	112	3.44
NT001-06X	94.3	213.0	1.2	308.4	3.9
NT002-06X	26.5	37.8	0.3	64.5	0.6
NT012-06X	27.6	61.0	0.8	89.4	0.3
NT014-06X	13.6	156.0	1.9	171.5	0.9
75th percentile	70.0	130.5	2.8	184.5	4.1

Dust development and consequently the exposure is considered lower than during indoor seed treatment, therefore this is a different scenario compared to seed treatment in plants.

It is considered that the exposure is only a result of the actual treatment. Exposure due to background contamination of the equipment or surfaces is considered as less relevant compared to the indoor treatment scenario in a seed treatment plant. Thus, the normalization to the amount of active ingredient used during the monitoring time is reasonable and in line with the normalization approach US EPA is using to generate surrogate exposure values for seed treatment.

Exposure is calculated with the following equation:

Esys=(ADE x DA + IE) x AR x WR / BW

With:

Esys: Systemic exposure (mg/kg bw/day)
ADE: Actual dermal exposure (mg /kg a.s.)
IE: Potential inhalation exposure (mg/kg a.s.)
DA: dermal absorption (%)
AR: Application rate (kg a.s./ tonne of seed)
WR: work rate (tonnes of seed /day)
BW: body weight (kg)

Figure A.3.6: Mobile seed treatment devices

A3.3.3 SEED TREATER, ON-FARM (DRUM MIXER/ SMALL BATCH TREATERS)

These are the most basic form of seed treaters, often improvised from drum mixers or similar small batch mixing equipment. They are commonly used for on-farm treatment of seeds in smaller quantities. While these systems are cost-effective and accessible, they generally lack the advanced safety features found in commercial or mobile units. Therefore, operators must exercise extra caution, including the use of appropriate Personal Protective Equipment (PPE), to minimize exposure during the seed treatment process.

Exposure algorithms were derived from an exposure study conducted in 2002 under GLP and according to the OECD Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application, Series on Testing and Assessment No. 9, 1997. The study took place at two agricultural contractors' sites in March 2001, using a drum mixer and a Trans-Mix device, both common tools for this task. Twelve monitoring units were monitored, performed by eight operators over shifts ranging from 1½ to 2¼ hours. Dermal was measured using whole body dosimeters. Operators wore standard work clothes and added protective gear, including gloves, masks, and aprons. Hand exposure was assessed by washing and analyzing the hands and gloves. Inhalation exposure was gauged using personal air sampling pumps.

A similar normalization approach was selected as used in the Seed TROPEX model for the mixing/loading, calibration, and cleaning task. It assumes that operators are exposed to a certain volume of the treatment liquid when preparing the slurry, applying the slurry to the seeds in the drum and when handling the not fully dried seeds after treatment. The measured exposure is normalized to the amount of liquid an operator is exposed to in one hour of work (mL slurry/hour) and corrected for the content of the active ingredient in the treatment slurry. The maximum value was selected as surrogate value for the exposure modelling.

Table A.3.4: normalized operator exposure results for drum mixers

	OA	OB	OC	OD	OE	OG	OI	OK	OF	OH	OJ	OL	
	All activities	All activities	All activities	All activities	M/L, operation of treater, seed supply	M/L, operation of treater, seed supply	M/L, operation of treater, seed supply	M/L, operation of treater, seed supply	Bagging, stitching stacking	Bagging, stitching stacking	Bagging, stitching stacking	Bagging, stitching stacking	Maximum
Seed handled (kg)	862	862	862	1016	1618	1618	1685	1780	1618	1618	1685	1780	
active ingredient handled (kg a.s.)	3.93	4.32	4.27	4.06	8.18	8.18	8.61	8.66	8.18	8.18	8.61	8.66	
Work duration (min)	137	135	131	138	88	83	89	107	90	96	97	99	
A.s. contentent slurry (g/L)	500	500	500	500	500	500	500	500	500	500	500	500	
Measured exposure [µg/person/day]													
Potential Body Exposure	955.6	1809	1135	1162	2226	2937	2226	3765	24372	6200	8813	20169	
Potential Hand Exposure	3624	3888	6311	10019	103889	951.4	822.2	503.0	5060	10571	5036	4269	
Actual Body Exposure	31.11	30.10	35.01	21.26	41.44	43.60	40.00	87.63	247.7	129.6	92.55	341.2	
Actual Hand Exposure	14.33	4.09	1.31	1.92	2.05	3.40	1.86	4.52	8.75	11.12	9.25	43.46	
Potential Inhalation Exposure	19.33	23.08	34.62	45.76	54.78	23.02	83.16	72.31	41.74	118.87	76.89	185.14	
Normalized exposure [µL slurry/hour]													
Potential Body Exposure	0.837	1.608	1.039	1.010	3.035	4.246	3.001	4.223	32.50	7.750	10.90	24.45	32.50
Potential Hand Exposure	3.174	3.456	5.781	8.713	141.7	1.376	1.109	0.564	6.747	13.21	6.230	5.175	141.7
Actual Body Exposure	0.045	0.054	0.066	0.047	0.156	0.140	0.159	0.217	0.433	0.456	0.264	3.039	3.039
Actual Hand Exposure	0.013	0.004	0.001	0.002	0.003	0.005	0.003	0.005	0.012	0.014	0.011	0.053	0.053
Potential Inhalation Exposure	0.017	0.021	0.032	0.040	0.075	0.033	0.112	0.081	0.056	0.149	0.095	0.224	0.224

Work rates in this type of seed treatment are generally low when considering that small holder farmers use the drum to treat seeds to be sown on the own farm. Up to 500 kg of seeds can be treated per hour in a small drum treater resulting in a daily work rate of 2 hours in which an amount cereal seed for approx. 10 ha could be treated.

Exposure is calculated with the following equation:

Esys=(ADE x DA + IE) x C x WR / BW

With:

Esys: Systemic exposure (mg/kg bw/day)

ADE: Actual dermal exposure (mL slurry/hour)

IE: Potential inhalation exposure (mL slurry/hour)

DA: dermal absorption (%)

C: concentration of a.s. in slurry (mg/mL))

WR: work rate (hours /day)

BW: body weight (kg)



Figure A.3.7: Drum Mixers used for seed treatment

A3.4 SEED SOWING

A3.4.1 DRILL SOWING OF TREATED SEEDS

Tractor driven sowing is the sowing method used for the majority of the planted area. Sowing machines are designed to guarantee a homogeneous distribution of the seeds on the field in an equal sowing depth. The whole process consists in general of two steps: Loading of treated seeds into the seed hopper of the sowing machine and sowing of the treated seeds. Whilst during the loading direct contact to the treated seeds and seed dust is possible and appropriate PPE is recommended, the exposure during the sowing phase occurs mainly via dust and when getting into contact to contaminated surfaces e.g., during maintenance activities.

Exposure estimates for these types of equipment are provided by the SeedTROPEX model. We specifically utilize the database of the French version of the model, as it offers the advantage of separating exposure by body parts. This feature facilitates the recommendation of appropriate Personal Protective Equipment (PPE) for operators. Nevertheless, normalization of the exposure data in the specific work tasks is according to the original Seed TROPEX model, i.e., mg a.s./hour. For initial, tier 1 assessments, we employ the SeedTROPEX model for all crops, except for tubers. For more advanced, higher-tier assessments—such as those focusing on specific crops like corn and sugar beet, —we rely on dedicated exposure studies. These specialized studies are particularly relevant for single kernel precision sowing with advanced technical capabilities, as they provide a more accurate representation of worker exposure.

The following surrogate values were extracted from the database and applied in exposure modelling. Available data were generated for operators wearing one layer of cotton/polyester work clothing. The presented dermal actual body exposure represents this level of protection. Hand exposure was measured via hand-washes or cotton gloves. Only few of the monitored operator’s hands were protected with nitrile gloves during loading seeds into the hopper. Potential dermal hand exposure represents the unprotected operator. Values for the protected hands either uses the measured exposure for the replicates using the gloves or applying a safety factor of 0.1 (90% protection) for operators monitored bare handed.

Table A.3.5: Normalized surrogate values for operator exposure during drill sowing

Exposure [mg/hour]	
Potential hand exposure	0.900
Actual hand exposure with gloves measured or 90% protection	0.116
Potential Body exposure	0.550
Actual Body exposure	0.0484
Potential Inhalation exposure	0.0107
Total actual dermal exposure / no gloves[1]	0.961
Total actual dermal exposure / with gloves [1]	0.178
Potential Inhalation exposure	0.011

[1] Mean calculated from total exposure of single operators

Systemic operator exposure during sowing is calculated according to the established algorithm of the SeedTROPEX model as presented below:

Esys=(ADE x DA + IE) x WR / BW

With:

Esys: Systemic exposure (mg/kg bw/day)

ADE: Actual dermal exposure (mg /hour)

IE: Potential inhalation exposure (mg/hour)

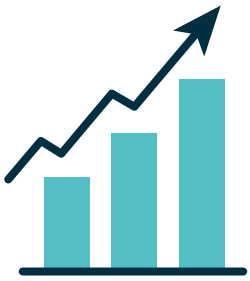
DA: dermal absorption (%)

WR: work rate (hours /day)

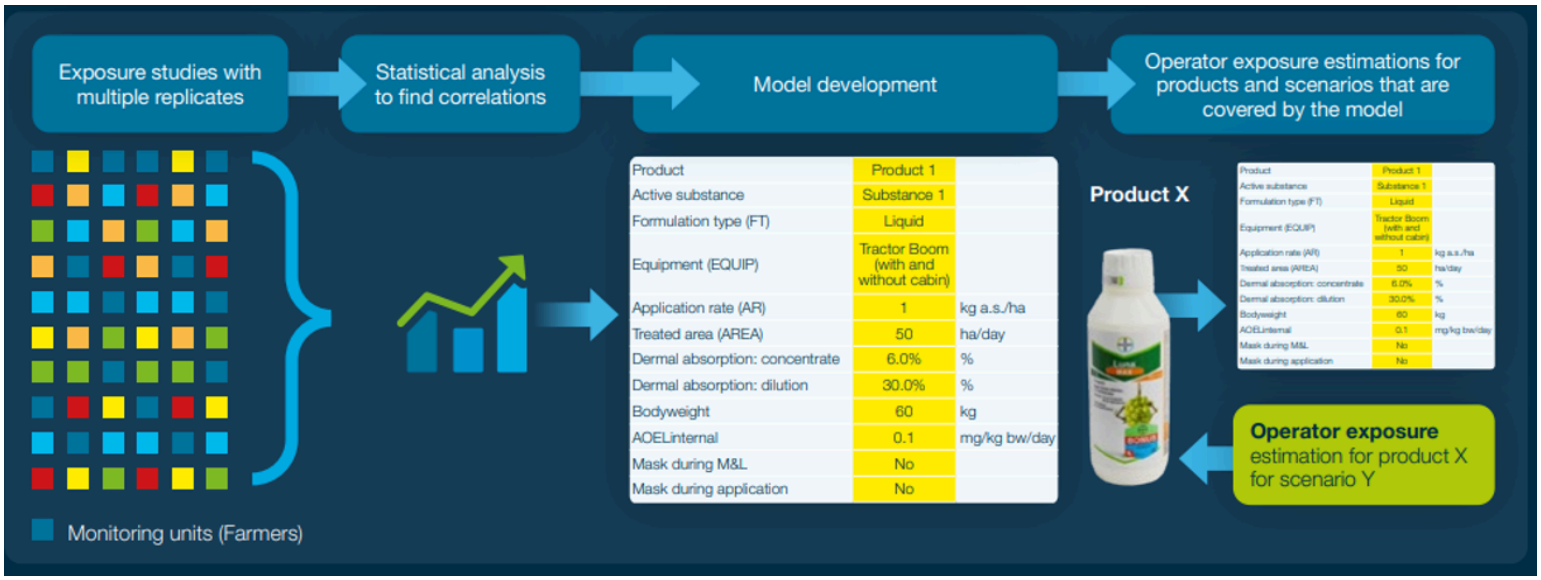
BW: body weight (kg)



Figure A.3.8: Mechanical sowing of treated seeds



Product:	**Product 1**	
Active substance:	**Substance 1**	
Formulation type (FT):	**Liquid**	
Equipment (EQUIP):	**Tractor Boom (with and without cabin)**	
Application rate (AR):	**1**	**kg a.s./ha**
Treated area (AREA)	50	**ha/day**
Dermal absorption: concentrate	**6.0%**	**%**
Dermal absorption: dilution	**30.0%**	**%**
Bodyweight	**60**	**kg**
$AOEL_{internal:}$	**0.1**	**mg/kg bw/day**
Mask during M&L	**No**	
Mask during Application	**No**	



Our overarching goal is to support authorities to develop or refine regulations for operator safety and develop harmonized safety standards. For instance, operator exposure studies, which were conducted by Bayer, were provided free of charge to PROHUMA, a local industry association in Brazil that collaborates closely with Brazilian regulators, to support their work on the development of an operator exposure model. In addition, Bayer supports an initiative by FAO for the development of a global harmonized operator exposure model for developing countries. We actively support the scientific dialogue with authorities and academic key opinion leaders that will allow application of a best-practice standard for assessing exposure and risk.

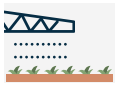
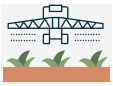
	Spray Application							Granule Application		Seed Treatment		
	Ground-boom	Airblast	Handheld (normal crop)	Handheld (dense crop)	Aerial (airplane)	Drone	Drip Irrigation	Manual application	Application via tractor	Professional facility	On-farm high troughput	Small-scale equipment
												
Origin of the approach	Europe	Europe	Bayer	Bayer	FAO	Bayer	Europe	FAO	FAO	Europe	Bayer	Bayer

Table 3.8: *Bayer operator risk assessment approach*

4.3 UNCERTAINTIES

IN A NUTSHELL

"All models are just simplifications of the reality and only as good as the data and the assumptions from which the model is built". This statement is an alternative variant of the famous sentence by the British statistician George E.P. Box, "all models are wrong, but some are useful". It means that more data and more solid assumptions lead to better predictions. When constructing a model, you leave out all the details which you, with the knowledge at your disposal, consider inessential. Models may not be absolutely true, but it is important that they are applicable, and whether they are applicable for any given purpose must, of course, be investigated. This also means that a model is never final, only on trial.13 This general perception of modelling also holds true for our current operator risk assessment approach, which is by far not perfect, but we are working on it.

4.3.1 MISSING DATA

In the safety standard created by Bayer, the most common pesticide application scenarios are already covered or will be covered in future versions. We hereby cover more exposure scenarios than considered by many leading regulatory authorities, because we also consider local requirements and practices, which can be often high exposure drivers. However, it must be said in all honesty that our current model approaches do not cover all possible ways to work with plant protection products, either because we are not aware of some rare use scenarios or don't have enough data to appropriately estimate operator exposure. If a use scenario is not covered by our model approach, we may also consider a bridging from a more conservative scenario (handheld -> drone).

A PPP application according to the label results in a safe use scenario for operators. Thus, it is our objective that farmers work according to Good Agricultural Practice by following the individual use restrictions on the label of each PPP. However, many use scenarios are not supported by us, because they are not according to Good Agricultural Practice and often lead to high exposure scenarios. It's our overarching objective to train farmers to effectively reduce theses high exposure scenarios by further professionalizing the application of plant protection products according to the label.

13. Rasch, G. (1960), Probabilistic Models for Some Intelligence and Attainment Tests, Copenhagen: Danmarks Paedagogiske Institut, pp. 37–38; republished in 1980 by University of Chicago Press

3.2.2.2 The determination of substance-specific dermal absorption values

In a first-tier approach, we decided to define substance-specific dermal absorption values in a multi-to-one approach when measured data from in vitro human skin studies are available. Some regulations claim that co-formulants have a major impact on the dermal absorption of an active substance, which trigger the conduct of product-specific dermal absorption studies. However, based on our dermal absorption database, which contains values from more than 250 dermal absorption studies, we cannot verify this assumption and consider the influence of co-formulants on the dermal absorption of an active substance as rather negligible (especially for typical in-use dilutions). The observed intrinsic variability caused by the study design is higher than the influence of other parameters.

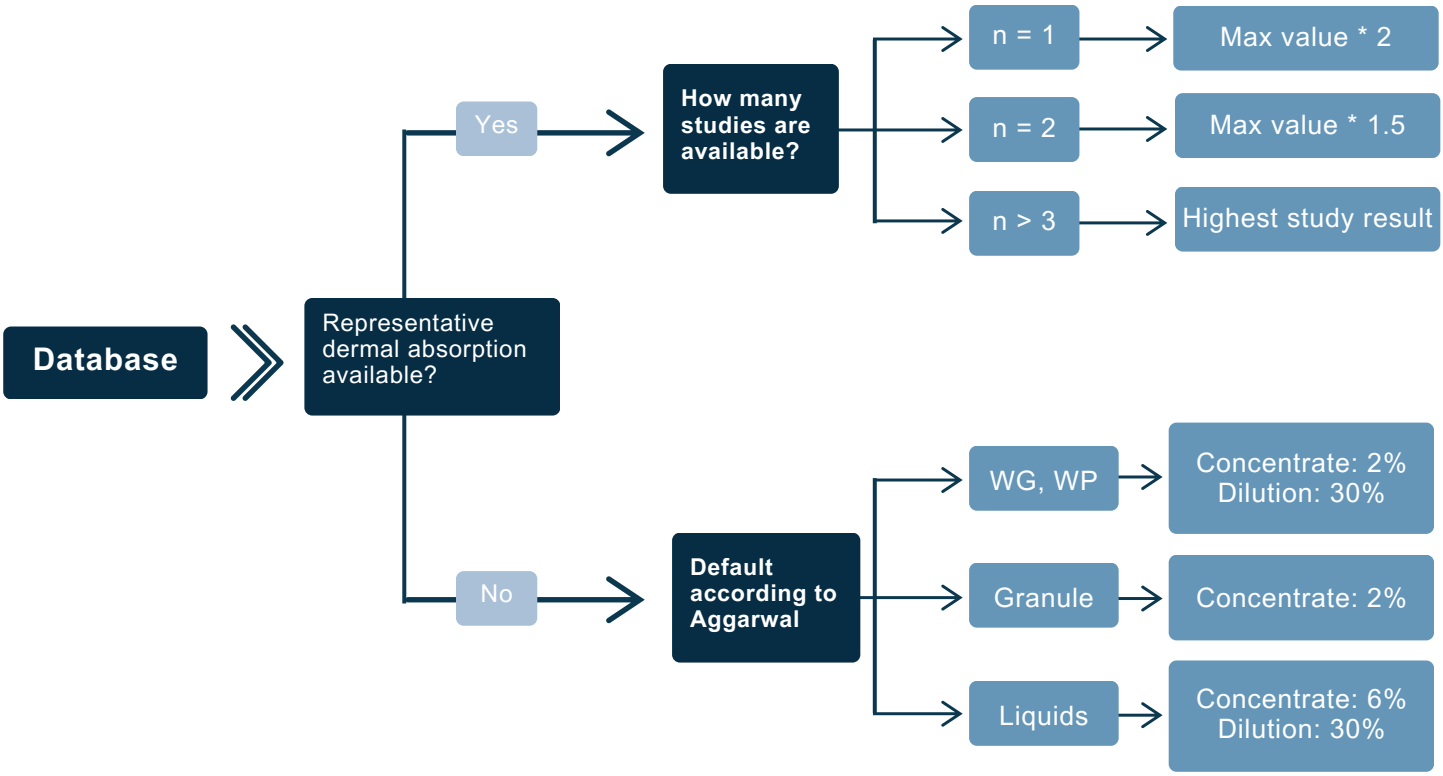
Therefore, for each substance three data pools were established:
// Dermal absorption of the concentrate (liquid)
// Dermal absorption of the concentrate (solid)
// Dermal absorption of the dilution (it is assumed that solid and liquid formulations act similarly once diluted in water)

Depending on the number of independent studies which are available for each substance, the following workflow is used to define substance-specific default dermal absorption figures for each data pool.

Number of independent studies (n=)	Approach taken	Comment
1	Study result -> max value * 2	The safety factor of 1.5 or 2 is needed to cover potential variability. If the so derived value exceeds the defined default dermal absorption, the used value is limited to 30%.
2	The highest study result, max value * 1.5	
>3	The highest study result	

Table 3.2: Approach to consider the normal variability

In conclusion, the following decision tree was followed:



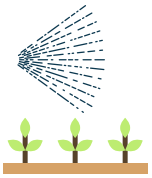
OPERATOR RISK ASSESSMENT

Determination of reference value

Acceptable Operator Exposure Level (AOEL)

Determination of exposure

Application type



Application rate (g/ha, g/t seeds)

Work rate (ha/day)

Exposure

Crop type and growth stage

Formulation type

EXPOSURE MODEL

Main refinement options for exposure determination

Work rate (ha/day)

Crop density

Dermal absoprtion

Stewardship/Risk Management

Personal protective equipment

- Use restrictions
- Farmer trainings
- Formulation changes
- Product substitutions

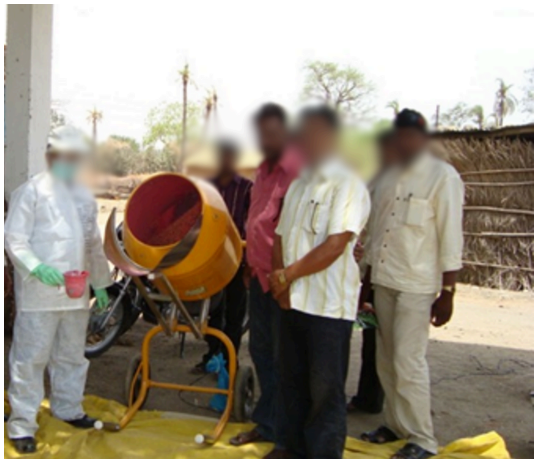
Exposure < AOEL

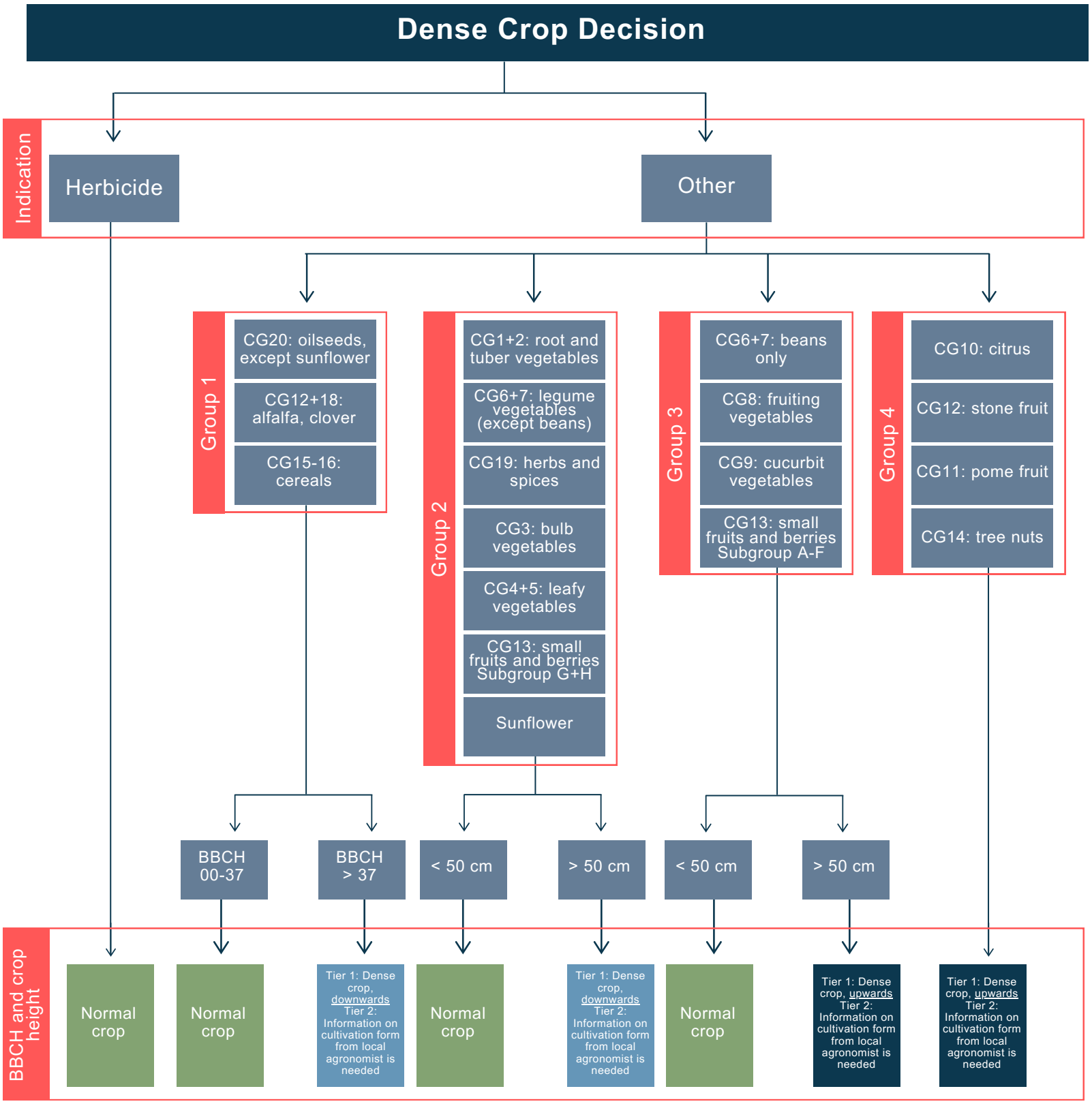
Exposure > AOEL

Type:	Engineering Controls	Advanced PPE	
Equipment:	**Closed transfer system (CTS)** 	**Apron** 	**Impervious clothing** 
Exposure mitigation:	Significant reduction of dermal inhalation exposure during mixing and loading	Reduction of body exposure during mixing and loading	Significant reduction of dermal body exposure during mixing and loading and application
Assumption for exposure assessment:	95% protection dermal and inhalation	50% protection dermal body (excluding hands and head)*	95% protection for body exposure (excluding hands and head)







Dense Crop Decision
Indication
Herbicide
Other
Group 1
CG20: oilseeds, except sunflower
CG12+18: alfalfa, clover
CG15-16: cereals
Group 2
CG1+2: root and tuber vegetables
CG6+7: legume vegetables (except beans)
CG19: herbs and spices
CG3: bulb vegetables
CG4+5: leafy vegetables
CG13: small fruits and berries Subgroup G+H
Sunflower
Group 3
CG6+7: beans only
CG8: fruiting vegetables
CG9: cucurbit vegetables
CG13: small fruits and berries Subgroup A-F
Group 4
CG10: citrus
CG12: stone fruit
CG11: pome fruit
CG14: tree nuts
BBCH 00-37
BBCH > 37
< 50 cm
> 50 cm
< 50 cm
> 50 cm
BBCH and crop height
Normal crop
Normal crop
Tier 1: Dense crop, downwards Tier 2: Information on cultivation form from local agronomist is needed
Normal crop
Tier 1: Dense crop, downwards Tier 2: Information on cultivation form from local agronomist is needed
Normal crop
Tier 1: Dense crop, upwards Tier 2: Information on cultivation form from local agronomist is needed
Tier 1: Dense crop, upwards Tier 2: Information on cultivation form from local agronomist is needed